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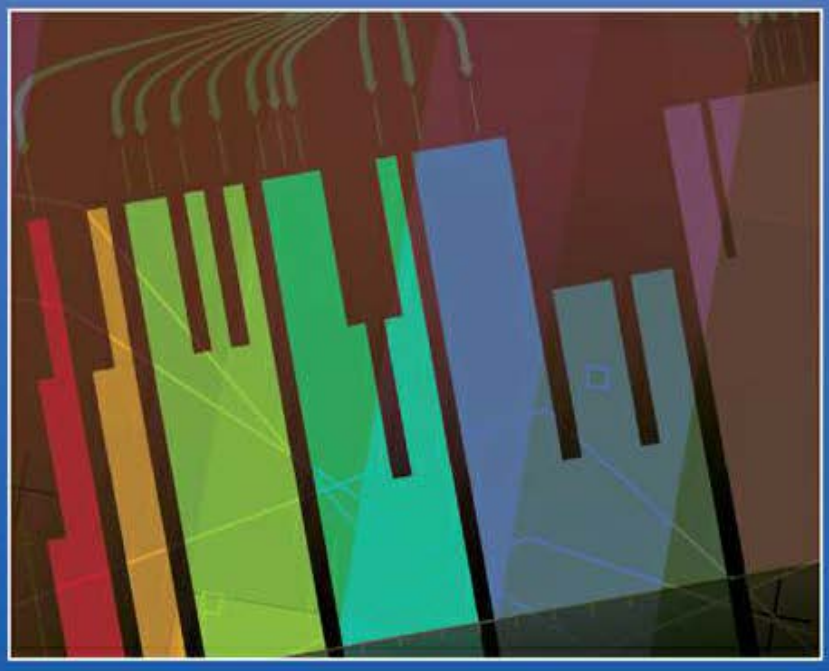
Samuels's Manual of Neurologic Therapeutics

NINTH EDITION

Martin A. Samuels
Allan H. Ropper



Wolters Kluwer

SAMUELS'S MANUAL OF NEUROLOGIC THERAPEUTICS

Ninth Edition

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Dedication

This edition of *Samuels's Manual of Neurologic Therapeutics* is dedicated to H. Richard Tyler who died during the preparation of this book. Rick was a brilliant neurologist, teacher, and bibliophile, who preceded one of us (MAS) as the Chief of Neurology at the Brigham. He arrived at the then Peter Bent Brigham Hospital in 1951 as an intern, having received his medical degree from Washington University. He then trained in neurology at the Boston City Hospital. After stints at the National Hospital for Neurology and Neurosurgery in London and the Salpêtrière Hospital in Paris, he was recruited back to the Brigham to become the first full-time neurologist and then in the Department of Medicine. During his 32-year tenure in that leadership role, neurology was greatly expanded. Through merger with the Boston Hospital for Women and the Robert Breck Brigham Hospital, the institution became the Brigham and Women's Hospital in 1975 in which Rick led neurology until he stepped down in 1988. After leaving the leadership position in Brigham Neurology, he continued to practice full-time, right up until his sudden death in 2016.

As the lone neurologist in a general hospital, Rick Tyler focused on the neurologic aspects of medical and surgical diseases, particularly those in which the Brigham was a leading institution. He characterized the physiologic nature of asterixis and tremor, the typical movement disorders seen in patients with metabolic encephalopathies. The Brigham was the site of the first renal transplantation, so Rick became the reigning expert on the neurologic manifestation of chronic kidney disease, including renal replacement therapy, dialysis, and transplantation. He was expert in the neurologic manifestation of alcoholism and malnutrition, including vitamin and mineral deficiency syndromes. He also articulated the most important neurologic aspects of congenital heart disease in adults.

Rick Tyler was a serious medical historian and collector of rare books. His extraordinary collection was donated to the American Academy of Neurology where it is curated and displayed at his medical alma mater, Washington University in St. Louis. Residents and students from several generations were treated to his dissertations on important landmarks in neurologic history, illustrated by one or more of his rare books. The library in the Department of Neurology at the Brigham is dedicated to Rick and serves as the epicenter of

all of the academic activities of the department.

Harvard medical students from several eras all remember his compelling lectures on neurology, which emphasized his dedication to a careful neurologic history and examination. His patients adored and respected him, realizing that he would always be there to help them with their suffering—always willing to listen and to offer new ideas for relief. To him, medicine was a calling, not just an occupation. He worked days, nights, weekends, and holidays. Rick Tyler represented a brand of personalized medicine that we can only hope to emulate in the modern era.

Despite his dedication to work, he demonstrated a deep commitment to his family, his wife and children, many of whom paid him the greatest compliment by becoming distinguished physicians and surgeons in their own rights. The editors and authors, almost all of whom are now working in the Department of Neurology at the Brigham, are delighted and honored to dedicate this ninth edition of *Samuels's Manual of Neurologic Therapeutics* to one of great treating neurologists, H. Richard Tyler.

Martin A. Samuels
Allan H. Ropper

Cover design adapted with permission from Leavitt S, Tyler HR. Studies in asterixis, part I. *Arch Neurol*. 1964;10(4):360–368. Figure 9, page 366. Association of asterixis with an absolute silent period, synchronous in three muscle groups.

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Foreword

Surely we can refer to *Samuels's Manual of Neurologic Therapeutics* as a "standard"—how many books achieve a ninth edition? Dr. Samuels's first edition of this *Manual* was a surprise because it was published in the era when neurology was viewed as a "diagnose and adios" specialty. The literature probably had to be scoured to produce this first effort. Now, neurology departments are dividing into increasing numbers of subspecialty groups. This multiplication is driven mostly by the burgeoning growth of therapeutic measures. The headache chapter alone in this *Manual* refers to 35 drugs, and there are more than 25 agents in the seizure chapter! But it is not the numbers of treatments that is the most daunting in daily practice of neurology but rather serious nature of the side effects and interactions. The treatment of multiple sclerosis, for example, forces the consideration of hepatic failure, vascular collapse, fatal superinfection (John Cunningham [JC] virus), severe hematopoietic dysfunction, and visual loss. Much care has been taken for the accuracy of drug names and dosage in the text and numerous tables.

Do not look for a narrative in this *Manual*. This is done in an outline format, and the data streams at light-bending density and keeps the volume small and accessible. The editors rely on a group of esteemed colleagues to produce most of the chapters, but effective editing is reflected in the consistency of organization and style in the presentation.

The work successfully captures the therapeutic advances since the eighth edition (2010). Important changes include the recent success in endovascular treatment and newer anticoagulants methods for stroke, the new oral managements of multiple sclerosis, and attention to the management of nonmotor features of parkinsonism. Drs. Samuels and Ropper deserve our gratitude for their work in keeping classical bedside neurology alive in a useful and current way. This book will always be close at hand in my practice and soon well thumbed.

Thomas Sabin, MD
Boston, Massachusetts
June 2017

Preface

It has now been almost a half century since the inception of the *Manual of Neurologic Therapeutics*, and it is now eminently clear that the old saw that "neurologic therapeutics" was an oxymoron is only a bad old joke. Treatment of neurologic diseases now has rightfully taken its place alongside all the other medical specialties. Young neurologists now enter the field with not just the hope but the reality that they will be able to significantly help patients. With this revolutionary change in neurologic treatments comes the reality that it is difficult, if not impossible, for one person to competently manage the entire array of neurologic disorders from those affecting cognition to those affecting muscle and everything in between. More than ever, a concise manual on the therapy of neurologic conditions has become a necessity to help clinicians use informed and discerning judgment to choose among therapies and medications. Of course, correct diagnosis remains a prelude to rational therapy. This *Manual* does not endeavor to opine about the complexities of diagnosis. Many other fine texts exist for this purpose. Proper use of this *Manual* requires the clinician to use the neurologic method to arrive at the most likely diagnosis.

For this edition, most of the chapters are written by a pair of authors, with a junior person, chosen specifically for their active clinical work on the wards and outpatient service, joining a senior author to ensure modernization of the material as well as succession in the future. Matthew B. Bevers has joined Galen V. Henderson in the chapter on coma and on traumatic brain and spinal cord diseases. Rani A. Sarkis joins Barbara Dworetzky in the epilepsy chapter, which includes a panoply of new drugs as well as the nonpharmacologic treatments for seizures. Gregory T. Whitman joins his mentor, Robert W. Baloh, in the chapter on dizziness. Eudocia Quant Lee joins Patrick Y. Wen in the extensive revision and enhancement of the chapter on cancer neurology, which includes the newest molecular techniques or personalized approaches to therapy. Mohammad Kian Salajegheh joins Anthony A. Amato on the two chapters on peripheral neurology: one on motor neuronopathies and neuropathies and the other on diseases of the neuromuscular junction and muscle. A chapter on pain has been extensively updated and rewritten by Daniel D. Vardeh, a dually trained neurologic pain specialist. Henrikas Vaitkevicius has joined Steven K. Feske in updating the

stroke chapter to include the recent information about intra-arterial therapy for acute stroke. Lewis R. Sudarsky is joined by Jordan D. Paulson in updating the information about the management of movement disorders. Seth A. Gale joins Kirk Daffner in the chapter on cognitive and behavioral neurology, and Shamik Bhattacharyya, working with Martin A. Samuels, enhanced the chapter on metabolic and toxic disorders. Allan H. Ropper has revised the chapter on back and neck pain, and Jennifer Lyons joins Tracey A. Cho in extensively updating the chapter on neurologic infectious diseases. The modern approach to sleep disorders is contributed by Milena Pavlova.

In addition to the 17 chapters from the last edition, 2 entirely new ones have been added. Aaron L. Berkowitz, the Director of the Global Neurology Program in the Brigham and Women's Hospital Department of Neurology, has created a novel chapter on the management of common neurologic disorders in resource-limited environments. In addition to its utility in large parts of the world, the physician working in many developed countries also will find its advice invaluable for the cost-effective treatment of these disorders. Ivana Vodopivec and Henrikas Vaitkevicius have added a chapter on the treatment on the whole array of autoimmune conditions, separate from multiple sclerosis and the paraneoplastic diseases. This group of disorders, now diagnosable using modern serologic tests, is managed with immune modulation using drugs, which had been largely the province of rheumatologists and oncologists.

All authors have been chosen for their clinical abilities and experience as well as their capacity to make the material crystal clear, well-organized, and easily accessible. As in the past, the material is organized in an accessible outline format that has been the hallmark of the popular *Spiral Manual* series for over 50 years. Electronic availability of this material enhances the utility of this *Manual* at the bedside, in the office, or in the emergency department. As one can ascertain from the author affiliations, the book arises substantially from the Department of Neurology at the Brigham and Women's Hospital. The editors are indebted to our colleagues for sharing their expertise in the creation of the ninth edition of this *Manual*.

Martin A. Samuels
Allan H. Ropper

Preface to the First Edition

Until very recently the neurologist's primary task was to categorize and organize the structure and pathologic alterations of the nervous system. In fact, neurology has long been known as a discipline with elegantly precise and specific diagnostic capabilities but little or no therapeutic potentiality. Further, many surgeons, pediatricians, and internists have traditionally thought of the neurologist as an impractical intellectual who spends countless hours painstakingly localizing lesions while ignoring pragmatic considerations of treatment. Perhaps this conception is largely attributable to the peculiar complexity of the nervous system and the consequent relative naivete of physicians in their understanding of its functions.

Many of the classic descriptions of disease states in other medical disciplines were completed in the last century; in neurology, these have only been described in the past generation, and only in the last 10 years has neurology begun to be characterized by subcellular mechanistic concepts of disease. This maturity has meant that the neurologist is now as much involved in the therapeutic aspects of his specialty of medicine as any of his colleagues. Certain neurologic diseases, such as epilepsy, have been treatable for relatively long periods of time, but understanding of the subcellular mechanisms of other diseases has led to newer, more effective forms of therapy.

An example of this is the enlarged understanding we now have of the biochemical alterations in Parkinson disease, and the resultant therapeutic implications. Now, much as the endocrinologist treats diabetes with insulin and the cardiologist treats congestive heart failure with digitalis, the neurologist treats Parkinson disease with L-dopa. In all these situations, the underlying condition is not cured; rather, an attempt is made to alter the pathophysiologic processes by utilizing a scientific understanding of the function of the diseased system.

This manual embodies a practical, logical approach to the treatment of neurologic problems, based on accurate diagnosis, that should prove useful to both the clinician and student. No attempt is made to reiterate the details of the neurologic examination; it is assumed that the reader is competent to examine the patient—although particularly important or difficult differential diagnostic

points are mentioned when appropriate. In this regard, it should be emphasized that this manual is only a guide to diagnosis and therapy, and each patient must be treated individually. The manual is organized to best meet the needs of the clinician facing therapeutic problems. Thus, the first seven chapters are concerned with symptoms, such as dizziness and headache, while the last ten consider common diseases, such as stroke and neoplasms.

Martin A. Samuels
1977

1 Coma, Head Trauma, and Spinal Cord Injury

Galen V. Henderson and Matthew B. Bevers

COMA

Background

Impaired States of Consciousness

1. *Coma* describes total or near-total unresponsiveness. It is a sleep like state of unconsciousness from which the patient cannot be aroused by external or internal stimuli. The degree of coma varies; in its deepest stage, no reaction of any kind is obtainable; corneal, papillary, and pharyngeal responses are absent. With lesser degrees, there is slight stirring to stimuli and brainstem reflexes are preserved. In such lighter stages of coma, sometimes referred to by the ambiguous and unhelpful terms *semicoma* or *obtundation*, most of the brainstem reflexes can be elicited. Respiration rate and pattern also vary with the depth of coma.
2. *Stupor* refers to a state in which the patient can be only transiently roused by vigorous and repeated stimuli, but arousal cannot be sustained without repeated stimulation. Verbal output is unintelligible or absent, and there is some purposeful movement to noxious stimulation. Restless or stereotyped motor activity is common, and there is a reduction of the natural shifting of body positions.
3. *Drowsiness* and *lethargy* denote reduced wakefulness resembling sleep that allows easy and usually sustained arousal.
4. *Confusion* refers to impaired attention and implies inadequate arousal to sustain coherent thoughts and actions.
5. *Delirium*, as used by neurologists, usually refers to a state of confusion with

periods of agitation and sometimes hypervigilance, active irritability, and hallucinations, typically alternating with periods during which the level of arousal is depressed.

Pathophysiology

1. Excitatory inputs emanating from the midbrain and rostral pons (reticular-activating system [RAS]) ascend to the thalamus, exciting thalamocortical neurons of the thalamic intralaminar, and midline nuclei. The neurons project widely throughout the cerebral cortex and this RAS supports arousal. The anatomic boundaries of the upper brainstem RAS are indistinct.
2. These ascending reticulothalamic neurons have cholinergic activity.
3. The act of attention is conceived as depending on both the diffuse arousal system and cortical systems for directed attention in various spheres:
   - **a.** Posterior parietal lobes (sensory awareness).
   - **b.** Frontal association cortex (motor attention: directed movements of the eyes, limbs, and body).
   - **c.** Cingulate cortex (motivational aspects of attention).
   - **d.** Lesions that affect these areas cause global inattention and confusional states.
   - **e.** Acute confusional states are therefore caused by
     - **1)** Diffuse disease in the cerebral cortex
     - **2)** Focal lesions in various regions of the cortex
     - **3)** Thalamic cortical connections
     - **4)** Forebrain and subcortical structures

Diagnosis

Clinical Presentation

1. The primary goal of the examination of the unresponsive patient is to determine the cause of destruction of brain tissue as, for example, from cerebral hemorrhage or from metabolic disturbances that are extrinsic to the brain, such as uremic or hypoglycemic encephalopathy.
2. The electroencephalogram (EEG) reflects cortical and thalamic neurophysiologic function and is helpful in determining the level of cerebral disturbance and disease progression.

3. The Glasgow Coma Scale (GCS; Table 1-1) is a standardized instrument designed for rapid assessment and communication about patients who have traumatic brain injury (TBI).
   a. This scale measures the patient's best response in three areas: eye opening, motor activity, and language.
   b. GCS scores range from 3 to 15. A score of 8 or less is consistent with the diagnosis of coma

Components of the Examination

1. Observing the patient yields considerable information. The predominant postures of the limbs and body; the presence or absence of spontaneous movements on each side; the position of the head and eyes; and the rate, depth, and rhythm of respirations give substantial formation.
   a. Level of consciousness is measured by the patient's reaction to:
      1) Calling name
      2) Simple commands
      3) Progressively intense noxious stimuli such as tickling the nares, supraorbital or sternal pressure, pinching the side of the neck or inner parts of the arms or thighs, or applying pressure to the knuckles

Table 1-1 Glasgow Coma Scale

Points	Eye Opening	Verbal	Motor
6	—	—	Obeys
5	—	Oriented	Localizes to pain
4	Spontaneous	Confused	Withdraws to pain
3	To speech	Inappropriate	Flexion (decorticate)
2	To pain	Unintelligible	Extensor (decerebrate)
1	None	None	None

2. Examination of the pupils is of great diagnostic importance.
   a. Normal pupillary size, shape, and light reflexes indicate integrity of the midbrain structures and therefore direct attention to a cause of coma other than destruction or secondary compression of this area by a hemispheral mass.
   b. Pupillary reactions are diminished with rostral midbrain lesions.

1) A unilaterally enlarged pupil (>5.5 mm) is an early indicator of stretching or compression of the third nerve and reflects a cerebral mass on that side.
2) Loss of light reaction usually precedes enlargement of the pupil.
3) The pupil may become oval or pear-shaped and may appear to be off center (corectopia) because of differential loss of innervation of portions of the pupillary sphincter.
4) As midbrain displacement continues from a mass lesion, both pupils dilate and become unreactive to light, probably from compression of the oculomotor nuclei in the rostral midbrain.
5) As the upper brainstem is further compressed, there tends to be a slight reduction in pupillary size on both sides to 5 mm or smaller.

c. Pupillary reactions with pontine lesions.

1) Pontine lesions cause miotic pupils less than 1 mm in diameter with barely perceptible reaction to strong light.

    a) The Horner syndrome (miosis and ptosis) may be observed ipsilateral to the lesions of the brainstem or hypothalamus or as a sign of dissection of the internal carotid artery.

d. Coma caused by drug intoxications and intrinsic metabolic disorders spares pupillary reactions, but there are several exceptions.

1) High concentrations of opiates cause coma and very small pupils that are barely light reactive.
2) High-dose barbiturates may act similarly, but the pupillary diameter tends to be 1 mm or more.
3) Systemic poisoning with atropine or with drugs that have atropinic qualities, for example, tricyclic antidepressants, is characterized by wide dilatation and fixity of the pupils.
4) Hippus or fluctuating pupillary size is characteristic of metabolic encephalopathy.

3. Movements of the eyes, eyelids, and corneal response

a. In light coma of metabolic origin, the eyes rove conjugately from side to side in seemingly random fashion, sometimes resting briefly in an eccentric position.

b. These movements disappear as coma deepens, and the eyes then remain motionless and slightly exotropic.

c. Lateral and downward deviation of one eye suggests the presence of a

third nerve palsy, and medial monocular deviation, a sixth nerve palsy.

d. Persistent conjugate deviation of the eyes to one side (gaze deviation) is away from the side of paralysis with a large cerebral lesion (looking toward the lesion) and toward the side of the paralysis with a unilateral pontine lesion (looking away from the lesion).

e. "Wrong-way" conjugate deviation may occur with thalamic and upper brainstem lesions.

f. During a focal seizure, the eyes turn or jerk toward the convulsing side (opposite to the irritative focus).

g. The globes turn down and inward (looking at the nose) with hematomas or ischemic lesions of the thalamus and upper midbrain.

h. Retraction and convergence nystagmus occurs with lesions in the tegmentum of the midbrain.

i. Ocular bobbing (rapid downward and slower upward movements) accompanies bilateral horizontal gaze paresis with damage to the pons.

j. Ocular dipping (slow downward and return rapidly to the meridian) is observed with coma caused by anoxia and drug intoxications.

k. Coma-producing structural lesions of the brainstem abolish most if not all conjugate ocular movements, whereas metabolic disorders generally do not (except for certain deep drug intoxications, particularly from antiepileptic medications).

l. Oculocephalic reflexes (doll's eye movements) are elicited by brisk turning of the head. The response in coma of metabolic origin or that caused by bihemispheric structural lesions consists of conjugate movements of the eyes in the opposite direction.

m. Elicitation of these ocular reflexes in a comatose patient provides two pieces of information:

1) Evidence of unimpeded function of the midbrain and pontine tegmental structures that integrate ocular movements and of the ocular motor nerves.

2) Loss of the cortical inhibition that normally holds these movements in check.

n. Asymmetry of elicited eye movements remains a dependable sign of focal brainstem disease. In coma caused by a large mass in one cerebral hemisphere that secondarily compresses the upper brainstem, the oculocephalic reflexes are usually present, but adduction of the eye on the

side of the mass is impeded as a result of a compressive third nerve paresis.

o. Irrigation of one ear with 10 mL of cold water causes slow conjugate deviation of the eyes toward the irrigated ear, followed in a few seconds by a compensatory nystagmus (fast component away from the stimulated side). This is the vestibuloocular, oculovestibular, or caloric test.

p. The ears are irrigated separately, several minutes apart. In the comatose patient, the corrective phase of the nystagmus is lost and the eyes are tonically deflected to the side of irrigation with cold water. This position may be held for 2 to 3 minutes.

q. Brainstem lesions disrupt these vestibuloocular reflexes (VORs); if one eye abducts and the other fails to, one can conclude that the medial longitudinal fasciculus has been interrupted.

r. Abducens palsy is indicated by an esotropic resting position and a lack of outward deviation of one eye with the reflex maneuvers.

s. Complete absence of ocular movement in response to oculovestibular testing indicates a severe disruption of brainstem tegmental system in the pons or midbrain.

4. A reduction in the frequency and eventual loss of spontaneous blinking, then a loss of response to touching the eyelashes, and finally, a lack of response to corneal touch (the signs of deepening coma). A marked asymmetry in corneal responses indicates either an acute lesion of the opposite hemisphere or less often, an ipsilateral lesion in the brainstem.

5. Skeletal motor and reflex signs

a. Restless movements of all the limbs and grasping and picking movements signify that the corticospinal tracts are more or less intact. Oppositional resistance to passive movements (paratonic rigidity), complex avoidance movements, and discrete protective movements has the same meaning. Abduction movements (away from midline) have the same significance and differentiate a motor response from posturing. Patients who have hemispheric lesions typically lie in comfortable-appearing, relatively normal postures.

b. Patients who have brainstem lesions often display abnormal postures. The symmetry of spontaneous movement may give a clue to the side of a focal lesion.

c. The terms "decorticate" and "decerebrate rigidity" refer to experimental studies of animals and do not accurately reflect the clinicopathologic correlations that they imply.
  1) Decorticate posturing: Lower extremity extension and internal rotation with flexion of both upper extremities.
  2) Decerebrate posturing: Lower and upper extremity extension.

d. Upper extremity flexion reflects more superficial, less severe, and more chronic lesions at the level of the diencephalon or above. Upper and lower extremity extension often accompanies brainstem lesions; however, as mentioned, the upper extremity extension depends on the degree and acuteness of the lesion and being reflexively driven, on the stimulus applied at the time of the examination. The responsible lesions may also be reversible, as in severe toxic and metabolic encephalopathies.

e. Exaggerated deep tendon reflexes and extensor plantar responses also suggest a lateralized lesion, but they may be misleading.

f. Careful observation for subtle movements suggesting seizures should be sought in all cases of coma; these implicate nonconvulsive status epilepticus as the cause of coma.

5. Respiratory patterns

a. Hyperventilation is common and has poor localizing value. Differential diagnosis includes
  1) Fever
  2) Sepsis
  3) Metabolic acidosis
  4) Drug toxicity
  5) Cardiopulmonary disease
  6) Rarely, pontine lesions, particularly central nervous system (CNS) lymphoma

b. *Cheyne–Stokes respirations* refer to a periodic breathing pattern of alternating hyperpnea and apnea.

c. Apneustic breathing
  1) Characterized by a prolonged pause at the end of inspiration and is also called "inspiratory cramp" (a pause of 2 to 3 seconds in full inspiration). This localizes to a lesion in the mid-to-caudal pons.

d. Biot breathing (ataxic breathing)
  1) Characterized by chaotic or ataxic breathing pattern with loss of

regularity of alternating pace and depth of inspirations and expirations that may occur when the neurons in the respiratory center are damaged.

2) This pattern progresses to one of intermittent prolonged inspiratory gasps that are recognized by all physicians as agonal in nature and finally to apnea. In fact, respiratory arrest is the mode of death of most patients with serious CNS disease. A variety of lesions cause this pattern terminally.

Reason for Decreased Level of Consciousness with Structural Lesions

1. Structural coma can result from diffuse or bilateral cerebral hemispheric or primary brainstem involvement.
   - **a.** Purely unilateral cerebral lesions do not produce coma.
   - **b.** Loss of consciousness from unilateral cerebral lesions indicates pressure or displacement of the opposite hemisphere or upper brainstem.
   - **c.** Persisting loss of consciousness from cerebral hemispheric disease indicates bilateral cerebral hemispheric damage.
2. As the mass effect progresses, it causes displacement of the upper brainstem through the tentorial notch—herniation—thereby interrupting activity ascending to the cerebral hemisphere from the RAS.
   - **a.** Secondary hemorrhages occur in the brainstem tegmentum, in contrast to primary brainstem hemorrhage, which is usually in the base of the pons.
   - **b.** Secondary ischemic and hemorrhagic lesions lead to permanent coma and brainstem tegmental signs involving eye movements and pupils.
   - **c.** Supratentorial tissue shifts may compress the posterior cerebral arteries against the incisura of the tentorium, causing infarction of the occipital lobes. Patients may survive this compressive effect to be left with visual field defects or blindness from damage to the occipital lobes.

Locked-in Syndrome

1. Lesion is located bilaterally in the base of the pons.
2. The patient is awake, has lost horizontal eye movements, and is unable to talk or move the arms or legs. The patient is therefore “de-efferented” but remains conscious.

a. The only way the patient can express alertness and communication is through eyelid and vertical eye movements.
b. Midbrain involvement can also cause the locked-in syndrome accompanied by bilateral ptosis and third nerve palsies. The only clue that the patient is conscious is some remnant of movement such as the orbicularis oculi in response to command.
c. These patients require meticulous nursing and psychological care.
d. Survival may be prolonged, and recovery is possible in patients depending on the lesion type and extent of damage.

Vegetative State

1. Coma after an acute event that damages the hemispheres diffusely seldom lasts more than 2 to 4 weeks, and most patients transition to the vegetative state. These patients exhibit wakefulness but not consciousness; they open their eyes in response to painful stimuli or spontaneously and may blink to threat. Caloric and oculocephalic movements are retained. Intermittently, the eyes may move from side to side seemingly following objects or fixate momentarily on the physician or a family member giving the erroneous impression of recognition. Respirations may quicken in response to stimulation, and certain automatisms such as swallowing, bruxism, grimacing, grunting, and moaning may be observed. However, the patient remains totally inattentive, does not speak, and show no signs of awareness of the environment or inner need; responsiveness is limited to primitive or inner need and primitive postural reflexes movements of the limbs. There is loss of sphincter control. There may be arousal or wakefulness in alternation cycles as reflected in partial eye opening, but the patient regains neither awareness nor purposeful behavior of any kind.
2. In a minimally conscious state, the patient retains minor and often intermittent function such as moving a limb to command, making facial expressions or tracking visually, sometimes to command and at other times, spontaneously. It is separated from vegetative state and from other states of severe disability.

Psychogenic Unresponsiveness

The eye movements are particularly helpful in distinguishing psychogenic

unresponsiveness and catatonia from coma and the vegetative state.

1. If the patient lies with the eyes closed, lifting the eyelids results in a slow closure in genuine coma but rapid or forceful closure of the eyes demonstrates responsiveness.
2. Smooth roving eye movements cannot be produced voluntarily.
3. Caloric testing elicits nystagmus in psychogenic coma but not in metabolic or structural coma. Occasional patients who feign unresponsiveness can inhibit caloric-induced nystagmus by concentrated visual fixation. However, they do not exhibit deviation of the eyes without nystagmus fast phases, as the comatose patient does. Similarly, in psychogenic coma during oculocephalic maneuvers, visual fixation enhances the VOR so that the eyes move in the orbit, stabilizing the gaze in one spot. In comatose patients, the VOR may be hypoactive or lost with deep metabolic coma or with structural lesions in the pontine tegmentum.
4. Patients with psychogenic unresponsiveness often look away from the examiner, toward the mattress.

Treatment

Approach to Patient

1. As with all acutely ill patients, the approach to the comatose patient should follow a rapid and prioritized algorithm that ensures stabilization of vital functions and rapid assessment and therapy for potential disorders that threaten life (Tables 1-2 and 1-3).
2. The ABCs (*a*irway, *b*reathing, and *c*irculation) of acute resuscitation top the list.
3. Acute cervical stabilization is crucial whenever there is any possibility of cervical trauma or spinal instability caused by medical disease, as in rheumatoid arthritis.
4. Maneuvers that require neck movement should be modified to minimize movements or should be avoided (oculocephalics stimulation) until after adequate radiographs have eliminated any concern of cervical instability.

TRAUMATIC BRAIN INJURY

Background

1. There are approximately 1.7 million new traumatic brain injuries in the United States each year, approximately 52,000 deaths occur annually because of TBI.
2. There are 275,000 people who are hospitalized annually because of TBI.
3. TBI contributes to a third of all injury-related deaths in the United States.
4. The incidence of TBI is highest in the young (0 to 19 years old) and old (>65 years old); males are affected more commonly than are females.

Table 1-2 Approach to the Assessment and Management of Acute Coma

Stabilization
- Airway control
- Oxygenation and ventilation
- Adequate circulation (includes avoidance of hypotension in strokes)
- Cervical spine stabilization

Immediate therapies given to all patients
- Thiamine 100 mg IV
- Dextrose 50% 50 mL IV (may be held if immediate finger stick glucose establishes adequate serum glucose)
- Naloxone 0.4–2 mg IV (may be repeated)
- Obtain blood for CBC, PT/PTT, chemistry panel, toxic screen, blood cultures, anticonvulsant levels

Threatening conditions to be considered for possible early therapy
- Elevated ICP → head CT
- Meningitis, encephalitis, or both → antibiotics, LP, blood cultures
- Myocardial infarction → ECG
- Hypertensive encephalopathy → early therapy
- Status epilepticus → EEG
- Acute stroke → consider thrombolytic therapy

IV, intravenous; CBC, complete blood count; PT, prothrombin time; PTT, partial thromboplastin time; ICP, intracranial pressure; CT, computed tomography; LP, lumbar puncture; ECG, electrocardiogram; EEG, electroencephalogram.

Reprinted from Feske SK. Coma and confusional states: Emergency diagnosis and management. *Neurol Clin*. 1998;16(2):237–256, with permission from Elsevier.

Pathophysiology

1. TBI is a heterogeneous pathologic entity.

2. TBI has primary and secondary components.
   a. Primary injuries are the result of mechanical events such as acceleration, deceleration, rotational, penetrating, and blunt forces that occur at the moment of impact. Injury to the blood vessels is evident by small tissue hemorrhages, intracerebral, subdural, or epidural hematomas (EDHs) all of which can in turn result in secondary injury. Coronal translational forces are more apt to produce widespread axonal injuries. Patients with diffuse axonal injury (DAI) are less likely to have increased intracranial pressure (ICP) and lucid intervals. Amyloid precursor protein topography shows that axons in the corpus callosum and fornices are the most susceptible to injury.
   b. Secondary injuries are caused by biochemical reactions and cascades that can occur from the time of the initial event to minutes, hours, and even days after primary injury particularly from pulmonary and circulatory physiologic abnormalities. For example, the occurrence of hypotension, with or without hypoxia, doubles the mortality and increases the morbidity of severe head injury. Hypotension occurring in the initial phase of resuscitation is associated with increased mortality, even when episodes are relatively brief. About 6% of patients with severe TBI as the main presenting feature also have a cervical spine injury. About 24% of patients with cervical spine injury as the main presenting feature also have a TBI.

Table 1-3 Main Causes of Coma

1. Focal disease
   a. Trauma (contusion, ICH)
   b. Nontraumatic ICH
   c. Ischemic stroke
   d. Infection (abscess, subdural empyema, focal encephalitis)
   e. Tumor
   f. Demyelination (MS, ADEM)
2. Nonfocal disease
   a. Trauma (elevated ICP, diffuse axonal injury)
   b. Vascular syndromes
      1) SAH
      2) Aneurysm in posterior fossa with mass effect
      3) Hypoxic–ischemic encephalopathy
      4) Stroke (focal strokes with nonfocal presentations, posterior fossa infarct with mass effect, hydrocephalus)
      5) Hypertensive encephalopathy

- **c.** Infection (meningitis, diffuse encephalitis)
- **d.** Tumor related
  - **1)** Tumor (brainstem invasion, posterior fossa mass, elevated ICP, and hydrocephalus), paraneoplastic syndromes (brainstem encephalitis, vasculitis)
- **e.** Toxic and metabolic
  - **1)** Toxic
  - **2)** Metabolic
  - **3)** Withdrawal symptoms
  - **4)** Nutritional deficiencies
  - **5)** Disordered temperature regulation
- **f.** Seizures (postictal state, nonconvulsive status epilepticus)
- **g.** Others
  - **1)** Basilar migraines
  - **2)** Transient global amnesia
  - **3)** TTP and other syndromes of medical illness
  - **4)** Sleep deprivation
  - **5)** Situational (i.e., ICU psychosis)
  - **6)** Psychiatric (conversion, depression, mania, catatonia)

ICH, intracranial hemorrhage; MS, multiple sclerosis; ADEM, acute disseminated encephalomyelitis; ICP, intracranial pressure; SAH, subarachnoid hemorrhage; TTP, thrombotic thrombocytopenic purpura; ICU, intensive care unit.

Reprinted from Feske SK. Coma and confusional states: Emergency diagnosis and management. *Neurol Clin*. 1998;16(2):237–256, with permission from Elsevier.

Scalp Laceration

1. Tend to bleed profusely because of the ample blood supply and poor vasoconstrictive ability of the scalp vasculature.
2. They should be inspected, palpated, irrigated, debrided, and sutured.

Skull Fractures

1. Linear fractures are usually benign unless they occur in the area of (or involve) the middle meningeal artery or dural sinus, which may result in epidural hemorrhage, subdural hemorrhage, or dural sinus thrombosis.
2. Depressed fractures may cause dural tears and injury to underlying brain tissue.
3. Comminuted fractures are multiple linear fractures with depression at the site of impact.

Basal Skull Fractures

1. Linear fractures extend into the anterior, middle, or posterior cranial fossa at the skull base.
2. They are often difficult to visualize on plain skull films or axial computed tomography (CT) scans. The diagnosis is often based on clinical signs and symptoms.
3. There is a risk of meningitis if the dura is penetrated; however, prophylactic antibiotics are not indicated.
4. Anterior fossa fractures generally involve the frontal bone and ethmoid and frontal sinuses.
   a. Characterized by bilateral periorbital ecchymosis ("raccoon eyes").
   b. Anosmia from damage to the olfactory apparatus is common.
   c. Rhinorrhea occurs in 25% of patients, usually lasts 2 to 3 days, and is often self-limiting with conservative measures (e.g., elevating the head of the bed, cautioning the patient against blowing nose, and lumbar drain placement).
5. Middle fossa fractures are characterized by ecchymosis over the mastoid process behind the ear that may not appear for up to 24 hours (Battle sign) and otorrhea.
   a. Otorrhea indicates tympanic membrane rupture that allows free flow of cerebrospinal fluid (CSF) through the ear; this problem is often self-limiting with conservative measures (e.g., elevating the head of the bed).
   b. May be associated with cranial nerve VI, VII, and VIII palsies.
6. Avoid inserting a nasogastric tube into a patient with a suspected basal skull fracture.
   a. This warning should probably be applied to all comatose patients with TBI until the presence of basal fracture has been addressed.
   b. Use an orogastric tube instead.

Concussion

1. Patients may or may not have loss of consciousness; being "stunned," confused, having their "bell rung" are equivalents of concussion.
2. Retrograde and anterograde amnesias are common.
3. There are guidelines for the performance of CT scanning after concussion. Vomiting, older age, presence of fracture on examination, and dangerous

mechanism of injury are all predictive of finding a cerebral lesion if CT is done.

4. Patients commonly complain of subsequent headache, dizziness, irritability, short-term memory loss, fatigue, and reduced attention span. These "minor" head injuries may have sequelae that may greatly disrupt activities of daily living (postconcussive syndrome).

Cerebral Contusion

1. Contusion is bruising of brain tissue and does not occupy much space in the beginning but may blossom within 24 to 48 hours after injury days and cause significant intracranial hypertension. They most commonly involve the tips of the frontal and temporal lobes.
2. Contusions may be caused by coup or contrecoup injuries.
3. It is important to check coagulation studies (e.g., prothrombin and partial thromboplastin times) and platelet counts and to correct clinically important abnormalities with fresh frozen plasma and platelet than fusions.

Subdural Hematoma

1. Classification
   - **a.** "Acute" is used for those less than 3 days old.
   - **b.** "Subacute" for age 3 days to 3 weeks old.
   - **c.** "Chronic" more than 3 weeks from injury.
2. Acute subdural hematoma (ASDH) is the most common traumatic intracranial hematoma (35% to 40% of patients with severe TBI) and carries the highest associated mortality. There is evidence that early evacuation improves outcome.
3. ASDHs usually arise from venous bleeding caused by tearing of bridging veins in the subdural space between the dura and the arachnoid.
4. Surgical treatment options include burr holes, limited, or full craniotomy for evacuation of the clot.

Epidural Hematoma

1. EDH is most commonly caused by arterial bleeding into the epidural space, between the skull and dura.

2. Associated with temporal bone fractures causing a tear in the middle meningeal artery. Arterial blood rapidly accumulates, and patients can deteriorate quickly.
3. Acute EDH carries 5% to 10% mortality; emergent surgical intervention is necessary.
4. Determinants of outcome include GCS score, age, presence of pupillary abnormalities, associated intracranial lesions, presence of traumatic subarachnoid hemorrhage, time between deterioration and surgery, and ICP.
5. Acute EDH is seen in 1% to 10% of patients with TBI.
   a. Nine percent of patients who are comatose after injury have an EDH requiring craniotomy.
   b. The peak incidence of EDH occurs in the second decade of life, and it is rare after age 50 years.
   c. The mean age for EDH in children is 6 to 10 years, and EDH is less frequent in very young children and neonates.
   d. As with TBI in general, 53% (range, 30% to 73%) of EDHs are traffic-related; falls account for 30% (range, 7% to 52%) and assaults 8% (range, 1% to 19%).
   e. Acute EDH results from injury to the middle meningeal artery (36%) or a venous structure (32%) such as the middle meningeal vein, diploic veins, or one of the venous sinuses, and this explains why the most common locations are temporoparietal or temporal lobes.
6. The clinical presentation of EDH is focal deficits, hemiparesis, and decerebration. From 22% to 56% of patients are comatose on admission.
   a. The classic lucid interval is seen in 47%; this is where the patient is unconscious, wakes up, and then deteriorates.
      1) Twelve percent to 42% remain conscious; 18% to 44% with pupillary abnormalities.
      2) Three percent to 27% present neurologically intact.
      3) Eight percent present with seizures.
7. Treatment
   a. Reasonable guidelines are that EDH should undergo urgent evacuation if GCS score is less than 9 or if there is anisocoria, or more than 30 mL of EDH; evacuation may be considered for EDH that is
      1) Less than 30 mL in volume, less than 15-mm thick, and less than 5 mm

of midline shift, as long as the GCS score is above 8.

2) These patients should undergo serial CT scanning and close observation.

Traumatic Intracerebral Hematoma

1. Intraparenchymal hemorrhages (IPHs) are unusual in nonpenetrating head trauma.
2. Enlarging cerebral contusions can coalesce into frank intraparenchymal clots requiring surgical intervention.
3. It is more common to see IPH with penetrating injuries (i.e., gunshot and stab wounds).
4. The lesion size and patient status dictate treatment.
5. As with contusion, clotting factors should be checked.

Diffuse Axonal Injury

1. Deceleration and rotation of the brain may result in widespread mechanical shearing of axons.
2. Mortality after DAI is as high as 50%.
3. DAI is the most common cause of a posttraumatic vegetative state.
4. The findings of the initial CT scan are normal in 50% to 85% of patients.
5. Magnetic resonance imaging (MRI) is more sensitive than CT scanning for detecting the hallmark of small punctate hemorrhages that are presumably caused by shearing of small perforating arteries.

Cerebral Edema

1. Cerebral edema from any of the earlier described lesions, especially contusions, leads to increased water content and brain swelling.
2. Steroids have not been effective to treat posttraumatic edema (see in the following section).

Herniation Syndromes

1. Herniation is the shifting of brain tissue to an abnormal area and is secondary to ICP differentials.

2. The associated signs and symptoms depend on the location of herniation and anatomy of the structures being compressed.
3. The most commonly seen syndromes are cingulate/subfalcine herniation, uncal/ transtentorial herniation, and tonsillar herniation.
   a. Cingulate (or "subfalcine") herniation
      1) Characteristic of unilateral space-occupying lesions in the frontal lobe that force the cingulate gyrus under the falx cerebri.
      2) Compression of the anterior cerebral artery may occur, resulting in ischemia/infarction.
      3) No clinical signs or symptoms are specific to cingulate herniation; involvement of the legs is not uncommon.
   b. Uncal (or "transtentorial") herniation
      1) Most commonly seen with expanding mass lesions in the middle cranial fossa causing the uncus of temporal lobe to herniate between the brainstem and the tentorial edge.
      2) Signs and symptoms include
         a) Decreased consciousness from compression of the reticular formation in the rostral brainstem.
         b) Dilated ipsilateral pupil from compression of cranial nerve III.
         c) Contralateral hemiplegia from compression of the opposite cerebral peduncle.
   c. Tonsillar herniation (cerebellar herniation)
      1) Arises from expansion of posterior fossa lesions (or supratentorial lesions invading the posterior fossa) causing the cerebellar tonsils to herniate through the foramen magnum into the upper spinal canal, compressing the medulla.
      2) Signs and symptoms include
         a) Guarding against neck flexion.
         b) Systemic hypertension.
         c) Cardiorespiratory impairment or arrest.

TREATMENT OF SEVERE HEAD INJURY

Prehospital Management

1. The evaluation and treatment of traumatic injuries should be initiated from

the time prehospital emergency personnel arrive at the scene and continue during transport and through acute management in the emergency department.

2. The priorities for assessment and treatment of the patient with a head injury can be summarized as the ABCs: airway, breathing, and circulation.

a. Airway/breathing

1) Securing and maintaining an airway is top priority to ensure adequate oxygenation and ventilation.

2) Airway patency is often compromised by the presence of foreign objects; obstruction by the tongue and/or pharyngeal/laryngeal soft tissue; accumulation of blood, secretions, or vomitus; and airway collapse by direct trauma.

3) Ventilation can be compromised by pulmonary contusions, rib fractures (flail chest), diaphragmatic rupture, presence of hemo- or pneumothorax, brainstem injury affecting the respiratory centers, or cervical cord injury affecting phrenic nerve function.

4) In the absence of airway obstruction, supplemental oxygen should be given via face mask. Otherwise, an airway should be secured via endotracheal tube.

5) Direct tracheotomy or cricothyroidotomy offer alternatives in the presence of massive facial trauma or upper airway swelling.

6) If needed, respiration can be supported with bag ventilation either via face mask or tracheal tube.

7) Do not prophylactically hyperventilate. Present evidence, including a randomized clinical trial, suggests that aggressive prophylactic hyperventilation may actually worsen tissue hypoxia and lead to secondary brain injury.

b. Circulation

1) In concert with securing the airway and procuring ventilation, blood flow to the brain and other organs must be supported.

2) Hemodynamic collapse is most often associated with blood loss, although cardiac dysfunction and neurogenic causes are also common.

3) External hemorrhage should be controlled via direct wound pressure.

4) Internal hemorrhage can only be addressed in the hospital.

5) Treat hypovolemic shock with aggressive intravenous (IV) volume replacement of isotonic crystalloid solution (normal saline or lactated Ringers).

6) Use the initial response to fluid to determine need for blood products,

using blood in those with a transient or minimal response to crystalloid.

7) Massive transfusion (>10 units of packed red blood cells in 24 hours) requires replacement of platelets and clotting factors (fresh frozen plasma), in a 1:1:1 ratio.

Surgical Management

1. There are multiple unresolved issues regarding surgical management. For example, should hemorrhagic contusions be removed? Should dominant lobe intraparenchymal hematomas be evacuated? What is the role of decompressive craniotomy in the treatment, or avoidance, of intracranial hypertension?
2. In 2007, the Brain Trauma Foundation, the American Association of Neurological Surgeons (AANS), and the Joint Section on Neurotrauma and Critical Care of the AANS and Congress of Neurological Surgeons published an evidence-based tome to improve nonpenetrating TBI care. Table 1-4 is an outline of those guidelines. There are several similar monographs for penetrating head injury and prehospital care, and one pending regarding surgical management of TBI.

ACUTE SPINAL CORD INJURY

Background

1. Spinal cord injury occurs in about 12,500 people in North America each year, and the prevalence is approximately 270,000 patients.
2. Management is directed by guidelines developed by a joint committee from the American Academy of Neurologic Surgeons and the Congress of Neurological Surgeons, as summarized in the following section.

Pathophysiology

1. The causes of spinal cord injury are multiple and vary within geographic regions within each country. In industrialized nations, motor vehicle collisions are the most common cause.

2. Of those who experience trauma to the spinal column, approximately 15% will have a neurologic injury.
   a. The cervical spine is at greatest risk, with 50% of cervical spine fractures or ligamentous disruptions resulting in neurologic injury.
   b. The most common mechanisms of spinal cord injury are hyperflexion, hyperextension, axial loading, and penetrating injury.
   c. Spinal cord injuries are classified as complete or incomplete.
      1) Complete injuries imply loss of all motor, sensory, and reflex function below the level of the injury.
      2) Incomplete injury implies some intact neurologic function below the level of the injury.

         a) Central cord injury (Schneider syndrome)
            • Most commonly results from hyperextension.
            • Greater motor dysfunction is seen in the upper extremities compared with the lower extremities.
            • High risk with preexisting acquired canal stenosis from spondylotic disease.
            • The central part of the cord is the watershed area and is more susceptible to ischemia.

         b) Anterior cord syndrome
            • Anterior cord syndrome has traditionally been described to traumatic disc herniation.
            • The disc theoretically damages the anterior and lateral areas of the spinal cord, leaving the posterior columns intact.

         c) Brown–Sequard syndrome
            • Hemiplegia with contralateral loss of pain and temperature sensation.
            • Typically from penetrating wounds or severe unilateral fractures leading to a hemisection of the spinal cord. For injuries that result in quadriplegia, the 5-year survival rate is 85%.

Table 1-4 Guidelines for Managing Traumatic Brain Injury

Levels of Recommendation

Level I, II, and III are derived from Class I, II, and III evidence, respectively. Level I recommendations are based on the strongest evidence for effectiveness and represent principles of patient management that reflect a high degree of clinical certainty. Level II recommendations reflect a moderate degree of clinical certainty. For Level III

recommendations, the degree of clinical certainty is not established.

Blood pressure and oxygenation

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Blood pressure should be monitored and hypotension (systolic blood pressure ≤90 mm Hg) avoided.
Level III	Oxygenation should be monitored and hypoxia (Pao_2 <60 mm Hg or O_2 saturation <90%) avoided.

Hyperosmolar therapy

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Mannitol is effective for control of raised ICP at doses of 0.25 g/kg to 1 g/kg body weight. Arterial hypotension (systolic blood pressure <90 mm Hg) should be avoided.
Level III	Restrict mannitol use prior to ICP monitoring to patients with signs of transtentorial herniation or progressive neurologic deterioration not attributable to extracranial causes.

Prophylactic hypothermia

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	There are insufficient data to support a Level II recommendation for this topic.
Level III	Pooled data indicate that prophylactic hypothermia is not significantly associated with decreased mortality when compared with normothermic controls. However, preliminary findings suggest that a greater decrease in mortality risk is observed when target temperatures are maintained for more than 48 hours. Prophylactic hypothermia is associated with significantly higher GOS scores when compared to scores for normothermic controls.

Infection prophylaxis

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Periprocedural antibiotics for intubation should be administered to reduce the incidence of pneumonia. However, it does not change length of stay or mortality. Early tracheostomy should be performed to reduce mechanical ventilation days. However, it does not alter mortality or the rate of nosocomial pneumonia.

Level III	Routine ventricular catheter exchange or prophylactic antibiotic use for ventricular catheter placement is not recommended to reduce infection.

Deep vein thrombosis prophylaxis

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	There are insufficient data to support a Level II recommendation for this topic.
Level III	Graduated compression stockings or IPC stockings are recommended, unless lower extremity injuries prevent their use. Use should be continued until patients are ambulatory. LMWH or low-dose unfractionated heparin should be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage. There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for DVT.

Indications for intracranial pressure monitoring

Level I	There are insufficient data to support a treatment standard for this topic.
Level II	ICP should be monitored in all salvageable patients with a severe TBI (GCS score of 3–8 after resuscitation) and an abnormal CT scan. An abnormal CT scan of the head is one that reveals hematomas, contusions, swelling, herniation, or compressed basal cisterns.
Level III	ICP monitoring is indicated in patients with severe TBI with a normal CT scan if two or more of the following features are noted at admission: Age over 40 years, unilateral or bilateral motor posturing, or systolic blood pressure <90 mm Hg.

Intracranial pressure thresholds

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Treatment should be initiated with ICP thresholds above 20 mm Hg.
Level III	A combination of ICP values, and clinical and brain CT findings, should be used to determine the need for treatment.

Cerebral perfusion thresholds

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors should be avoided because of the risk of ARDS.
Level III	CPP of ≤50 mm Hg should be avoided. The CPP value to target lies within

	the range of 50–70 mm Hg. Patients with intact pressure autoregulation tolerate higher CPP values. Ancillary monitoring of cerebral parameters that include blood flow, oxygenation, or metabolism facilitates CPP management.

Brain oxygen monitoring and thresholds

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	There are insufficient data to support a Level II recommendation for this topic.
Level III	Jugular venous saturation (<50%) or brain tissue oxygen tension (<15 mm Hg) are treatment thresholds. Jugular venous saturation or brain tissue oxygen monitoring measure cerebral oxygenation.

Anesthetics, analgesics, and sedatives

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Prophylactic administration of barbiturates to induce burst suppression EEG is not recommended. High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy. Propofol is recommended for the control of ICP but not for improvement in mortality or 6-month outcome. High-dose propofol can produce significant morbidity.
Level III	

Nutrition

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Patients should be fed to attain full caloric replacement by day 7 postinjury.
Level III	

Antiseizure prophylaxis

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Prophylactic use of phenytoin or valproate is not recommended for preventing late PTS. Anticonvulsants are indicated to decrease the incidence of early PTS (within 7 days of injury). However, early PTS is not associated with worse outcomes.
Level III	

Hyperventilation

Level I	There are insufficient data to support a Level I recommendation for this topic.
Level II	Prophylactic hyperventilation (Pco_2 of 25 mm Hg or less) is not recommended.
Level III	Hyperventilation is recommended as a temporizing measure for the reduction of elevated ICP. Hyperventilation should be avoided during the first 24 hours after injury when CBF is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation (SjO_2) or brain tissue oxygen tension ($PbrO_2$) measurements are recommended to monitor oxygen delivery.

Steroids

Level I	The use of steroids is not recommended for improving outcome or reducing ICP. In patients with moderate or severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated.
Level II	
Level III	

ICP, intracranial pressure; GOS, Glasgow Outcome Scale; IPC, intermittent pneumatic compression; LMWH, low molecular weight heparin; DVT, deep vein thrombosis; TBI, traumatic brain injury; GCS, Glasgow Coma Scale; CT, computed tomography; CPP, cerebral perfusion pressure; ARDS, adult respiratory distress syndrome; EEG, electroencephalogram; PTS, posttraumatic seizures; CBF, cerebral blood flow.

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Treatment of Acute Spinal Cord Injuries

Care at the Scene of the Accident

1. Treatment in the field begins with the ABCs, which are followed by a brief neurologic examination.
2. It is suggested that all trauma patients with a cervical spinal column injury or with a mechanism of injury having the potential to cause cervical spinal injury, including head injury, should be immobilized at the scene and during transport using a combination of a rigid cervical collar and supportive

blocks on a backboard with straps to limit motion of the cervical spine.

Management in the Hospital

1. Start by repeating what was done in the field—the ABCs are reassessed, and further respiratory support is given via supplemental oxygen with a nasal cannula or intubation.
   - **a.** Blood pressure management may include fluids and pressors.
   - **b.** Placement of a nasogastric tube if no basal skull fracture.
   - **c.** Foley catheter.
   - **d.** Warming blankets are utilized if hypothermia is present.
   - **e.** The American Spinal Injury Association (ASIA) international standard for neurologic and functional classification of spinal cord injury is a recommended neurologic examination tool for clinicians involved in the assessment and care of acute spinal cord injury patients.
2. In asymptomatic patients—Radiographic assessment of the cervical spine is not recommended in trauma patients who are awake, alert, and not intoxicated; who are without neck pain or tenderness; and who do not have significant associated injuries that detract from their general evaluation.
3. In symptomatic patients—A CT scan is recommended for radiographic evaluation of the cervical spine in patients who are symptomatic following traumatic injury. Only if CT is not available should a three-view plain radiograph spine series be used.
   - **a.** It is recommended that cervical spine immobilization in awake patients with neck pain or tenderness and normal cervical spine CT be discontinued following:
     - **1)** Normal and adequate dynamic flexion/extension radiographs.
     - **2)** Normal MRI study obtained within 48 hours of injury.
     - **3)** At the discretion of the treating physician
   - **b.** Cervical spine immobilization of obtunded patients with normal cervical spine x-rays (including supplemental CT as necessary) may be discontinued:
     - **1)** Following a normal MRI study obtained within 48 hours of injury
     - **2)** At the discretion of the treating physician
4. Initial closed reduction of cervical spinal fracture–dislocation injuries.
   - **a.** Early closed reduction of cervical spinal fracture–dislocation injuries

with craniocervical traction is recommended for the restoration of anatomic alignment of the cervical spine in awake patients.

b. Closed reduction in patients with an additional rostral injury is not recommended.

c. Patients with cervical spinal fracture–dislocation injuries who are not able to be examined during attempted closed reduction, or prior to open posterior reduction, should undergo MRI prior to attempted reduction. The presence of a significant disc herniation in this setting is a relative indication for a ventral decompression prior to reduction.

d. MRI study of patients who fail attempts at closed reduction is recommended.

5. Management of acute spinal cord injuries in an intensive care unit (ICU) or other monitored setting.

a. Management of patients with acute spinal cord injury, particularly patients with severe cervical-level injuries, in an ICU or similar monitored setting is recommended.

b. Cardiac, hemodynamic, and respiratory monitoring devices to detect cardiovascular dysfunction and respiratory insufficiency should be used in patients following acute cervical spinal cord injury.

6. Blood pressure management following acute spinal cord injury.

a. Hypotension (systolic blood pressure <90 mm Hg) should be avoided if possible or corrected as soon as possible.

b. Mean arterial blood pressure should be maintained at 85 to 90 mm Hg for the first 7 days following acute spinal cord injury to improve spinal cord perfusion.

Therapy after Acute Cervical Spinal Cord Injury

Pharmacologic Treatment

1. There is insufficient evidence to support treatment standards for neuroprotection after cord injury.

2. Methylprednisolone should not be used in the management of acute spinal cord injury. There is insufficient evidence to support any benefit to its use;

however, there is evidence of increased side effects associated with the use of high-dose steroids in acute spinal cord injury.

Deep Venous Thrombosis and Thromboembolism in Patients with Cervical Spinal Cord Injuries

1. Prophylactic treatment of thromboembolism (pulmonary embolus) in patients with severe motor deficits because of spinal cord injury is recommended.
2. Low-dose unfractionated or low molecular weight heparin in combination with pneumatic compression stockings is recommended as a prophylactic treatment strategy.
3. Low-dose heparin therapy alone is not recommended as a prophylactic treatment strategy.
4. Oral anticoagulation alone is not recommended as a prophylactic treatment strategy.
5. Duplex Doppler ultrasound, impedance plethysmography, and venography are recommended for use as diagnostic tests for deep vein thrombosis (DVT) in the spinal cord–injured patient population.
6. Three months of prophylactic treatment for DVT and pulmonary embolism are recommended.
7. Vena cava filters are recommended for patients who fail anticoagulation or who are not candidates for anticoagulation and/or mechanical devices.

Nutritional Support after Spinal Cord Injury

Nutritional support of spinal cord injury patients is recommended. Energy expenditure is best determined by indirect calorimetry in these patients as equation estimates of energy expenditure and subsequent caloric need tend to be inaccurate.

Spinal Cord Injury without Radiographic Abnormality

1. CT scan with attention to the suspected level of neurologic injury to exclude occult fractures is recommended.

2. MRI of the region of suspected neurologic injury may provide useful diagnostic information.
3. Plain radiographs of the entire spinal column may be considered.
4. Neither spinal angiography nor myelography is recommended in the evaluation of patients with this type of injury.

Diagnosis and Management of Traumatic Atlanto-Occipital Dislocation Injuries

1. A CT scan is recommended for the diagnosis of atlanto-occipital dislocation (AOD). Alternatively, a lateral radiograph may be used.
2. The presence of upper cervical prevertebral soft-tissue swelling on an otherwise nondiagnostic plain radiograph should prompt additional imaging.
3. Treatment is with internal fixation. Traction is not recommended and is associated with risk for neurologic deterioration.

Occipital Condyle Fractures

1. CT imaging is recommended for establishing the diagnosis of occipital condyle fractures. Clinical suspicion should be raised by the presence of one or more of the following criteria:
   a. Blunt trauma patients sustaining high-energy craniocervical injuries
   b. Altered consciousness
   c. Occipital pain or tenderness
   d. Impaired cervical motion
   e. Lower cranial nerve palsies (or retropharyngeal soft-tissue swelling)
2. MRI is recommended to assess the integrity of the craniocervical ligaments.

Isolated Fractures of the Atlas in Adults

Treatment options in the management of isolated fractures of the atlas are based on the specific fracture type. Isolated fractures of the atlas with an intact transverse atlantal ligament can be treated with cervical immobilization alone. Disruption of the transverse atlantal ligament should be treated with either cervical immobilization or surgical fixation and fusion.

Isolated Fractures of the Axis in Adults

1. Fractures of the odontoid
   - **a.** Type I is fracture through the tip, above the transverse ligament; type II is through the base of the neck of the odontoid (dens fracture); type III is through the body of C2.
   - **b.** Type II odontoid fractures in patients 50 years of age and older should be considered for surgical stabilization and fusion.
   - **c.** Type I, type II, and type III fractures may be managed initially with external cervical immobilization. Type II and type III odontoid fractures should be considered for surgical fixation in cases of dens displacement 5 mm or greater, comminution of the odontoid fracture (type IIA), and/or inability to achieve or maintain fracture alignment with external immobilization.

2. Traumatic spondylolisthesis of the axis (hangman's fracture)
   - **a.** Traumatic spondylolisthesis of the axis may be managed initially with external immobilization in the majority of cases. Surgical stabilization should be considered in cases of severe angulation of C2 on C3, disruption of the C2–C3 disc space, or inability to establish or maintain alignment with external immobilization.

Management of Combined Fractures of the Atlas and Axis

Treatment of atlas–axis combination fractures is based primarily on the specific characteristics of the axis fracture. External immobilization is recommended for the majority of C1–C2 combination fractures. C1–type II odontoid combination fractures with an atlanto-dens interval (ADI) of 5 mm or greater and C1–hangman's combination fractures with C2–C3 angulation of 11 degrees or greater should be considered for surgical stabilization and fusion.

Os Odontoideum

Plain radiographs of the cervical spine (anteroposterior [AP], open mouth odontoid, and lateral) and plain dynamic lateral radiographs performed in flexion and extension are used for diagnosis. CT and/or MRI of the craniocervical junction may also be considered. Clinical/radiographic

surveillance may be used in asymptomatic patients. Those with neurologic symptoms should be treated with internal fixation.

Treatment of Subaxial Cervical Spinal Injuries

1. Closed or open reduction of subaxial cervical facet dislocation injuries is recommended, with the goal of decompressing the spinal cord.
2. Treatment is recommended with either external immobilization or internal fixation.
3. Treatment of subaxial cervical facet dislocation injuries with prolonged bed rest in traction is recommended if more contemporary treatment options are not available.

Management of Acute Central Cervical Spinal Cord Injuries

1. ICU (or other monitored setting) management of patients with acute central cervical spinal cord injuries (ACCSCI), particularly patients with severe neurologic deficits, is recommended.
2. Medical management including cardiac, hemodynamic, and respiratory monitoring, and maintenance of mean arterial blood pressure at 85 to 90 mm Hg for the first week after injury to improve spinal cord perfusion is recommended. Early reduction of fracture–dislocation injuries is recommended. Surgical decompression of the compressed spinal cord, particularly if the compression is focal and anterior, is recommended.

Management of Vertebral Artery Injuries Following Nonpenetrating Cervical Trauma

CT angiography or conventional angiography is used for the diagnosis of vertebral artery injury (VAI) after nonpenetrating cervical trauma in patients who have complete cervical spinal cord injuries, fracture through the foramen transversarium, facet dislocation, and/or vertebral subluxation.

Treatment

1. Treatment with an antiplatelet is recommended for patients with VAI.

2. Use of anticoagulation with IV heparin may be considered in patients with VAI and associated posterior circulation ischemia or infarction.
3. Caution should be exercised in anticoagulating those patients with large posterior circulation infarct given the concern for possible hemorrhagic conversion.

Prevention of Complications

1. Aspiration precautions: Placement of a nasogastric tube reduces the risk of aspiration and pneumonia.
2. Urinary retention: Placement of a Foley catheter reduces the risk of hydronephrosis and renal impairment.
3. Warming blanket: Hypothermia can promote systemic complications and is commonly seen in trauma victims and patients with spinal cord injury.
4. Cervical immobilization.
   - **a.** The short-term goal of immobilization is to prevent further misalignment and additional injury to the spinal cord.
   - **b.** Immobilization can be achieved by bed rest, traction, or spinal orthosis.
   - **c.** Orthosis for immobilization of the spine allows early mobilization of the patient and can help in achieving spinal column alignment.
5. Cervical collar for treatment of cervical spine injuries.
   - **a.** Standard procedure: Initially, all patients are placed in a firm cervical collar.
   - **b.** Contraindications: Associated tracheal injury or soft-tissue injury in the neck.
   - **c.** Complications: Skin ulceration caused by pressure from the collar.
   - **d.** Special points:
     - **1)** The Philadelphia collar can be used to treat stable fractures.
     - **2)** A sternooccipital-mandibular immobilization (SOMI) brace or halo device is used for unstable fractures.
6. Braces for treatment of thoracic and lumbar spine injuries.
   - **a.** Standard procedure: A brace such as the thoracic lumbar sacral orthosis (TLSO), or Jewett brace, is used to treat fractures of the thoracic spine. In the lumbar spine, a corset brace, Boston overlap hard-shell brace, or body cast is used.

b. Contraindications: Severe thoracic or abdominal trauma.
c. Complications: Skin ulceration from the brace.
d. Special points:
1) Once these braces are in place, a flat and upright lateral thoracic spine or lumbar spine radiograph should be obtained.
2) If movement of the spinal column is noted, the patient is placed back on bed rest and surgical stabilization is considered.

7. Oxygenation: Respiratory complications are the largest cause of morbidity and mortality in the patient with spinal cord injury. Because half the patients with spinal cord injuries arrive with complete injuries, the need for respiratory support is high. The goals are to guard against respiratory failure and to ensure adequate oxygenation to the injured spinal cord.
a. Standard procedure: A nasal cannula or face mask to provide supplemental oxygen should be used in the acute phase of treatment in those patients who do not require intubation.
b. Endotracheal intubation is warranted in those patients with respiratory distress. Impending respiratory failure should be suspected in those patients with absent chest wall movement and excessive abdominal wall movement.
c. If the blood gas has a P_{O2} less than 70 mm Hg or a P_{CO2} greater than 45 mm Hg, the patient should be intubated.
d. Contraindications: In the case of major facial or skull base trauma, tracheotomy should be performed instead of nasal or endotracheal intubation.
e. Complications: Endotracheal intubation may worsen a cervical spine cord injury in cases with unstable cervical spine fractures or ligament injury.
f. Special points: Most high cervical injuries will require intubation.
1) Intubation is indicated with lesions at or above C3 because there is no diaphragmatic or intracostal muscle function.
2) Lower cervical or upper thoracic injuries may require intubation because of delayed ascending cord swelling.

Patient Placement, Catheters, and Vasopressors

1. Neurogenic shock can happen with injuries above T6.
a. The sympathetic outflow tracts are found from T1 to L2.
b. Lesions at T6 (or above) disrupt a significant proportion of these tracts,

which results in the loss of sympathetic nervous system control over peripheral vascular tone. This results in pooling of blood and reduces central venous return.

c. Examination reveals warm extremities, good urine output, and vital signs that show bradycardia and hypotension.

2. Standard procedure: Placement of the patient in Trendelenburg position (head down) helps reduce the pooling of blood in the lower extremities.

a. Vasopressors are used to augment blood pressure.

3. Contraindications: Relative contraindication in those patients with impaired cardiac function.

4. Complications: Development of heart failure from fluid overload.

5. Special points: Hypovolemic shock is commonly seen in patients with spinal cord injury and additional systemic trauma. Treatment for this type of shock is fluid replacement and transfusion of red cells if there are active losses.

a. It is possible to have both neurogenic and hypovolemic shock in the same patient.

6. Norepinephrine is the agent of choice for treatment of neurogenic shock.

a. Standard dosage: Start at 8 to 12 μg/min, titrate to effect.

b. Goal is a systemic blood pressure (SBP) of >90 mm Hg at a minimum, ideally a mean arterial pressure (MAP) of 80 to 90 mm Hg to optimize cord perfusion.

c. Phenylephrine should be avoided because it can cause reflex bradycardia.

7. Atropine

a. Standard dosage: Symptomatic bradycardia is treated with 0.4 mg atropine administered IV.

b. Contraindications: Unstable cardiovascular status; acute angle closure glaucoma.

c. Diphenhydramine is addictive with synergetic effects. Scopolamine also is addictive with synergistic effects.

d. Main side effects: May precipitate ventricular fibrillation in patients with cardiac history.

e. Special points: CNS effects such as confusion and hallucinations can confuse the clinical picture if an associated head injury exists.

BRAIN DEATH

Background

1. In most countries, the principle that death can be diagnosed by two means, either cardiac asystole or by neurologic criteria (designated as brain death), is the basis of the Uniform Determination of Death Act in the United States, although the law does not define any of the specifics of the clinical diagnosis.
2. There is a clear difference between severe brain damage and brain death. Brain death implies that life support is futile and is, under a different set of ethical principles, the principal requisite for the donation of organs for transplantation.
3. There are many ethical, religious, and philosophical considerations regarding the definition of death.

Pathophysiology

1. In adults, the chief causes of brain death are TBI and subarachnoid hemorrhage.
2. In children, physical abuse is a more common cause than motor vehicle collisions or asphyxia.

Diagnosis

In 1995, the American Academy of Neurology published suggested practice measures, an evidence-based review. This report specifically addressed the tools of clinical examination and the validity of confirmatory tests and provided a practical description of apnea testing. The guideline was updated in 2010.

Neurologic Examination

1. Before the neurologic examination for the determination of brain death can be performed, the following prerequisites are met:
   - **a.** Ruling out the presence of complicated medical conditions that may confound the clinical assessment, such as
     - **1)** Severe electrolyte, acid–base, or endocrine disturbances

2) Absence of hypothermia, defined as a core temperature of 36◦C or lower
3) Hypotension, defined as SBP less than 100 mm Hg
4) Absence of evidence of drug intoxication, poisoning, or neuromuscular blocking agents

b. A clear cause of brain injury must be established. Interpretation of the CT or MRI is essential. Usually, CT scanning demonstrates a mass with brain herniation, multiple hemispheric lesions with edema, or edema alone. However, such a finding on the CT scan does not obviate the need for a careful search for confounders. Conversely, the CT scan findings can be normal in the early period after cardiorespiratory arrest or with patients with fulminant meningitis or encephalitis.

c. If the clinical suspicion is high, examination of the CSF should be performed to exclude infection in the CNS.

2. The clinical neurologic examination remains the standard for the determination of brain death and has been adopted in most countries. The clinical examination of patients who are presumed to be brain dead must be performed with consistency and precision. The declaration of brain death requires:

a. Serial neurologic examinations (this has become optional in some jurisdictions)
b. Establishment of the cause of coma
c. Ascertainment of irreversibility
d. Resolution of any misleading clinical neurologic signs
e. Recognition of possible confounding factors
f. Interpretation of the findings on neuroimaging
g. Performance of any confirmatory laboratory tests that are deemed necessary

Coma or Unresponsiveness

1. Motor responses of the limbs to painful stimuli may be absent after supraorbital pressure and nail-bed pressure.

2. Motor responses ("Lazarus sign") may occur spontaneously during apnea testing, often during hypoxic or hypotensive episodes, and are of spinal origin.

3. Neuromuscular blocking agents can produce prolonged weakness.
   a. If neuromuscular agents have recently been administered, examination with a bedside peripheral nerve stimulator is needed.
   b. A train of four stimuli should result in four thumb twitches.

Absence of Brainstem Reflexes

1. The pupillary response to bright light should be absent in both eyes.
2. Round, oval, or irregularly shaped pupils in brain death are in middle position (4 to 6 mm, but the size of the pupils may vary from 4 to 9 mm).
3. Dilated pupils are compatible with brain death because intact sympathetic cervical pathways connected with the radially arranged fibers of the dilator muscle may remain intact.
4. Many drugs can influence pupil size, but light responses remain intact.
   a. In conventional doses, atropine given intravenously has no marked influence on papillary response.
   b. Because nicotine receptors are absent in the iris, neuromuscular blocking drugs do not noticeably influence pupil size.
   c. Topical ocular instillation of drugs and trauma to the cornea or bulbus oculi may cause abnormalities in pupil size and can produce nonreactive pupils.
   d. Preexisting anatomic abnormalities of the iris or effects or previous surgery should be excluded.
5. Ocular movements.
   a. Ocular movements are absent after head turning and caloric testing with ice water. (Testing is only done when no fracture or instability or the cervical spine is apparent, and in patients with head injury, the cervical spine must be imaged to exclude potential fractures, instability, or both.)
   b. The oculocephalic reflex, elicited by fast and vigorous turning of the head from middle position to 90 degrees on both sides, normally results in the eye deviation to the opposite side of the head turning. Vertical eye movements should be tested with brisk neck flexion. Eyelid opening and vertical and horizontal eye movements must be absent in brain death.
   c. Caloric testing should be done with the head elevated to 30 degrees during irrigation of the tympanum on each side with 50 mL of ice water. Tympanum irrigation can be accomplished by inserting a small tube into

the external auditory canal and connecting it to a 50-mL syringe filled with ice water. Tonic deviation of the eyes directed to the cold caloric stimulus is absent. The investigator should allow up to 1 minute after injection, and the time between stimulation on each side should be at least 5 minutes.

d. Drugs that can diminish or completely abolish the caloric responses are sedatives, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, and chemotherapeutic agents.

e. After closed head injury or facial trauma, lid edema and chemosis of the conjunctive may restrict movement of the globes. Clotted blood or cerumen may diminish the caloric response, and repeated testing is advisable after direct inspection of the tympanum. Basal fracture of the petrous bone abolishes the caloric response only unilaterally and may be identified by an ecchymotic mastoid process.

6. Facial sensation and facial motor response.

a. Corneal reflexes should be tested with a cotton swab.

b. Corneal reflex should be absent.

c. Grimacing to pain can be tested by applying deep pressure with a blunt object on the nail beds, pressure on the supraorbital ridge, or deep pressure on both condyles at the level of the temporomandibular joint.

d. Severe facial trauma may limit interpretation of all brainstem reflexes.

7. Pharyngeal and tracheal reflexes.

a. The gag response, tested by stimulation of the posterior pharynx with a tongue blade or by manipulation of the endotracheal tube, should be absent.

b. Lack of cough response to bronchial suctioning should be demonstrated.

8. Apnea testing.

a. Disconnect the ventilator.

b. Deliver 100% O_2 at 6 L/min. Option: Place a cannula at the level of the carina. Look closely for respiratory movements. Respiration is defined as abdominal or chest excursions that produce adequate tidal volumes. If present, respiration can be expected early in the apnea test. When respiratory-like movements occur, they can be expected at the end of the apnea test, when oxygenation may become marginal. When the result is in doubt, a spirometer can be connected to the patient to confirm that tidal volumes are absent.

c. Measure arterial P_{O_2}, P_{CO_2}, and pH after approximately 8 minutes and reconnect the ventilator.

d. If respiratory movements are absent and the P_{CO_2} is equal to or greater than 60 mm Hg (option: 20-mm Hg increase in P_{CO_2} over a baseline normal P_{CO_2}), the apnea test result is positive (i.e., it supports the clinical diagnosis of brain death).

e. If during the apnea testing, the systolic blood pressure is below 90 mm Hg, the pulse oximeter indicates marked desaturation, and cardiac arrhythmias occur, immediately draw a sample, connect the ventilator, and analyze arterial blood gas. The apnea test result is positive if the arterial P_{CO_2} is above 60 mm Hg or the P_{CO_2} increase is equal to or greater than 20 mm Hg above baseline normal P_{CO_2}.

Summary Requirements for Brain Death Criteria

1. Coma of a known cause
2. Absence of motor responses
3. Pupils: No response to light and mid-position (4 to 6 mm)
4. Absence of corneal reflexes
5. Absence of caloric response
6. Absence of gag reflex
7. Absence of coughing in response to tracheal suctioning
8. Absence of respiratory drive at a Pa_{CO_2} that is 60 mm Hg or 20 mm Hg above the baseline values
9. Interval between two examinations according to the patient's age
   a. Usually 6 hours for adults but this time period varies depending on state/country
10. **Perform confirmatory tests (see in the following section) if required.**

Neurologic States that Can Mimic Brain Death

1. The locked-in syndrome is usually a consequence of the destruction of the base of the pons.
   a. The patient cannot move the limbs, grimace, or swallow, but the upper rostral mesencephalic structures involved in voluntary blinking and

vertical eye movements remain intact.

b. Consciousness persists because the tegmentum, with the reticular formation, is not affected. The condition is most often caused by an acute embolus to the basilar artery.

2. Guillain–Barré syndrome involving all the peripheral and cranial nerves.

a. The progression occurs over a period of days, and knowledge of the history should prevent the error of diagnosing brain death.

3. Hypothermia from prolonged environmental exposure may mimic loss of brain function, but alcohol intoxication and head injury are often major confounders.

a. Hypothermia causes a downward spiral of loss of brainstem reflexes and pupillary dilatation. The response to light is lost at core temperatures of 28◦C to 32◦C, and brainstem reflexes disappear when the core temperature drops below 28◦C.

b. These deficits are all potentially reversible, even after extreme hypothermia.

4. Many sedative and anesthetic agents can closely mimic brain death, but aspects of brainstem function, particularly the pupillary responses to light, remain intact. When ingested in large quantities, many drugs can cause a partial loss of brainstem reflexes.

5. A reasonable approach to drug/toxin exposure is as follows:

a. If it is known which drug or poison is present but the substance cannot be quantified, the patient should be observed for a period that is at least 4 times the elimination half-life of the substance, provided that the elimination of the drug is not interfered with by other drugs or organ dysfunction. In the setting of hypothermia, the metabolism is expected to be delayed or altered.

b. If the particular drug is not known but high suspicion persists, the patient should be observed for 48 hours to determine whether a change in brainstem reflexes occurs; if no change is observed, an ancillary test should be considered.

Confirmatory Tests

1. Ancillary tests are optional in adults but recommended in children younger

than 1 year. In several European, Central and South American, and Asian countries, confirmatory testing is required by law. Certain countries (e.g., Sweden) require only cerebral angiography. In the United States, the choice of tests is left to the discretion of the physician, but bedside tests seem to be preferred. There is great variability in brain death policies regarding ancillary examinations; please adhere to the policy of your individual institution.

2. Cerebral angiography may document nonfilling of the intracranial arteries at the entry to the skull because the systolic pressure is not high enough to force blood through the intracranial vascular tree.
   - **a.** Perivascular glial swelling and the formation of subintimal blebs caused by ischemia may cause the collapse of smaller vessels, leading to increased intravascular resistance.
   - **b.** Cerebral angiography is performed with an injection in the aortic arch to visualize both the anterior and the posterior circulation. Arrest of flow is found at the foramen magnum in the posterior circulation and at the petrosal portion of the carotid artery in the anterior circulation.

3. EEG may be used.
   - **a.** Recordings are obtained for at least 30 minutes with a 16- or 18-channel instrument. In a patient who is brain dead, electrical activity is absent at levels higher than 2 μV with the instrument set at a sensitivity of 2 μV/mm.
   - **b.** High levels of sensitivity set on the EEG machine increase artifacts.

4. Transcranial Doppler ultrasonography has a sensitivity of 91% to 99% and a specificity of 100% for absence of cerebral blood flow (CBF).
   - **a.** A portable, 2-Hz, pulsed-wave Doppler ultrasonographic instrument is used, insonating both middle cerebral arteries and vertebral arteries.
   - **b.** The absence of a signal may be artifactual if a bone window interferes with insonation.
   - **c.** In patients who are brain dead, transcranial Doppler ultrasonography typically reveals the absence of the diastolic or reverberating flow that is caused by the contractile force of the arteries; the pulsatility index is very high, with systolic velocities that are only a fraction of the normal level.

5. Nuclear imaging with technetium may demonstrate an absence of intracerebral uptake of the tracer. The correlation with conventional angiography is good.

Continuation of Mechanical Ventilation and Support

When mechanical ventilation and support are continued because of ethical or legal objections to their discontinuation, what usually follows is an invariant heart rate from a de-efferented sinoatrial node, structural myocardial lesions leading to a marked reduction in the ejection fraction, decreased coronary perfusion, the need for increasing use of inotropic drugs to maintain blood pressure, and a fragile state that usually leads to cardiac arrest within days or weeks.

INCREASED INTRACRANIAL PRESSURE (INTRACRANIAL HYPERTENSION)

Background

1. Increased ICP, or intracranial hypertension, is a pathologic condition common to a wide variety of serious neurologic illnesses (Table 1-5).
2. Proper understanding of the pathophysiology of each entity allows prompt recognition and rational therapeutic goals and, it is hoped, allows better neurologic outcomes.

Table 1-5 Conditions Associated with Increased Intracranial Pressure

Intracranial mass lesions
Cerebral hemorrhage
Subdural hematoma
Epidural hematoma
Intracerebral hemorrhage
Subarachnoid hemorrhage
Brain tumor
Cerebral abscess
Increased cerebrospinal fluid volume
Hydrocephalus
Increased brain volume (cerebral edema)
Benign intracranial hypertension (pseudotumor cerebri)
Cerebral infarction

Global hypoxic–ischemia
Reye syndrome
Acute hyponatremia
Hepatic encephalopathy
Head trauma
Meningitis
Encephalitis
Lead encephalopathy
Eclampsia
Hypertensive encephalopathy
Dural sinus thrombosis

Pathophysiology

1. The principles of intracranial hypertension are based on the Monro–Kellie doctrine.
   - **a.** The skull, a rigid compartment, is filled to capacity with noncompressible contents—brain matter (80%), intravascular blood (10%), and CSF (10%).
   - **b.** The volume of these three components remains nearly constant in a state of dynamic equilibrium. If any one component increases the volume, other components must decrease for the overall volume to remain constant; otherwise, ICP will rise.
   - **c.** As a result, most therapeutic modalities for the treatment of increased ICP (e.g., CSF drainage, hyperventilation, mannitol) are directed toward reducing intracranial volume.
2. Normal range of ICP is 3 to 15 mm Hg or 5 to 20 cm H_2O.
   - **a.** Elevations above these levels can rapidly lead to brain damage or death by
     - **1)** Global hypoxic–ischemic injury resulting from the reduction of cerebral perfusion pressure (CPP) and CBF.
     - **2)** Mechanical compression, distortion, and herniation of brain tissue by compartmentalized ICP gradients.
3. Relationship between neurologic decline and elevated ICP.
   - **a.** Depending on the clinical situation, global increases in ICP begin as regional cerebral edema, but regional cerebral edema initially causes profound tissue shifts and brainstem distortions without causing global ICP elevations.

b. Neurologic deterioration correlates with horizontal displacement of the anterior septum and the pineal gland rather than global ICP.

c. ICP elevation is a terminal and most likely an irreversible circumstance that results when mass expansion exceeds intracranial compliance.

d. The clinical signs of increased ICP are well known but are unreliable indicators of raised ICP.

1) Depressed level of consciousness
2) Reflex hypertension, with or without bradycardia
3) Headache
4) Papilledema
5) Vomiting
6) Cranial nerve palsies

e. Because these clinical signs are unreliable, it is important to remember that the most dependable way to diagnose increased ICP is to directly measure it.

4. Herniation syndromes (see section on Herniation Syndromes).
5. Prognosis depends on the etiology.

Diagnosis

Intracranial hypertension can rapidly lead to irreversible brain damage or death.

1. Only direct measurement of ICP can accurately determine and monitor efficacy of treatment.
2. Traditional neurologic practice depends on changes in the patient's neurologic examination as the primary monitoring technique. This approach is inadequate in critically ill patients with depressed level of consciousness, in whom early signs of neurologic deterioration cannot be appreciated.
3. The goal of ICP monitoring is to detect abnormal physiologic events before the loss of the neurologic function, therefore allowing clinicians to intervene and avoid additional brain injury.

Treatment

Physiologic Principles

1. Intracranial anatomy
   a. The components of volume within the nondistensible cranium of the normal adult brain are brain tissue (1,400 mL), blood (150 mL), and CSF (150 mL).
   b. CSF is produced constantly by the choroid plexus within the ventricles at a rate of 0.34 mL/min.
   c. CSF is transported into the dural sinuses via arachnoid granulations. Normally, this pathway offers little resistance to CSF outflow. As a result, jugular venous pressure is a major determinant in ICP.

2. Intracranial compliance
   a. Because the cranial vault is a rigid and fixed container, any additional intracranial volume can lead to increased ICP. The Monro–Kellie doctrine states that the volume of the rigid intracranial vault cannot change.

Table 1-6 Horizontal Displacement of Midline Structures on Computed Tomography Scans and Level of Consciousness

	True Dimensions from Midline (mm)	
Level of Consciousness	**Pineal**	**Septum Pellucidum**
Awake	0–3	2–7
Drowsy	3–6	2–10
Stupor	6–9	7–14
Coma	9–15	12–18

Data from Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispheral mass. *N Engl J Med*. 1986;314:953–958, with permission.

   b. As the volume increases, intracranial contents must be displaced (Table 1-6). As a mass lesion expands in the intracranial vault, there are minimal increases in pressure that occur initially because CSF and blood are displaced.
   c. When these mechanisms become exhausted, intracranial compliance falls sharply, and further small increments in intracranial volume lead to dramatic elevations of ICP (Fig. 1-1).
   d. Intracranial compliance can be described as change in volume divided

by the change in pressure.

3. Cerebral perfusion and autoregulation
   a. Brain tissue requires constant perfusion to ensure adequate delivery of substrate, principally oxygen and glucose.
   b. The hemodynamic response of the brain has the capacity to preserve perfusion across a wide range of SBPs.

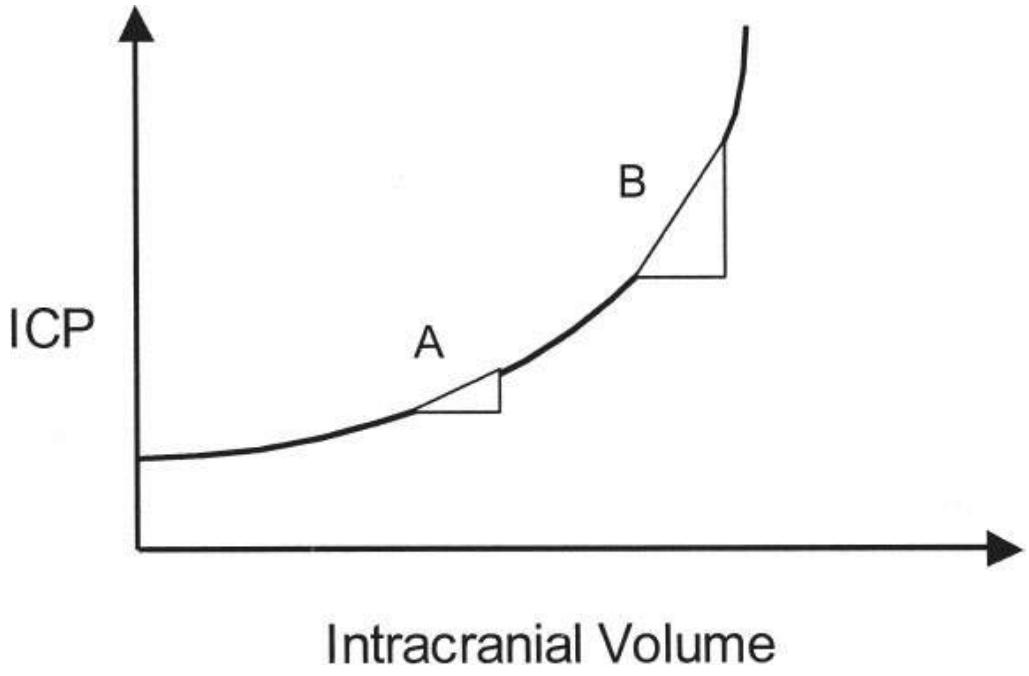

Figure 1-1. Intracranial compliance curve.

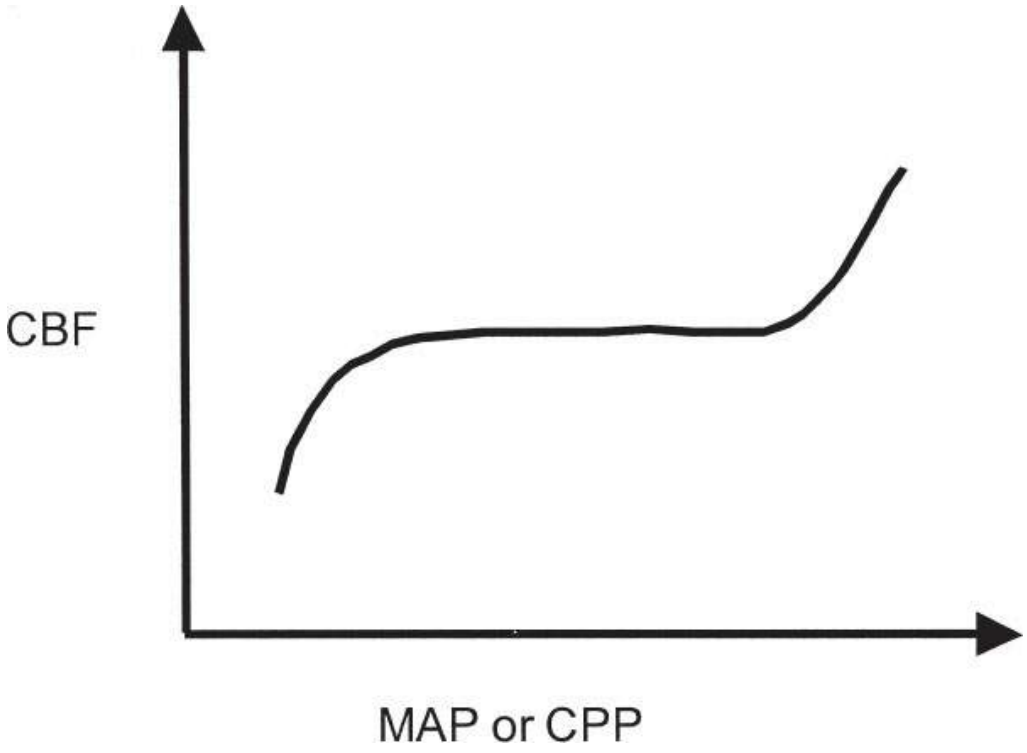

Figure 1-2. Cerebral autoregulation curve.

c. CPP, defined as the MAP minus the ICP, provides the driving force for circulation across the capillary beds of the brain.

d. Autoregulation refers to the physiologic response whereby CBF remains relatively constant over a wide range of blood pressures as a consequence of alterations of cerebrovascular resistance (Fig. 1-2).

1) If SBP drops, cerebral perfusion is preserved through vasodilatation of arterioles in the brain; likewise, arteriolar vasoconstriction occurs at high systemic pressures to prevent hyperperfusion. At the extreme limits of MAP or CPP (high or low), flow becomes directly related to perfusion pressure.

2) CBF is also strongly influenced by pH and P_{CO_2} (Fig. 1-3).

a) CBF increases with hypercapnia and acidosis and decreases with hypocapnia and alkalosis.

b) This forms the basis for the use of hyperventilation to lower ICP, and this effect on ICP is mediated through a decrease in intracranial blood volume.

3) Cerebral autoregulation is critical to the normal homeostatic functioning of the brain, and this process may be disordered focally and unpredictably in disease states such as TBI and severe focal

cerebral ischemia.

I. ICP waveforms

a. Normal ICP waveforms reflect a transient increase in cerebral blood volume that occurs with each arterial pulse.

b. Under normal conditions, the amplitude of ICP pulse pressure is relatively small (2 to 3 mm Hg).

1) Under pathologic conditions, when intracranial compliance is reduced, ICP pulse pressures increase to levels as high as 10 to 15 mm Hg.

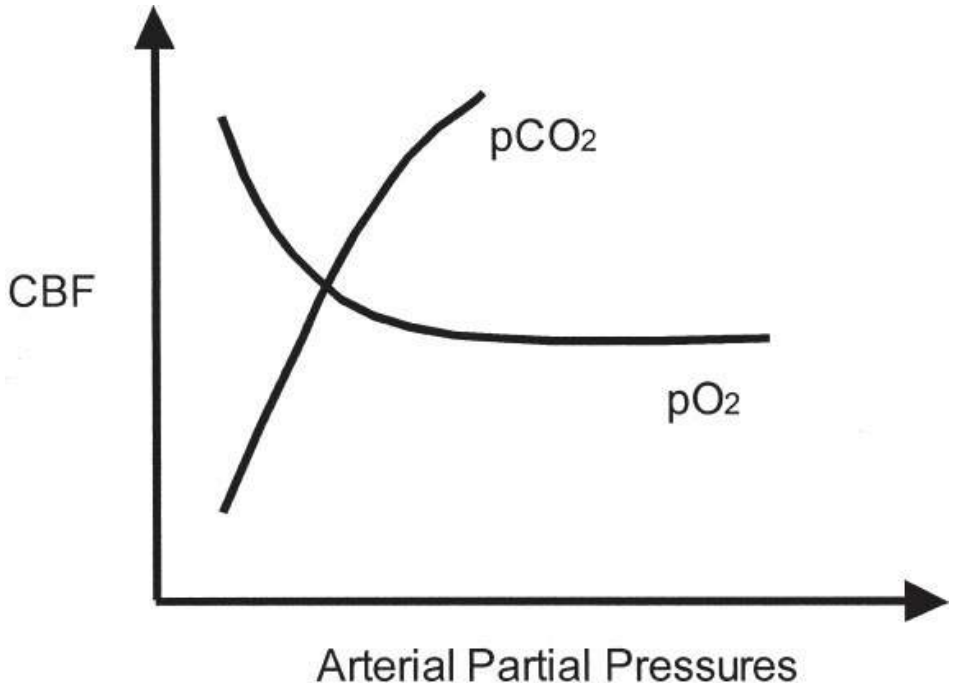

Figure 1-3. Arterial partial pressures curve.

2) Elevation of CSF pulse pressure in patients with mildly increased ICP can be a useful sign of reduced intracranial compliance, indicating that the patient is on a "steep" portion of the ICP–volume curve and is at risk for sudden elevations of ICP with minor increases in intracranial volume (Fig. 1-2).

3) In conditions of reduced intracranial compliance and/or inadequate CPP, pathologic CSF pressure waves may occur.

4) Normally, there are three pulse waves seen on ICP tracing:

a) They are reflections of cardiac systole (P1), diastole (P2), and emptying of the cerebral vessels (P3).

b) There are normal fluctuations that occur in the ICP with each respiratory cycle.

5) Two types of pathologic ICP waves have been described. The most important pressure changes are the Lundberg A waves, also called plateau waves, which can occur suddenly, reach levels of 20 to 80 mm Hg, and last from minutes to hours. Lundberg B waves are of lesser amplitude (5 to 20 mm Hg) and are less dangerous. Clinically, they are a useful marker of inadequate CPP and reduced intracranial compliance and may be harbingers of plateau waves.

Indications for Intracranial Pressure Monitoring

1. Monitoring of ICP can be an important tool in selected patients. Indications for ICP monitoring, as well as specific types of monitors, vary.
2. In general, patients who should be considered for ICP monitoring are those with primary neurologic disorders, such as stroke or TBI, who are not moribund and who are at significant risk for secondary brain injury because of elevated ICP and decreased CPP:
   - **a.** Severe TBI resulting in coma (GCS score of 8 or less).
   - **b.** Large tissue shifts from supratentorial ischemic or hemorrhagic stroke resulting in decreased consciousness.
   - **c.** Hydrocephalus from subarachnoid hemorrhage, intraventricular hemorrhage, or posterior fossa stroke.
   - **d.** Fulminant hepatic failure, in which elevated ICP may be treated with barbiturates or, eventually, liver transplantation.
3. In general, ventriculostomy is preferable to ICP monitoring devices that are placed in brain parenchyma because ventriculostomy allows CSF drainage as a method of treating elevated ICP.
4. Parenchymal ICP monitoring is most appropriate for patients with diffuse edema and small ventricles (which may make ventriculostomy placement more difficult) or any degree of coagulopathy (in which ventriculostomy carries a higher risk of hemorrhagic complications).

Management of Elevated Intracranial Pressure

1. General measures
   a. Head position elevated 15 to 30 degrees and in a neutral neck position to avoid jugular compression
   b. Hypotonic fluids (e.g., D5W, 0/5% NS) should be avoided.
   c. Intubation only to protect airway
   d. Glucose management
   e. Agitation, fever, and seizures should be treated.
   f. Blood pressure management to maintain CPP
   g. Neurosurgical consultation
2. Stepwise approach
   a. General measures as noted earlier
   b. Insert ICP monitor—ventriculostomy versus parenchymal device.
   c. General goals: Maintain ICP below 20 mm Hg and CPP 50 to 70 mm Hg, sustained CPP >70 mm Hg has been associated with increased risk of complications, notably adult respiratory distress syndrome (ARDS).
   d. For ICP above 20 to 25 mm Hg for longer than 5 minutes
   e. Drain CSF via ventriculostomy (if in place).
   f. Elevate head of the bed.
   g. Osmotherapy: Mannitol 25 to 100 g every 4 hours as needed (maintain serum osmolality initially up to 300 mOsm/L and then 315 mOsm/L). Hypertonic saline is an alternative (continuous 3% NS or bolus 23% NS).
   h. Glucocorticoids: Dexamethasone 4 mg every 6 hours for vasogenic edema from tumor, abscess (avoid glucocorticoids in head trauma, ischemic, and hemorrhagic stroke).
   i. Sedation (e.g., morphine, propofol, or midazolam); add neuromuscular paralysis if necessary (patient will require endotracheal intubation and mechanical ventilation at this point, if not before).
   j. Hyperventilation: Pa_{CO_2} 30 to 35 mm Hg
   k. Pressor therapy: Phenylephrine, dopamine, or norepinephrine to maintain adequate MAP to ensure CPP 50 to 70 mm Hg (maintain euvolemia to minimize deleterious systemic effects of pressors)
   l. Consider second-tier therapies for refractory elevated ICP.
      1) High-dose barbiturate therapy (“pentobarb coma”)
      2) Aggressive hyperventilation to Pa_{CO_2} of 25 to 30 mm Hg
      3) Hemicraniectomy

4) Hypothermia

5. Throughout ICP treatment, consider repeated head CT to identify mass lesions amenable to surgical evacuation.

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2 Epilepsy

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BACKGROUND

History

1. The term "epilepsy" is derived from Greek *epilepsia*: a taking hold of or seizing.
2. Ancient accounts over 2,500 years ago by Babylonians and Egyptians. Detailed descriptions in *On the Sacred Disease* attributed to Hippocrates in the 5th century BC. Use of "sacred" possibly meant to be ironic, as Hippocrates is regarded as wishing to replace the earlier, supernatural explanations of epilepsy with a natural one dependent on brain function.
3. Late 19th century:
   a. Jackson: Model of focal seizure beginning as aura and evolving to psychomotor or convulsive seizure and use of aura symptoms to localize seizure onset within gray matter of the brain.
   b. Gowers: Detailed descriptions of epileptic syndromes and related disorders; concept that "seizures beget seizures."
4. Mid-20th century:
   a. Berger, Walter, and Lennox: Ability to record human electroencephalogram (EEG) from scalp and correlate with epilepsy.
   b. Penfield and Jasper: Surgical resection facilitated by identification of epileptic focus on the basis of clinical manifestations and electrocorticography (EEG recorded from the brain surface) and identification of functional cortical regions by cortical electrical stimulation.
   c. Merritt and Putnam: Determination that phenytoin (PHT) was an

antiepileptic drug (AED) using an animal seizure model.

d. Gastaut: Advances in syndromic classification and treatment.

5. Late 20th century:

a. Widespread use of simultaneous video-EEG (vEEG) recording, allowing accurate correlations of EEG and behavior.

b. Neuroimaging, allowing visualization of lesions responsible for seizure generation and facilitating surgical treatment of epilepsy.

c. Development of many new AEDs by screening and synthesis based on knowledge of seizure mechanisms.

d. Emergence of epileptology as a defined specialty within neurology and the development of comprehensive epilepsy management programs, including long-term vEEG monitoring and epilepsy surgery.

6. 21st century:

a. Identification of genetic bases of many syndromic epilepsies.

b. Implantable stimulation techniques (e.g., vagal nerve stimulation, responsive neurostimulation, deep brain stimulation) for treatment-resistant epilepsy.

c. Use of laser ablation in epilepsy surgery.

Definitions

1. Seizure: The clinical manifestation of an abnormal, excessive, and hypersynchronous electrical discharge of a population of cortical neurons.

2. Epilepsy: A brain disorder characterized by recurrent seizures that are unprovoked by systemic or neurologic insults.

3. Epileptic syndrome: A particular form of epilepsy, often implying specific causes, clinical manifestations, and prognosis.

4. Aura: The earliest part of a seizure and typically the only subjective experience recalled by the patient.

5. Convulsion: The motor manifestations of a seizure, usually consisting of rhythmic tonic followed by clonic movements and postures.

6. Postictal period: Time between the end of the seizure and recovery to the baseline state.

7. Status epilepticus (SE): Five or more minutes of continuous or recurrent seizures without recovery.

3. Sudden unexpected death in epilepsy (SUDEP): Sudden, unexpected, witnessed or unwitnessed, nontraumatic, and nondrowning death of patients with epilepsy with or without evidence of a seizure and in whom postmortem examination does not reveal a structural or toxicologic cause.

Classification

Seizure Types

The fundamental types of seizures are (a) focal ("partial" in the old terminology) seizures that are presumed to originate in a specifiable lobe or hemisphere of the brain and (b) generalized seizures that start simultaneously throughout the entire cortex, or at least in widespread networks of both hemispheres. A further distinction is made between focal seizures without loss of consciousness (previously simple partial) and those with loss of consciousness (previously complex partial).

The following is a simplified version of the 2010 seizure classification system of the International League Against Epilepsy (ILAE):

1. Focal seizures (seizures beginning within networks limited to one hemisphere).
   - **a.** Without impairment of consciousness or awareness.
     - **1)** With observable motor or autonomic components (focal motor, autonomic seizures)
     - **2)** With subjective sensory or psychic phenomena only (aura)
   - **b.** With impairment of consciousness or awareness (dyscognitive).
   - **c.** Evolving to bilateral convulsive seizure (replaces secondarily generalized seizure).
2. Generalized seizures originate at some point within and rapidly engage bilaterally distributed networks.
   - **a.** Typical absence (petit mal): Arrest of behavioral activity with staring and minor motor activity (e.g., blinking); usual duration 5 to 10 seconds, rarely up to 30 seconds, longer absences may be accompanied by automatic behaviors or automatisms; EEG pattern of 3 Hz (rarely up to 6 Hz) generalized spike–wave complexes.
   - **b.** Atypical absence: Compared with typical absence, often less complete but longer and more gradual behavioral arrest and recovery; EEG pattern of

slow (1.5 to 2.5 Hz) spike–wave complexes.

c. Absence with special features: (1) Myoclonic absence: absence with associated rhythmic myoclonus and (2) eyelid myoclonia: myoclonus of eyelids with absence (also known as Jeavons syndrome).

d. Myoclonic: Brief, shocklike jerking of muscles on both sides of body; duration, less than 1 second; EEG pattern of generalized polyspike–wave complexes.

e. Clonic: Series of myoclonic jerks; duration, variable; EEG pattern of focal discharges if present.

f. Tonic: Stiffening or contraction in a fixed posture, often with abduction of the shoulders and partial flexion of the elbows; usual duration 10 to 20 seconds, but often in clusters; EEG pattern of rapid, diffuse polyspikes, often following a slow wave followed by voltage suppression and low amplitude fast activity.

g. Tonic–clonic (grand mal, convulsion): Stereotyped sequence of bilateral stiffening followed by clonic contractions; usual duration 50 to 120 seconds; EEG pattern of low-amplitude polyspikes increasing in amplitude until obscured by muscle artifact, then in bursts corresponding to clonic jerks.

h. Atonic: Sudden loss of postural tone, usually with altered awareness; duration, 5 to 30 seconds; EEG pattern of rapid, low-voltage spikes following a slow wave, or slow-spike/polyspike–wave complexes.

3. *Unknown*. This category includes epileptic spasms.

Epilepsy Syndromes

1. Epilepsy syndromes are classified predominantly by the seizure type, focal or generalized, and by the underlying cause of the epilepsy. The terms *symptomatic*, *cryptogenic*, and *idiopathic* are being used less often.
2. Epilepsy is genetic if it is the result of a known or presumed genetic defect.
3. Epilepsy is structural/metabolic if there is a distinct structural or metabolic condition demonstrated to be substantially associated with the increased risk of developing epilepsy.
4. Unknown cause.
5. Several of the common epilepsy syndromes are listed in Table 2-1.

Epidemiology

1. Seizures have a 9% to 10% cumulative lifetime incidence (3% to 4% febrile, 3% other acute symptomatic, 2% to 3% epileptic) in almost all populations.
2. The incidence of epilepsy is 30 to 50/100,000; cumulative incidence 2% to 3% by age 75 years; prevalence 0.5% to 0.8%.
3. There is a bimodal incidence for both seizures and epilepsy with the highest rate in the first year of life and increasing again after age 60.

PATHOPHYSIOLOGY

The hypersynchronous neuronal discharge that characterizes a seizure is the result of an imbalance between excitation and inhibition. Genetic epilepsies typically affect the structure and function of neurotransmitter receptors and their associated ion channels. The mechanisms by which cortical injuries produce epilepsy are unknown but probably are related to alterations in function and connectivity of excitatory and inhibitory neurons at the margins of the injury. The glia, astrocytes, and neuroinflammation also likely play a role in this process.

Table 2-1 Modified International League Against Epilepsy Classification of Epilepsy Syndromes and Other Epilepsies

1. Electroclinical syndromes arranged by age of onset
   - **a.** Neonatal
     Benign familial neonatal epilepsy (BFNE)
     Ohtahara syndrome
   - **b.** Infancy
     West syndrome
     Benign infantile epilepsy
     Dravet syndrome
   - **c.** Childhood
     Childhood absence epilepsy (CAE)
     Benign epilepsy with centrotemporal spikes (BECTS)
     Lennox–Gastaut syndrome (LGS)
     Landau–Kleffner syndrome (LKS)
   - **d.** Adolescence to adulthood
     Juvenile absence epilepsy (JAE)

Juvenile myoclonic epilepsy (JME)
Epilepsy with generalized tonic–clonic seizures alone

e. Unspecific age relationship
Reflex epilepsies
Familial focal epilepsy with variable foci

2. Distinct constellations
   a. Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)
   b. Rasmussen encephalitis
   c. Gelastic seizures with hypothalamic hamartoma
3. Epilepsies due to structural metabolic causes
   a. Malformations of cortical development (cortical dysplasia, heterotopias, etc.)
   b. Neurocutaneous syndromes (tuberous sclerosis complex, Sturge–Weber, etc.)
   c. Tumors
   d. Stroke
   e. Etc.
4. Conditions associated with seizures but not a diagnosis of epilepsy
   a. Febrile seizures (FS)
   b. Benign neonatal seizures (BNS)
5. Epilepsies of unknown cause

Selected syndromes are included.

Physiologic Mechanisms

1. Cellular: Alterations in distribution or function of ion channels, or in neurotransmitter synthesis, metabolism, or uptake.
2. Extracellular: Alterations in ionic environment (partially mediated by glial cells) or synaptic structure.
3. Network: Alterations in synaptic organization; alterations in number or function of inhibitory or excitatory neuronal populations. There is evidence that absence seizures result from aberration in the thalamocortical network that underlies sleep spindle generation.

Molecular Mechanisms

1. Main inhibitory neurotransmitter: γ-aminobutyric acid (GABA), which is a pleomorphic class of receptors linked to the chloride channel, activation of which hyperpolarizes neurons.
2. Main excitatory transmitter: Glutamate acts via several ionotropic (creating ion pores) receptors that are often divided into three groups on the basis of experimental agonists (*N*-methyl D-aspartate [NMDA], AMPA, and kainic

acid). Glutamate also acts on metabotropic receptors affecting intracellular processes more slowly via G-proteins.

Genetics

1. The current view is that a collection of genes and polymorphisms, coding mainly for neurotransmitter receptors and their associated ion channels, determine an individual's "seizure threshold." This threshold influences the likelihood that an individual will develop epilepsy after a brain injury or from a systemic or neurologic derangement.
2. There are also Mendelian syndromes with mutations affecting critical receptors or channels (e.g., autosomal dominant nocturnal frontal lobe epilepsy and the nicotinic acetylcholine receptor, juvenile myoclonic epilepsy [JME] families with mutations in the *GABR1* gene, Dravet syndrome with mutations in SCN1A).
3. Common epilepsy syndromes (childhood absence epilepsy [CAE] and most cases of JME) are likely due mutations of a number of genetic loci, although single gene mutations have also been described (i.e., GABA receptor mutations).
4. Inborn errors of metabolism or of brain development that are frequently accompanied by epilepsy may also have a Mendelian basis (e.g., tuberous sclerosis, lissencephaly syndromes).

PROGNOSIS

Natural History

1. A single unprovoked seizure has a 2-year recurrence rate of 23% to 71%. The recurrence rate after a second seizure is 73%; risk factors for recurrence include family history of epilepsy or an abnormal neurologic examination, seizures occurring out of sleep, somatic dysmorphisms, imaging, or EEG. Recurrent seizures and the presence of some of these additional features implicate a diagnosis of epilepsy.
2. Many childhood-onset epilepsy syndromes remit spontaneously (e.g., benign childhood epilepsy with centrotemporal spikes [BECTS], CAE).
3. Adolescent-onset genetic generalized syndromes (e.g., JME, juvenile

absence epilepsy [JAE]) and structural cases are less likely to remit.

4. Although most epilepsies that respond initially to medical treatment are controlled, there is no evidence that early treatment alters the natural history.

Response to Medical Treatment

1. Approximately half of new cases respond to the first well-tolerated AED.
2. Patients who continue to have seizures despite adequate treatment with one drug have only a 10% to 20% chance of complete response to another one and multiple medications are often instituted (see further on).

Nonmedical Treatment

1. Ketogenic diet
   - **a.** A high-fat diet that produces metabolic changes mimicking starvation can produce marked seizure reductions in 30% to 50% of children with various seizure types. The fat to carbohydrate ⩽ protein ratio is 3:1 or 4:1. Short-term risks of the diet include weight loss, renal stones, acidosis, hemolytic anemia, lethargy, and elevated liver function tests; treatment is usually initiated in the hospital and maintained with the assistance of a dietitian.
   - **b.** The ketogenic diet is very restrictive, time-consuming, and difficult to implement in some patients. As a result, a modification of the Atkins diet has been studied as a viable alternative. In the modified Atkins diet (MAD), the ratio of fat to carbohydrate ⩽ protein is 1:1 which leads to better compliance. Another option is the low glycemic index diet where the fat content is similar to the MAD but the carbohydrate content is higher and the protein content lower.
   - **c.** Much less data are available concerning feasibility, effectiveness, and long-term safety in adults of the ketogenic diet or of less restrictive high-fat, low-carbohydrate diets. In general, the ketogenic diet is less well tolerated in adults.
   - **d.** One of the first-line treatments of patients diagnosed with GLUT1 deficiency.
2. Resective surgery
   - **a.** Drug-resistant patients with an identifiable seizure focus (focal epilepsy)

should be considered for resection of the epileptic focus.

b. In appropriately selected candidates, long-term seizure-free rates range from 60% to 80%. The best prognosis is for those with structural lesions, even subtle ones, especially mesial temporal sclerosis, cavernomas, and low-grade tumors.

3. Palliative procedures

a. For those who are not candidates for resective surgery, several procedures have been shown to produce worthwhile benefit in many patients, although complete seizure remission in only a few.

b. These include disconnection procedures such as corpus callosotomy (section of the major interhemispheric commissures, often the anterior two-thirds of the corpus callosum) used most successfully for drop seizures from a frontal source, or neurostimulation including insertion of a vagus nerve stimulator (VNS), insertion of a responsive neurostimulator (RNS), or deep brain stimulator (DBS).

c. The VNS, which delivers controllable stimulations at programmable intervals to the left vagus nerve, produces a 50% decrease in seizure frequency in 25% to 45% of patients. It is U.S. Food and Drug Administration (FDA)-approved for patients 12 years of age or older with focal seizures, but younger patients and those with generalized epilepsies may respond.

d. Neurostimulation of deep gray nuclei (deep brain stimulation) such as the anterior nucleus of the thalamus has been somewhat successful with 35% to 76% seizure reduction (currently not yet approved in the United States).

e. Responsive neurostimulation involves the implantation of one or two intracranial (depth or surface) electrodes which stimulate the seizure focus upon detection of seizures using an automated algorithm. Median percent reduction at 2 years is 53% with higher rates noted with longer follow-up. Some of the data obtained from the device may lead to a respective surgery if a single “active” focus is identified with chronic monitoring.

f. Complementary and alternative therapies: Such activities as relaxation techniques, yoga, and exercise are under investigation, as are some herbal medicines and dietary supplements. While some of these may prove beneficial, and relaxation and related techniques appear safe, caution must

be exercised with herbal preparations, because some have potentially harmful effects (including lowering the seizure threshold) or may interact with AEDs. Preliminary nonrandomized data are becoming available on cannabidiol oil in children with epileptic encephalopathies, but caution is necessary here as randomized and blinded clinical trials are needed.

Medication Withdrawal

1. In general, patients who have had no seizures for at least 2 years can be considered for medication withdrawal, with the expectation that there will be a recurrence in 20% to 40%.
2. Those patients with only one seizure type, which responded promptly and was controlled for many years on modest doses of one medication, have the best prognosis, particularly if they have normal neurologic examinations, normal imaging studies, and normal EEG. Even a small risk of recurrence may be unacceptable to people with certain lifestyles or occupations that put them at risk for brief loss of consciousness.
3. Specific epilepsy syndromes, such as BECTS or JME, confer different recurrence risks than the overall statistics quoted in list item 1 above.

Mortality in Epilepsy

Patients with epilepsy have a standardized mortality ratio of 1.6 to 9.3 times higher than the general population with SUDEP accounting for 10% to 15% of these deaths. Seizure-related injuries (trauma, drowning), SE, and suicide are some of the other contributors to mortality. The exact pathophysiology of SUDEP is unclear but likely involves cardiac, respiratory, or autonomic compromise, and it tends to afflict patients aged 40 or younger. Risk factors include generalized tonic–clonic seizure frequency, drug-resistant epilepsy, being in a prone position, medication nonadherence, and nocturnal seizures. The duration of postictal generalized EEG suppression (PGES) has also been highlighted but remains controversial. Preventive measures to address SUDEP are unclear, but seizure control seems to be crucial, and other measures such as seizure detection technology or having a witness nearby may also be useful. The importance of counseling about SUDEP and the importance of taking seizure precautions cannot be emphasized enough.

DIAGNOSIS

Differential Diagnosis

1. Transient events that mimic focal or generalized seizures:
   a. Syncope, especially "convulsive syncope" with clonic shaking or tonic extension with pallor after the patient has fallen to the ground.
   b. Migraine (migraine with aura or basilar migraine).
   c. Transient ischemic attack (TIA) (carotid or vertebrobasilar, particularly the uncommon carotid syndrome of "limb-shaking" TIA) or amyloid spells.
   d. Movement disorder (tremor, nonepileptic myoclonus, dyskinesia).
   e. Sleep disorders (specifically narcolepsy–cataplexy syndrome, rapid eye movement [REM] behavior, and somnambulism).
   f. Toxic–metabolic disturbances (distinct from those that can cause seizures), particularly with tremulousness or asterixis.
   g. Psychiatric disorders (dissociative states, psychogenic nonepileptic seizures [PNES], or panic attacks).

Evaluation

1. History: Helpful aspects are recent or remote serious brain injury or illness; sleep deprivation or fever; presence, nature, and duration of warning before seizure and whether either the entire event or the warning was ever experienced before; witness accounts including level of responsiveness, motor manifestations, duration of event and recovery; patient and witness assessment of functioning afterward, particularly focal symptoms, incontinence, mouth/tongue biting, muscle soreness. Also, family history especially of epilepsy in a sibling increases risk for patient.
2. Physical examination: Mental status, focal features, signs of infection or trauma.
3. Laboratory studies: Electrolytes, calcium, magnesium, glucose, renal and liver function tests, toxic screen, and complete blood count (CBC, creatine phosphokinase [CPK]).
4. Ancillary tests: Neuroimaging (magnetic resonance imaging [MRI] preferred to computed tomography [CT]), EEG (as soon as available), lumbar

puncture if infection suspected. Specific MRI epilepsy protocols are available at different centers.

TREATMENT

Antiepileptic Drugs

I. Principles of use:

a. The differences between efficacy of AEDs are less than the differences in pharmacokinetics, drug–drug interactions, adverse effects, and cost.

b. Several AEDs work approximately equally well in any given clinical seizure type.

c. Unless a rapid therapeutic effect is essential, choose a low starting dose and slow upward titration. This is especially true when treating elderly, frail, or medically ill patients.

d. In general, increase the dose until an adequate observation period establishes that seizures are controlled or until dose-related side effects develop. In the latter case, decrease back to the previous dose and monitor response. If seizures are not controlled, another appropriate AED should be initiated and titrated, usually while weaning the patient off the first drug (i.e., monotherapy is always preferable to polytherapy unless there is no alternative).

e. Sometimes, increases in dose result in increased seizures. The dose should be reduced and the drug is replaced by an alternative AED.

f. Off-label use is justifiable if approved AEDs are not successful or the risk with the off-label alternative appears lower than that with the approved AED.

g. The most common drug interactions involving AEDs are based on induction, or, less commonly, inhibition, of the hepatic mixed-function oxidase or P450 enzyme system or other interactions that involve glucuronidation pathways. As a group, the older AEDs have much stronger effects on these systems than do the newer ones, although several of the latter are substrates whose metabolism is affected by addition or withdrawal of the older drugs. Chronic enzyme induction in the setting of AEDs has been associated with a decreased efficacy of chemotherapeutic,

immunosuppressive, and antiretroviral therapy. In addition, enzyme induction affects sex hormones and can lead to sexual dysfunction, osteopenia or osteoporosis (increased risk of fractures), and increased serologic markers of vascular risk including elevated cholesterol.

h. Serum drug concentrations (drug levels) can be useful in pregnancy in verifying adherence or in providing an initial target for patients with infrequent seizures, but if used mechanically as a guide to dosing, these can hinder rather than help in achieving the goal of treatment: no seizures and no side effects (and ultimately, optimizing quality of life). Even for the older AEDs, published therapeutic ranges have limited scientific support, and individuals may have therapeutic responses or adverse effects either below or above this range. For the newer AEDs, therapeutic ranges are even more provisional, but these are included in the following discussions for completeness.

2. Specific AEDs: The common medications for seizures are categorized in several ways. Classifications based on biochemical mechanism are logical but of limited clinical value in that several drugs work by more than one mechanism and, for many, the mechanisms are poorly understood. We find it more useful to group the drugs by their spectrum of action for specific seizure types:

a. The first and the largest group of AEDs is effective against focal seizures, including those evolving into bilateral convulsive seizures. Most, if not all, of these also prevent primarily generalized tonic–clonic seizures; however, they are not effective against, and may worsen, other generalized seizure types, including absence and myoclonic seizures. Drugs in this class include carbamazepine (CBZ), PHT, phenobarbital (PHB), primidone (PRM), gabapentin (GBP), oxcarbazepine (OXC), tiagabine (TGB), pregabalin (PGB), eslicarbazepine (ESL), lacosamide (LAC), retigabine (RTG), vigabatrin (VGB), and brivaracetam (BRV).

b. The second group is the “broad-spectrum” AEDs with activity against a variety of generalized and focal seizures. The most familiar drug with this characteristic is valproate (VPA). A similar broad spectrum has been attributed to some newer drugs such as lamotrigine (LTG), topiramate (TPM), levetiracetam (LEV), zonisamide (ZNS), perampanel (PER), felbamate (FBM), and rufinamide (RFA).

c. The third group includes drugs that do not easily fit in the above categories, including ethosuximide (ESX), a narrow-spectrum AED with established efficacy against only typical generalized absence seizures. (Interestingly, the closely related methosuximide has a broader spectrum and is effective against focal seizures as well.) There are other less commonly used adjunctive drugs, not strictly speaking antiepileptics, that have special uses, such as acetazolamide (ACZ), adrenocorticotropic hormone (ACTH) for infantile spasms, and pyridoxine.

d. Finally, there are medications used in seizure clusters and SE, alcohol, and other drug-related seizures. These include intravenous (IV), sublingual, intranasal, and rectal benzodiazepines, fosphenytoin (fosPHT), midazolam, propofol, and anesthetic agents.

e. Polytherapy: When adding a second agent to a first one, medications with similar mechanisms of action should be avoided (e.g., PGB ≤ GBP, ESL ≤ OXC, ESL ≤ OXC, OXC ≤ CBZ, ZNS ≤ TPM). There is some evidence for synergism with VPA ≤ LTG and VPA ≤ ESX.

3. A number of AEDs have a black box warning of increased suicidality. There has been criticism of the warning as the data did not account for prior psychiatric history and drugs were grouped together. Psychiatric comorbidities are common in epilepsy with a prevalence of 25% to 40% of mood disorders and 20% to 30% anxiety disorders. Medications that can worsen mood include barbiturates, LEV, TPM, and ZNS.

Drugs Predominantly Used for Focal Epilepsy

Carbamazepine

1. Advantages: Considered a first-choice drug for focal seizures and can also work for tonic–clonic seizures (primary and those evolving from focal); familiarity; slow-release preparations allow twice a day (b.i.d.) dosing.
2. Disadvantages: Need to titrate slowly to avoid dose-related adverse effects, pharmacokinetic interactions (P450 enzyme inducer and substrate). Ineffective against absence or myoclonic seizures and may trigger SE in these patients. Weight gain.
3. Major adverse effects:

a. Dose-related: dizziness, diplopia, nausea, sedation, mild leukopenia,

hyponatremia, bradyarrhythmias (elderly)

b. Idiosyncratic: rash (including Stevens–Johnson syndrome [SJS] especially in HLA-B*1502 carriers highest in those of Asian descent), agranulocytosis, hepatic failure, pancreatitis, lupus-like syndrome

c. Chronic: effects of chronic enzyme induction (drug–drug interactions), effects on hormones, osteopenia/osteoporosis (possibly mitigated by vitamin D supplementation), elevated cholesterol, and serum vascular risk markers.

4. Teratogenicity: Dose-dependent, low doses (<400 mg) are less teratogenic with a rate of 3.4%, whereas rates with higher doses (>1,000 mg) are 8.7%.
5. Initiation and titration: 100 to 200 mg at night (hs) or 100 mg b.i.d.; increase after 3 to 7 days to 200 mg b.i.d. Can check blood tests after 1 week on this dose: CBZ level, CBC/differential, electrolytes (Na), and perhaps albumin and aspartate aminotransferase (AST) levels. Dose can be increased at 3- to 7-day intervals to obtain a level of 4 to 12 mg/L; level is typically rechecked in 4 to 6 weeks, as autoinduction of enzymes may necessitate further increases. Usual maintenance doses in adults are as follows: 600 to 1,600 mg/d, up to 2,400 mg/d. In children, start at 5 to 10 mg/kg/d, maintenance 15 to 20 mg/kg/d, up to 30 mg/kg/d.
6. Pharmacokinetics: Half-life: 12 to 20 hours (shorter with enzyme-inducing drugs; autoinduction also occurs, with level falling after 2 to 6 weeks on stable dose), protein binding: 70% to 80%.
7. Usual therapeutic range: 4 to 12 mg/L.
8. Preparations: 100- and 200-mg tablets; suspension 100 mg/5 mL (can solidify in tube feedings); slow-release preparations including brand Tegretol-XR 100-, 200-, and 400-mg caplets and Carbatrol 200- and 300-mg capsules. Carnexiv-IV carbamazepine has FDA approval as replacement therapy for oral formulations when oral administration is not feasible.

Oxcarbazepine

1. Advantages: More rapid titration than CBZ, b.i.d. dosing, minor interactions, no known hepatic or hematologic adverse effects; approved as initial monotherapy for focal seizures.
2. Disadvantages: Dose-related effects similar to those of CBZ; although induces P450 only weakly, it can lower hormone (e.g., contraceptive)

levels. Ineffective against absence or myoclonic seizures. Weight gain.

3. Comment: Very similar chemically to CBZ but not converted into epoxide metabolite, which accounts for many adverse effects of CBZ.
4. Major adverse effects:
   a. Dose-related: dizziness, diplopia, hyponatremia (greater than CBZ), somnolence, ataxia, gastrointestinal (GI) upset
   b. Idiosyncratic: rash (25% cross-reactivity with CBZ)
   c. Chronic: Effects of chronic enzyme induction (drug–drug interactions), effects on hormones, osteopenia/osteoporosis (possibly mitigated by vitamin D supplementation), elevated cholesterol, and serum vascular risk markers.
5. Teratogenicity: Unknown.
6. Initiation and titration: Adults—150 to 300 mg b.i.d., increasing by 300 to 600 mg every 1 to 2 weeks to target of 1,200 to 2,400 mg/d; children (older than 4 years)—8 to 10 mg/kg/d titrated to 20 to 40 mg/kg/d. Note: Conversion from CBZ can be rapid, over 1 day to 2 weeks, at a ratio of 300 mg OXC to 200 mg CBZ.
7. Pharmacokinetics: Half-life of 2 hours but converted into active monohydroxy-derivative (MHD) with half-life of 8 to 10 hours; protein binding: 40%.
8. Therapeutic range: 10 to 35 mg/L (MHD).
9. Preparations: Trileptal or generic tablets 150, 300, 600 mg; syrup 300 mg/5 mL. Extended release also available (Oxtellar) 150, 300, 600 mg.

Eslicarbazepine

1. Advantages: Milder enzyme induction compared to CBZ and OXC; oral contraceptives may need to be adjusted. Once daily dosing, lower risk of rash and hyponatremia. Approved for conversion to monotherapy in refractory epilepsy.
2. Disadvantages: Weak cytochrome P450 induction. Ineffective against absence or myoclonic seizures.
3. Comment: Very similar chemically to CBZ and OXC but not converted into epoxide metabolite and exclusively to (S) enantiomer believed to be more effective and better tolerated.
4. Major adverse effects:

   a. Dose-related: dizziness, diplopia, somnolence, ataxia, GI upset
   b. Idiosyncratic: none
   c. Chronic: effects of chronic enzyme induction
5. Teratogenicity: Unknown.
6. Initiation and titration: 400 mg once daily (q.d.), increase by 400 mg every week. Aim for 800 to 1,200 mg in monotherapy, up to 1,600 mg with polytherapy. No data in children.
7. Pharmacokinetics: Hepatic clearance. Half-life of 13 to 20 hours; protein binding: <40%.
8. Therapeutic range: Unavailable.
9. Preparations: Aptiom 200, 400, 600, 800 mg.

Phenytoin

1. Advantages: Works for focal seizures and can also work for tonic–clonic seizures (those evolving from focal); physician familiarity and long history in medical use; long duration of action, especially with slow-release preparations—usually b.i.d. dosing but can be q.d.; parenteral loading options.
2. Disadvantages: As the dose of PHT increases, plasma levels rise to a disproportionate degree because of saturation of metabolic pathway, referred to as nonlinear or zero-order kinetics; pharmacokinetic interactions (strong P450 inducer); chronic cosmetic and other adverse effects. Levels can vary on a day-to-day basis and adjustments can lead to toxicity and breakthrough seizures.
3. Major adverse effects:
   a. Dose-related: dizziness, ataxia, diplopia, nausea
   b. Idiosyncratic: rash, including SJS; blood dyscrasias; hepatic failure; lupus-like syndrome
   c. Chronic: gingival hyperplasia, hirsutism, neuropathy, pseudolymphoma, and controversially, lymphoma, cerebellar degeneration; effects of chronic enzyme induction (drug–drug interactions), effects on hormones, osteopenia/osteoporosis (possibly mitigated by vitamin D supplementation), elevated cholesterol, and serum vascular risk markers
4. Teratogenicity: 2.9%. Risk of fetal hydantoin syndrome (distinctive dysmorphic features, risk of developmental delay, microcephaly) incidence

unknown.

5. Initiation and titration: Adults—in nonemergent situations, can load orally; two doses of 500 mg or three doses of 300 mg can be taken 4 to 6 hours apart. Parenteral loading can be achieved IV (15 mg/kg, or 20 mg/kg for SE, not more than 50 mg/min; precursor drug fos-PHT may be preferable for status). When loading is not needed, can initiate estimated maintenance dose of 300 to 400 mg/d, usually in two doses, checking levels in 1 to 2 weeks. Because of zero-order kinetics, increases must be proportionately less as the level rises; for example, if the steady-state level on 300 mg/d is 12 mg/L, then 330 mg/d, a 10% dose increase, may be sufficient to raise the level to 18, a 50% increase. Pediatrics: 4 to 5 mg/kg/d, up to 8 mg/kg or more depending on level.
6. Pharmacokinetics: Half-life depends on the serum concentration and is longer at higher concentrations, for example, 20 to 30 hours when in usual therapeutic range; protein binding: 90% (lower with renal failure or hypoalbuminemia).
7. Usual therapeutic range: 10 to 20 mg/L (arguably 5 to 25 mg/L).
8. Preparations: Dilantin tablets 50 mg, Dilantin and generic extended-release capsules 30 and 100 mg, and suspension 125 mg/5 mL (must be adequately mixed in bottle); Phenytek capsules 200 and 300 mg. Fos-PHT used for rapid loading IV.

Gabapentin

1. Advantages: Rapid titration, relatively well tolerated, no pharmacokinetic interactions, additional uses (neuropathic pain).
2. Disadvantages: Three or four times daily (t.i.d. and q.i.d., respectively) dosing recommended (although it can be given b.i.d.); less efficacious than other AEDs except perhaps in elderly.
3. Major adverse effects:
   a. Dose-related: sedation, dizziness, ataxia
   b. Idiosyncratic: weight gain, rash (rare), behavioral changes in children, myoclonus
   c. Chronic: none known
4. Teratogenicity: Unknown.
5. Initiation and titration: 300 mg hs, increasing by 300 mg every 1 to 7 days to

target of 1,800 to 3,600 mg/d; in elderly, 100 mg hs or b.i.d., increasing in 100- to 200-mg increments; pediatrics (older than 3 years), 10 to 20 mg/kg/d increasing to target of 30 to 60 mg/d.

6. Pharmacokinetics: Half-life: 5 to 7 hours (but brain kinetics likely slower); protein binding: none.
7. Therapeutic range: 4 to 16 mg/L.
8. Preparations: Neurontin or generic capsules 100, 300, 400 mg; tablets 600 and 800 mg; solution 250 mg/5 mL. XR formulation (Horizant) is only approved for restless leg syndrome.

Pregabalin

1. Advantages: No pharmacokinetic interactions, additional uses (neuropathic pain, migraines).
2. Disadvantages: Relatively slow titration owing to sedation, weight gain.
3. Major adverse effects:
   - **a.** Dose-related: sedation (may potentiate ethanol, benzodiazepine effects), dizziness, ataxia
   - **b.** Idiosyncratic: weight gain, rash (rare), myoclonus
   - **c.** Chronic: none known
4. Teratogenicity: Unknown.
5. Initiation and titration: 75 to 100 mg hs, increasing by a similar amount mg every 1 to 2 weeks to target of 300 to 600 mg/d in two divided doses; adjust for renal impairment.
6. Pharmacokinetics: Half-life: 4 to 7 hours (but brain kinetics likely slower); protein binding: none.
7. Provisional therapeutic range: 4 to16 mg/L.
8. Preparations: capsules 25, 50, 75, 100, 150, 200, 225, 300 mg.

Tiagabine

1. Advantages: May have antianxiety or analgesic effects; can sometimes be given b.i.d.
2. Disadvantages: Sedating; risk of nonconvulsive SE (NCSE); P450 induction.
3. Major adverse effects:
   - **a.** Dose-related: dizziness, somnolence, nausea, cognitive slowing

   b. Idiosyncratic: rash, mood changes, generalized NCSE (doses 48 mg/d or greater)
   c. Chronic: unknown
4. Teratogenicity: Unknown.
5. Initiation and titration: 2 to 8 mg/d, increasing by 2 to 8 mg/d at weekly intervals to target of 24 to 56 mg/d in two to four doses; pediatrics (older than 12 years): 4 mg/d, increasing by 4 mg/wk to target of 20 to 32 mg/d.
6. Pharmacokinetics: Half-life: 4 to 9 hours, protein binding: 96%.
7. Provisional therapeutic range: 0.1 to 0.3 mg/L.
8. Preparations: Gabitril film tabs 2, 4, 12, 16, 20 mg.

Phenobarbital

1. Advantages: Long half-life (daily dosing), inexpensive.
2. Disadvantages: Drowsiness, cognitive and behavioral side effects, interactions (induces P450).
3. Major adverse effects:
   a. Dose-related: sedation, depression, cognitive impairment
   b. Idiosyncratic: rash, hyperactivity (children), hepatic failure (rare), aplastic anemia (rare)
   c. Chronic: connective tissue disorders (e.g., frozen shoulder, Dupuytren contractures); effects of chronic enzyme induction (drug–drug interactions), effects on hormones, osteopenia/osteoporosis (possibly mitigated by vitamin D supplementation), elevated cholesterol and serum vascular risk markers
4. Teratogenicity: Yes, 5.5% rates of major malformations.
5. Initiation and titration: 90 to 250 mg/d, can load IV with up to 20 mg/kg (<100 mg/h for SE), but sedation is universal; check steady-state levels in 2 to 3 weeks (4 to 5 weeks in presence of VPA); pediatrics: 2 to 7 mg/kg/d.
6. Pharmacokinetics: Half-life: 72 to 168 hours (less in children; more when coadministered with VPA).
7. Usual therapeutic range: 10 to 40 mg/L.
8. Preparations: Tablets 15, 30, 60 (or 62.5), 100 mg; suspension 15 or 20 mg/5 mL; parenteral 30, 60, 130 mg/mL.

Primidone

1. Advantages: Parent compound may have efficacy beyond that of PHB metabolite, at least against myoclonic seizures; effective against tremor at low doses.
2. Disadvantages: Possibly more sedating than PHB alone; must be taken in divided doses, usually t.i.d. or q.i.d.; strongly induces P450.
3. Comment: Metabolized to PHB.
4. Major adverse effects:
   a. Dose-related: same as PHB
   b. Idiosyncratic: same as PHB
   c. Chronic: same as PHB
5. Teratogenicity: Yes, but rate unclear.
6. Initiation and titration: 100 to 125 mg hs, increasing by 125 to 250 mg every 2 to 7 days to target of 500 to 1,500 mg/d; pediatrics: 50 mg/d increasing to 10 to 25 mg/kg/d.
7. Pharmacokinetics: Half-life: 6 to 22 hours (72 to 168 hours for PHB metabolite); P450 inducers promote conversion to PHB.
8. Usual therapeutic range: 5 to 12 mg/L (10 to 40 mg/L for PHB).
9. Preparations: Mysoline and generic tablets 50 and 250 mg; suspension 250 mg/5 mL.

Lacosamide

1. Advantages: Rapid titration, relatively well tolerated, low pharmacokinetic interactions (limited metabolism by CYP2C19), availability of IV and oral solution, additional use (neuropathic pain). Some preliminary data also for efficacy in primary generalized tonic–clonic seizures.
2. Disadvantages: Narrow effective dose range.
3. Major adverse effects:
   a. Dose-related: dizziness, headache, diplopia/blurred vision, ataxia, nausea/vomiting; increase in P-R interval on EKG
   b. Idiosyncratic: none
   c. Chronic: unknown
4. Teratogenicity: Unknown.
5. Initiation and titration: Start 50 mg p.o./IV b.i.d. and increase by 50 mg b.i.d. up to 100 to 200 mg b.i.d. to maximum of 400 mg/d unless severe hepatic or renal impairment. In the acute setting, a loading dose of 100 to

300 mg can be used, with a maintenance dose of up to 600 mg.

6. Pharmacokinetics: Renal clearance. Half-life: 13 hours; protein binding: less than 15%.
7. Provisional therapeutic range: 2.5 to 18 mg/L.
8. Preparations: Vimpat 50-, 100-, 150-, 200-mg tablets; 200 mg/20 mL solution IV; 10 mg/mL solution p.o.

Vigabatrin

1. Advantages: Efficacious for infantile spasms; also works in focal epilepsy.
2. Disadvantages: Main limitation is its effects on peripheral vision loss (up to 30% in adults). In clinical practice, now limited to children with infantile spasms. Use of the medication necessitates frequent ophthalmologic evaluations.
3. Major adverse effects:
   - **a.** Dose-related: somnolence, headache, dizziness, sedation, upper respiratory tract infections (more common in infants)
   - **b.** Idiosyncratic: loss of peripheral vision, increases with cumulative exposure
   - **c.** Chronic: unknown
4. Teratogenicity: Unknown.
5. Initiation and titration: Adults: 500 mg b.i.d., increase by 500 mg weekly until 1.5 g b.i.d. In children, 250 mg b.i.d. with a maximal dose of 1 g b.i.d. For infants with infantile spasms, 50 mg/kg/d divided into two doses, increase by 25 to 50 mg/kg every 3 days up to 150 mg/kg/d.
6. Pharmacokinetics: Renal clearance. Half-life: 5 to 10 hours.
7. Usual therapeutic range: 0.8 to 36 mg/L.
8. Preparations: Sabril 500-mg tablets.

Retigabine

1. Advantages: Unique mechanism of action by affecting potassium channels. May have a role in genetic epilepsies affecting potassium channels.
2. Disadvantages: Its use has been limited because of retinal and skin pigment changes. Patients require serial ophthalmologic testing.
3. Major adverse effects:
   - **a.** Dose-related: dizziness, drowsiness, fatigue

   b. Idiosyncratic: retinal and skin pigment changes (bluish discoloration), urinary retention
   c. Chronic: unknown
4. Teratogenicity: Unknown.
5. Initiation and titration: 100 mg t.i.d., increase by 100 to 150 mg every week up to a total dose of 400 mg t.i.d.
6. Pharmacokinetics: Hepatic clearance. Half-life: 7 to 11 hours; protein binding: 80%.
7. Usual therapeutic range: Unknown.
8. Preparations: Potiga 50-, 200-, 300-, 400-mg tablets.

Brivaracetam

1. Advantages: No drug–drug interactions, several solutions. May also turn out to be a broad-spectrum agent similar to LEV. Quick titration.
2. Disadvantages: New; data limited. In studies, it did not offer an additional advantage when patients were on LEV.
3. Major adverse effects:
   a. Dose-related: dizziness, drowsiness, fatigue
   b. Idiosyncratic: none
   c. Chronic: unknown
4. Teratogenicity: Unknown.
5. Initiation and titration: 50 mg b.i.d. to a maximum of 100 mg b.i.d.; can also be titrated down to 25 mg b.i.d.
6. Pharmacokinetics: Renal clearance. Half-life: 8 to 10 hours; protein binding: <20%.
7. Usual therapeutic range: Unknown.
8. Preparations: Briviact 10-, 25-, 50-, 75-, 100-mg tablets; oral solution 10 mg/mL; injection (50 mg/5 mL).

Broad-Spectrum Medications

Including absence and myoclonic. These drugs also are effective against focal seizures and primary generalized tonic–clonic seizures.

Valproate

1. Advantages: Familiarity, best-established broad-spectrum AED; beneficial effects on migraine, bipolar illness; slow-release preparations allow b.i.d. or possibly daily dosing.
2. Disadvantages: Acute and chronic adverse effects, particularly weight gain; interactions (P450 inhibitor, also competes for protein-binding sites).
3. Major adverse effects:
   a. Dose-related: GI upset, anorexia, tremor, thrombocytopenia
   b. Idiosyncratic: pancreatitis (up to 1 in 200), hepatic failure (especially infants on polytherapy), stupor and coma, rash, hyperammonemia, thrombocytopenia/thrombocytopathy
   c. Chronic: weight gain, hair loss, or change in texture; possibly polycystic ovarian syndrome
4. Teratogenicity: Yes, higher rates of all AEDs 9.5% but can be as high as 24% with doses >1,500 mg. Higher rates of autism and lower IQ in children exposed.
5. Initiation and titration: 250 mg b.i.d. to t.i.d., increasing by 250 to 500 mg weekly to target of 750 to 2,000 mg/d (higher if also on enzyme-inducing drugs); pediatrics: 10 to 15 mg/kg/d, increasing by 5 to 10 mg/kg/wk to 15 to 30 mg/kg/d (maximum, 60 mg/kg/d).
6. Pharmacokinetics: Half-life: 10 to 20 hours; up to 95% protein bound, less at higher levels; partial P450 inhibitor, elevating particularly PHB and LTG.
7. Usual therapeutic range: 50 to 120 mg/L.
8. Preparations: Depakene or generic valproic acid capsules 250 mg, syrup 250 mg/5 mL; Depakote delayed-release tablets 125, 250, and 500 mg; Depakote sprinkles slow-release capsules 125 mg; brand Depakote and generic VPA-ER extended-release capsules 250 and 500 mg; Depacon infusion 100 mg/5 mL.

Lamotrigine

1. Advantages: Broad spectrum, including Lennox–Gastaut syndrome (LGS); well tolerated, relatively nonsedating; good evidence suggesting safety during pregnancy; approved as monotherapy (for focal seizures) when transitioned from enzyme-inducing AED; b.i.d. dosing.
2. Disadvantages: Slow titration needed to minimize rash risk; susceptible to enzyme induction and significant reduction with hormones and pregnancy.

3. Major adverse effects:
   a. Dose-related: dizziness, ataxia, drowsiness (or insomnia)
   b. Idiosyncratic: rash 5% to 10% (including 0.1% SJS, higher in children), hypersensitivity syndrome
   c. Chronic: none known
4. Teratogenicity: Favorable profile (2% to 3% but not different than baseline risk in women).
5. Initiation and titration: Differs greatly depending on concurrent use of other drugs, for example, if used to supplement enzyme-inducing AEDs (i.e., CBZ, PHT): 50 mg/d for 2 weeks, then 50 mg b.i.d. for 2 weeks, then increase by 50 to 100 mg weekly to target of 300 to 500 mg/d; however, with noninducing AEDs (or for off-label initial monotherapy), 25 mg every other day (q.o.d.) for 2 weeks, then 25 mg q.d. for 2 weeks, then increase by 25 to 50 mg every 1 to 2 weeks to 100 to 300 mg/d. Pediatrics (older than 2 years): With enzyme-inducing AEDs, 2 mg/kg/d for 2 weeks, increasing by similar amount to 5 to 15 mg/kg/d; extra caution with VPA, 0.1 to 0.2 mg/kg/d for 2 weeks, increasing by 0.5 to 1 to 5 mg/kg/d.
6. Pharmacokinetics: P450 substrate; half-life approximately 24 hours alone (or combination of inducing drugs and VPA), 15 hours with inducing drugs, 60 hours with VPA and no inducing drugs.
7. Therapeutic range: 2 to 20 mg/L.
8. Preparations: Lamictal or generic tablets 25, 100, 150, and 200 mg; chewable dispersible tablets 2, 5, 10, and 25 mg; Lamictal XR or generic 25, 50, 100, 200, 250, 300 mg.

Topiramate

1. Advantages: Broad spectrum, including LGS; sometimes effective at low dose; weight loss; b.i.d. dosing.
2. Disadvantages: Slow titration needed to minimize central nervous system (CNS) adverse effects; weight loss; at high dose can interfere with oral contraceptives.
3. Major adverse effects:
   a. Dose-related: cognitive slowing, word-finding difficulties, paresthesias, dizziness
   b. Idiosyncratic: rash, GI upset, narrow-angle glaucoma; irritability

c. Chronic: renal stones (1% to 2%; less in women), weight loss

4. Teratogenicity: Yes, 4.2%; highest rates of in utero growth restriction.
5. Initiation and titration: 25 mg/d, increasing by 25 mg/d per 1 to 2 weeks to 200 mg/d or higher. Pediatrics (>2 years): 1 to 3 mg/kg/d, increasing by similar amount every 1 to 2 weeks to 5 to 9 mg/kg/d.
6. Pharmacokinetics: Renal and hepatic; is susceptible to enzyme induction; may elevate PHT levels slightly.
7. Therapeutic range: 5 to 20 mg/L provisionally.
8. Preparations: Topamax or generic tablets 25, 100, 200 mg; sprinkles capsules 15, 25 mg; Trokendi XR capsule or Qudexy XR sprinkle 25, 50, 100, 150, 200 mg.

Levetiracetam

1. Advantages: Therapeutic starting dose; efficacy, lack of interactions; b.i.d. dosing.
2. Disadvantages: Irritability and behavioral effects including depression.
3. Major adverse effects:
   a. Dose-related: sedation, dizziness
   b. Idiosyncratic: GI intolerance, depression, irritability
   c. Chronic: none known

4. Teratogenicity: Some data showing favorable profile.
5. Initiation and titration: 250 to 500 mg b.i.d., increasing by 500 mg/d every 1 to 2 weeks to target of 1,000 to 3,000 mg/d. Pediatrics (older than 12 years): 10 to 20 mg/kg/d, increasing by 5 to 10 mg/kg every 1 to 2 weeks to 40 mg/kg/d.
6. Pharmacokinetics: Renally excreted; half-life: 6 to 8 hours, but water-soluble, suggesting brain kinetics slower.
7. Therapeutic range: 10 to 40 mg/L.
8. Preparations: Keppra or generic tablets 250, 500, 750, 1,000 mg; Keppra XR or generic 500, 750 mg long-acting tablet; suspension 100 mg/5 mL.

Zonisamide

1. Advantages: Broad spectrum, long half-life allowing q.d. dosing, weight loss.
2. Disadvantages: Slow titration, sedation.

3. Major adverse effects:
   a. Dose-related: fatigue, confusion, dizziness
   b. Idiosyncratic: rash (can progress to SJS; cross-reacts with sulfa drugs), hypohidrosis
   c. Chronic: renal stones
4. Teratogenicity: Unknown.
5. Initiation and titration: 50 mg/d for 2 weeks, then increase by 50 mg every 2 weeks to 400 mg/d. Pediatrics: 2 to 4 mg/kg/d, increasing by similar amount every 1 to 2 weeks to 8 mg/kg/d.
6. Pharmacokinetics: P450 substrate; half-life: 60 hours, but 25 to 30 with inducers.
7. Therapeutic range: 10 to 40 mg/L.
8. Preparation: Trade (Zonegran) or generic 25-, 50-, 100-mg capsule.

Perampanel

1. Advantages: Unique mechanism of action by affecting AMPA channels; evidence for broad-spectrum coverage; once daily administration.
2. Disadvantages: FDA warning regarding behavioral side effects (hostility, anger, irritability, homicidal ideation).
3. Major adverse effects:
   a. Dose-related: dizziness, vertigo, gait instability, aggressive behavior/hostility
   b. Idiosyncratic: drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome
   c. Chronic: unknown
4. Teratogenicity: Unknown.
5. Initiation and titration: Patients on enzyme-inducing drugs: 4 mg once a day, increase by 2 mg every 1 to 2 weeks up to 12 mg. On no enzyme-inducing drugs: 2 mg once a day, increase by 2 mg every 1 to 2 weeks up to 8 to 12 mg.
6. Pharmacokinetics: Half-life: 105 hours; protein binding: 95%.
7. Usual therapeutic range: 0.05 to 0.4 mg/L.
8. Preparations: 2-, 4-, 6-, 8-, 10-, 12-mg tablets.

Felbamate

1. Advantages: Broad spectrum, including LGS; efficacious, nonsedating; approved as initial monotherapy (for focal seizures). Can be dosed b.i.d., although t.i.d. usually better tolerated.
2. Disadvantages: Drug interactions; risk of potentially fatal aplastic anemia (1 in 5,000) and hepatic failure (1 in 10,000).
3. Major adverse effects:
   a. Dose-related: anxiety, insomnia, fatigue, ataxia
   b. Idiosyncratic: rash, aplastic anemia, hepatic failure
   c. Chronic: weight loss
4. Teratogenicity: Unknown.
5. Pharmacokinetics and interactions: Half-life: 15 to 20 hours but shortened by inducers. May act as enzyme inhibitor, elevating PHT, VPA, and PHB; however, reduces CBZ.
6. Initiation and titration: 600 mg b.i.d., increasing by 600 mg/d weekly to target of 2,400 to 4,800 mg/d. Pediatrics: 10 to 15 mg/kg/d, increasing to 20 to 40 mg/kg/d. Blood monitoring of blood counts and liver functions recommended 1 month after initiation and then every 3 months afterward.
7. Therapeutic range: Provisionally 40 to 100 mg/L.
8. Preparations: Felbatol or generic tablets 400, 600 mg; suspension 600 mg/5 mL.

Rufinamide

1. Advantages: Minimal drug interactions and low cognitive side effects. FDA-approved for LGS which is what it is mainly used for.
2. Disadvantages: Interacts with contraceptive pill; limited long-term experience.
3. Major adverse effects:
   a. Dose-related: sedation, dizziness, ataxia
   b. Idiosyncratic: AED hypersensitivity syndrome
   c. Chronic: none known
4. Teratogenicity: Unknown.
5. Initiation and titration: 400 to 800 mg b.i.d., increasing by 400 to 800 mg q.d. every 2 days to target of 3,200 mg. For pediatrics, 10 mg, increasing by 10 mg every 2 days to target of 45 mg divided b.i.d.
6. Pharmacokinetics: Half-life: 6–10 hours; protein binding: 34%.

7. Provisional therapeutic range: 30 to 40 μg/mL.
8. Preparations: Banzel capsules 200, 400 mg.

Drugs with Narrow Spectrum or Use in Specific Seizure Types

Ethosuximide

1. Advantages: Long half-life; usually b.i.d. dosing; effective against absence seizures.
2. Disadvantages: Narrow spectrum, absence seizures only well-established target.
3. Major adverse effects:
   a. Dose-related: sedation, headache
   b. Idiosyncratic: rash, psychiatric decompensation, GI upset, lupus-like syndrome
   c. Chronic: none known
4. Teratogenicity: Unknown.
5. Initiation and titration: 250 mg b.i.d., increasing by 250 mg/d at weekly intervals to 500 to 1,000 mg/d; pediatrics (older than 3 years): 250 mg/d increasing by 250 mg/wk to 15 to 20 mg/kg/d.
6. Pharmacokinetics: Hepatic metabolism, no protein binding; half-life: 30 to 60 hours.
7. Therapeutic range: 40 to 100 mg/L.
8. Preparations: Zarontin capsules or generic 250 mg; solution 250 mg/5 mL.

Methsuximide

1. Advantages: Broad spectrum, including focal seizures, long half-life—dosing usually b.i.d. but can be q.d. Mainly used for absences.
2. Disadvantages: Slow titration; CNS side effects, lack of familiarity to many clinicians.
3. Major adverse effects:
   a. Dose-related: sedation, headache
   b. Idiosyncratic: rash (including SJS), psychiatric difficulties, GI upset, lupus-like syndrome, leukopenia

c. Chronic: none known

4. Teratogenicity: Unknown.
5. Pharmacokinetics: Half-life of active metabolite, *N,N*-desmethylmethsuximide 34 to 80 hours in adults, 16 to 45 hours in children; level can be lowered by enzyme inducers; may elevate PHT, decrease CBZ.
6. Initiation and titration: 300 mg qhs for 1 to 2 weeks, increasing by 300 mg every 1 to 2 weeks to target of 900 to 1,200 mg/d. Pediatric dose of methsuximide: 150 mg/d increasing by 150 mg/wk until the blood level of the active metabolite *N*-desmethylmethsuximide (NDM) reaches 20 to 40 µg/mL.
7. Therapeutic range: 10 to 40 mg/L (*N,N*-desmethylmethsuximide).
8. Preparations: Celontin capsules 150 and 300 mg.

Acetazolamide

1. Advantages: Well tolerated, typically used adjunctively for absence seizures but may be used for partial seizures and intermittently for catamenial (menses-related) seizure exacerbations.
2. Disadvantages: Probably low efficacy; should not be used with TPM or ZNS (renal stones).
3. Major adverse effects:
   a. Dose-related: paresthesias, weakness, hyponatremia, hypokalemia
   b. Idiosyncratic: anorexia, rash, blood dyscrasias
   c. Chronic: osteomalacia
4. Teratogenicity: Yes.
5. Pharmacokinetics: Half-life: 2 to 13 hours.
6. Initiation and titration: 250 to 500 mg/d increasing to 500 to 1,000 mg/d (b.i.d. or t.i.d.); pediatrics (≥4 years): 4 mg/kg/d increasing over weeks to 8 to 30 mg/kg/d.
7. Therapeutic range: None determined.
8. Preparations: Diamox tablets 125 and 250 mg; slow release, 500 mg; suspension 50 mg/mL.

Benzodiazepines

These differ from each other mainly by pharmacokinetics and available routes of administration. Adverse effects include mainly sedation and slowed

cognition as well as ventilatory suppression when given IV.

1. Clonazepam: Adjunctive therapy for myoclonic and atonic seizures, less often partial seizures; half-life: 20 to 40 hours, shortened by enzyme inducers. Initial dose 0.5 mg q.d. or b.i.d., increasing in 0.5 mg/d intervals every 3 to 7 days to target of 1.5 to 4 mg/d. Preparations: tablets 0.5, 1, and 2 mg. Disintegrating tablet formulations available.
2. Clorazepate: Same as clonazepam (although approved for partial seizures); half-life: 55 to 100 hours. Initial dose 3.75 mg b.i.d. to t.i.d., increasing by 3.75 to 7.5 mg every week to 15 to 45 mg/d. Preparations: tablets 3.75, 7.5, and 15 mg; slow-release tablets 11.25 and 22.5 mg.
3. Diazepam (DZ): Rarely used orally but widely used intravenously for SE and rectally for acute repetitive seizures. Half-life of active metabolite, desmethyldiazepam, is 20 to 40 hours, but when given IV, it is redistributed out of the brain into other fatty tissues; it is also highly protein bound (99%). Therefore, when given IV, although onset of action is extremely rapid, 1 to 2 minutes, duration of action is only 15 to 20 minutes. Preparation: 5 mg/mL solution. As rectal gel (Diastat), it is dosed according to age and weight and is available in rectal syringes of 2.5, 5, 10, 15, and 20 mg.
4. Lorazepam (LZ): Used IV for SE, onset of action is slightly faster than DZ, 4 to 5 minutes, but remains in brain much longer, with duration of action of 4 to 10 hours. Protein binding is 90%. Oral LZ rarely used chronically but can be given sublingually for seizure clusters, especially if the patient is too awake between seizures to tolerate rectal DZ gel. Preparations: tablets 0.5, 1, and 2 mg; solution 0.5, 1, or 2 mg/mL.
5. Midazolam: IM/IV for SE as alternative to DZ or LZ and as infusion when status becomes refractory. Half-life is 1 to 2 hours. Preparation: vials 1 or 5 mg/mL.
6. Clobazam: Approved for adjunctive therapy in LGS. Unlike other benzodiazepines, has a role in chronic treatment. Used in short courses in Europe for catamenial epilepsy and may have a role in myoclonic seizures. Dosing is 5 mg b.i.d. for 1 week, then increase by 10 mg every 1 to 2 weeks up to 40 mg/d. Renally cleared, half-life of 16 hours in children and up to 82 hours in adults. Formulations include Onfi tablets 5, 10, 20 mg and suspension 2.5 mg/mL.

Fosphenytoin

A water-soluble prodrug of PHT; may be given more quickly (up to 150 mg PHT equivalents per minute in adults) and without fear of tissue necrosis in case of extravasation; may also be given intramuscularly (IM) in nonemergent situations. Although it is not given in a propylene glycol vehicle, which has been thought to be largely responsible for the hypotensive effects of PHT, studies have not demonstrated a lower rate of this complication with fos-PHT. Advisable to monitor EKG with rapid infusion, similar to PHT.

Table 2-2 presents a summary of commonly used AEDs.

OVERVIEW OF EPILEPSY PRESENTATIONS AND SYNDROMES

The following describe approaches to common clinical situations and to specific seizure syndromes presented in approximate order of the usual age of presentation.

Neonatal Seizures

Background

1. Neonatal seizures are usually defined as those occurring during the first month or two of life.
2. Probably because brain development at this stage only allows a limited repertoire in comparison to adults, the clinical manifestations are primitive and seizures may be difficult to distinguish from normal behaviors. For example, well-formed tonic–clonic seizures do not occur at this age.
3. Clonic and tonic seizures do occur but typically involve parts of the body in a migrating or asymmetric manner.
4. Myoclonic jerks are more likely to occur bilaterally but may have a nonepileptic pathophysiology in neurologically abnormal neonates. While commonly manifestations of a seizure, apnea, diffuse tonic stiffening, repetitive sucking, pedaling movements, or eye deviation also have the same alternative causes.
5. In general, the EEG is much more essential to seizure diagnosis in neonates than in older children or adults.

Table 2-2 Summary of Commonly Used Antiepileptic Drugs

Drug	Initial Dose	Average Adult Daily Dose	Average Half-Life (hours)	"Therapeutic Range
Brivaracetam (Briviact)	50 mg b.i.d.	50–200 mg	8–10	Unknown
Carbamazepine (Tegretol)	100 mg hs or b.i.d.	600–1,800 mg (15–25 mg/kg)	12–20	6–12 mg/L
Clobazam (Onfi)	5 mg qd or b.i.d.	10–40 mg	10–46	0.03–0.3 mg/L
Clonazepam (Klonopin)	0.5–1.0 mg hs or b.i.d.	1–5 mg (0.03–0.30 mg/kg)	24–48	0.01–0.05 mg/
Eslicarbazepine (Aptiom)	400 mg qd	800–1,600 mg	13–20	Unknown
Ethosuximide (Zarontin)	250 mg hs	500–1,000 mg (10–30 mg/kg)	30–60	40–100 mg/L
Felbamate (Felbatol)	600 mg b.i.d.	3,600 mg	20–24	30–140 mg/L
Gabapentin (Neurontin)	300 mg b.i.d.	1,800 mg	5–7	4–16 mg/L
Lacosamide (Vimpat)	50 mg b.i.d.	200–400 mg	13	2.5–18 mg/L
Lamotrigine (Lamictal)	50 mg/d if added to PHT/CBZ; 25 mg q.o.d. if added to VPA	300–500 mg with PHT/CBZ; 100–150 mg with VPA	6–30 with PHT/CBZ; 30–100 with VPA	2–20 mg/L
Levetiracetam (Keppra)	250–500 mg b.i.d.	1,000–3,000 mg	8–12	20–60 mg/L
Oxcarbazepine (Trileptal)	150–300 mg b.i.d.	900–1,800 mg	8–10 (MHD;2 h for OXC)	10–35 mg/L (MHD)

Perampanel (Fycompa)	2–4 mg qd	8–12 mg	105	0.05–0.40 mg/
Phenobarbital (Luminal)	90 mg hs	90–180 mg (2–4 mg/kg)	72–168	10–40 mg/L
Phenytoin (Dilantin)	300 mg/d in 2 doses	300–500 mg (3–7 mg/kg)	10–30 or more	10–20 mg/L
Primidone (Mysoline)	125 mg hs	750–1,500 mg (10–20 mg/kg)	6–22	8–14 mg/L
Retigabine (Potiga)	100 mg t.i.d.	1,200–1,600 mg	7–11	Unknown
Rufinamide (Banzel)	200–400 mg b.i.d.	200–3,200 mg	6–10	Unknown
Valproate/divalproex sodium (Depakote)	250 mg hs or b.i.d.	1,000–3,000 mg (15–60 mg/kg)	10–20	50–120 mg/L
Topiramate (Topamax)	25–50 mg/d	200–400 mg/d	18–22	5–20 mg/L
Tiagabine (Gabitril)	4–8 mg	32–56 mg/d	5–8	5–70 mg/L
Vigabatrin (Sabril)	500 mg b.i.d.	1,500–3,000	5–10	0.8–36 mg/L
Zonisamide (Zonegran)	100 mg	200–400 mg	50–70	10–40 mg/L

OCPs, oral contraceptives.

Pathophysiology

1. Seizures occur in the neonate as the result of almost any focal or diffuse derangement. There may be acute symptomatic seizures only or an ongoing seizure tendency (i.e., epilepsy).
   - **a.** Certain electrolyte disturbances increase neuronal hyperexcitability; others may act in a nonspecific manner causing neuronal injury, or indirectly as in deficiency of pyridoxine, a necessary cofactor in the synthesis of GABA.
   - **b.** In about two-thirds of neonates with seizures, the cause of acute seizures or epilepsy can be identified as arising before, during, or after birth. These include congenital or postnatal infection, congenital malformation,

asphyxia (most common), intracranial hemorrhage, inborn errors of metabolism (especially pyridoxine or biotinidase deficiency), hypocalcemia (either early, within the first 3 days, usually in association with other insults, or late, usually day 5 to 14, after consuming a milk formula with a high phosphate concentration), hypomagnesemia (often with hypocalcemia), hypoglycemia (often appearing within hours of birth and in association with other insults), hypo- or hypernatremia, drug withdrawal (from maternal narcotics or depressants), or drug toxicity (inadvertent injection of local anesthetics).

2. Among the genetic causes of neonatal seizures, there are two important genetic syndromes, benign familial neonatal epilepsy, which has been linked to mutations in the voltage-gated potassium channel on chromosome 20 or 8, and benign neonatal convulsions, for which a genetic cause has not been clearly identified but which, unlike neonatal seizures or SE owing to an identifiable cause, is self-limiting. These often begin on the fifth day of life and are termed "fifth-day fits."

Prognosis

The prognosis of neonatal seizures is strongly related to the cause. Neonates whose seizures result from congenital malformation or postnatal infection do worse than those with a transient metabolic disorder. Animal studies suggest that seizures in the neonate are both more difficult to control and less likely to produce neuronal damage than uncontrolled seizures at older ages. Apart from etiology, those with a normal EEG background and a normal examination have the best prognosis; this includes those with the diagnoses of benign familial neonatal epilepsy or benign neonatal convulsions.

Diagnosis

1. Diagnosis of neonatal seizures depends on distinguishing these from normal or nonepileptic causes of repetitive movements in the neonate, such as normal chewing or sucking, or benign neonatal sleep myoclonus.
   a. EEG is critical in making this distinction. Although interictal discharges can be difficult to distinguish from nonspecific sharp transients, ictal discharges in the neonatal EEG are nonetheless rhythmic and evolve from a frequency at the lower end of 0.5 to 15 Hz to faster frequencies. Unlike

in adults, discharges can remain confined to a single electrode or, in some cases, "migrate" from one location to another.

b. To be termed an "electrographic seizure," the minimum discharge duration is arbitrarily defined as 10 seconds.

2. Metabolic and imaging tests are directed toward identifying the causes listed under the preceding section on Pathophysiology (list item 1.b.). If examination findings are normal and laboratory evaluation is negative, genetic testing can be performed to confirm an underlying channelopathy.

Treatment

1. The first priority is to identify and treat reversible infectious or metabolic causes.
2. While waiting for blood test results to return, many clinicians administer in a stepwise manner 2 to 4 mL/kg of 25% glucose, 50 to 100 mg of pyridoxine (ideally during EEG recording), 1 to 2 mL/kg of 10% calcium gluconate (over minutes during electrocardiogram [ECG] monitoring), and 0.1 to 0.2 mL/kg of 50% magnesium sulfate.
3. If ventilation and other autonomic functions are unaffected, the child can be observed or treated only with benzodiazepines. However, treatment in this group is usually initiated with PHB or PHT.
   a. PHB is given in two 10-mg/kg boluses at 2 to 3 mg/kg/min, followed by additional boluses as needed. If this is unsuccessful, PHT may also be given in two 10-mg/kg boluses no faster than 2 mg/kg/min. PHB is maintained orally at 5 mg/kg/d, following levels frequently because of more rapid and variable metabolism than in older children.
   b. Variations in PHT absorption and metabolism in the neonate complicate its use in oral maintenance.
   c. Other treatment options include lidocaine, LEV, and midazolam.

West Syndrome (Infantile Spasms)

Background

1. West syndrome (first identified by a 19th-century British pediatrician in his own child) is a generalized epilepsy syndrome, usually symptomatic or cryptogenic, that arises between 4 and 6 months of age and occurs only in

the first 2 years.

2. It is defined by clusters of myoclonic–tonic seizures, sometimes termed "jackknife seizures" or "salaam attacks," and a characteristic interictal EEG finding of hypsarrhythmia, consisting of a chaotic, high-amplitude background with multifocal spikes. Each spasm lasts 2 to 3 seconds, longer than true myoclonus but shorter than most tonic seizures, and can be mainly flexor, extensor, or both. Eye deviation or nystagmus can occur; asymmetric spasms occur often, but not always, in infants with focal brain lesions.
3. This syndrome is relatively common, appearing in up to 40/100,000 children.

Pathophysiology

1. The mechanism of generating clusters of spasms is not well understood, but the clinical manifestations and the ictal EEG showing low-amplitude fast activity or flattening, a so called "electrodecremental pattern," suggest the possibility of brainstem involvement.
2. Pathologic causes of the syndrome include nearly any kind of prenatal, perinatal, or postnatal insult, including hypoxic encephalopathy, trauma, meningitis, brain malformations, and inborn errors of metabolism.
3. Neuroectodermal disorders, particularly tuberous sclerosis, are strongly associated.

Prognosis

West syndrome has a poor prognosis, with only 80% to 90% of children surviving to age 5, up to 90% of survivors have developmental delay, and 50% have epilepsy. However, infants with normal neurologic development prior to onset of spasms and no identifiable cause (idiopathic cases) may have a good outcome. Onset before 6 months is also associated with a poor prognosis probably because it indicates one of several symptomatic etiologies. Infants with an abnormal examination or developmental history but without a known etiology have a prognosis intermediate between symptomatic and idiopathic cases. The possibility that early treatment may influence prognosis and the child's development is a spur to prompt diagnosis and aggressive management.

Diagnosis

1. Diagnosis depends on the occurrence of typical clinical events and a

characteristic interictal and ictal EEG.

   a. Hypsarrhythmia is not always present and may appear only after the syndrome has been established for weeks or longer.
   b. There are variants, termed "modified hypsarrhythmia," including EEG patterns with focal features, relatively few spikes, or relative synchrony between the two hemispheres.

2. Once the syndrome is diagnosed, evaluation is directed toward identifying potential causes and includes, in addition to neurologic examination and EEG, a careful skin examination with Wood's lamp and CT or MRI, which is abnormal in 70% to 80% of cases.
   a. Screening for inborn errors of metabolism should include urine and serum amino acids; serum organic acids, lactate, pyruvate, and ammonia levels; and liver function tests.
   b. Cerebrospinal fluid (CSF) should be examined for lactate, pyruvate, and amino acids if metabolic disease is a consideration.

Treatment

1. If no cause is found, pyridoxine deficiency, a very rare but treatable cause, should be considered and pyridoxine 100 to 200 mg administered IV during EEG recording; if this is the etiology, the EEG should improve within minutes.
2. The mainstay of treatment is ACTH, which often results in seizure control and EEG improvement within days.
   a. ACTH may be given IM at 40 IU q.d. for 2 weeks, and if seizures continue, increased by 10 IU weekly until seizures are controlled or to a maximum of 80 IU q.d.
   b. After seizures stop, the dose can be continued for a month and then tapered by 10 IU/wk. If seizures recur, the previously effective dose is resumed.
   c. Blood pressure, stool guaiac, electrolytes, calcium, phosphorus, glucose, and signs of infection must be monitored.
3. VGB is another viable alternative and is especially useful in patients with tuberous sclerosis.
4. Alternatives, typically used when ACTH fails or is not tolerated, include prednisone, VPA, CZP, LTG, ZNS, TPM, FBM, or TGB.
   a. VPA can be initiated at 15 mg/kg/d in three doses and increased in 5- to

10-mg/kg/d weekly increments.

b. Clonazepam is begun at 0.01 to 0.03 mg/kg/d in three doses, increasing by 0.25 to 0.50 mg every 3 days to 0.1 to 0.2 mg/kg/d.

Lennox–Gastaut Syndrome

Background

1. LGS is an epileptic encephalopathy characterized by multiple seizure types, including generalized tonic seizures, and by slow-spike–wave complexes (1.5 to 2.5 Hz) on EEG; mental retardation is usually part of the syndrome, although 10% of those have normal development. Other seizure types commonly include tonic–clonic, myoclonic, atonic, and atypical absence; "drop attacks," which may result from tonic, atonic, or myoclonic seizures that involve the postural musculature, also occur and can cause serious injury. Head drops are a fragmentary form of drop attack and may occur hundreds of times a day. Focal seizures occur less frequently but may be present, especially in older children.
2. Onset is between 6 months and 7 years, and incidence is approximately 30/100,000.
3. EEG findings include background slowing and sometimes multifocal discharges in addition to anterior predominant generalized slow-spike–wave complexes; the latter are sometimes nearly continuous, except during REM sleep. During slow-wave sleep, polyspike–wave complexes and bursts of fast spikes may occur, with or without myoclonic or tonic clinical manifestations.

Pathophysiology

The same range of processes that cause infantile spasms cause LGS, and in some cases, the former can evolve into the latter. Evidence that these or other early-onset epilepsies can be caused by diphtheria–pertussis–tetanus (DPT) vaccines is limited and highly controversial.

Prognosis

1. LGS is highly resistant to treatment, and seizures occur many times a day.
2. Developmental delay is present in approximately half at onset of seizures,

and the proportion increases with age.

3. In some patients, fluctuations in cognition and behavior may vary with epileptiform activity, leading to hope that the development of more effective treatments, as has occurred to some extent over the past decade, will have a long-lasting effect on overall functioning.

Diagnosis

Diagnosis is based on history, examination, and routine EEG; additional EEG techniques, such as vEEG monitoring, may be helpful in some cases to establish which clinical behaviors have an epileptic origin.

Treatment

1. A variety of the "broad-spectrum" AEDs have shown efficacy in the treatment of LGS, although responses are rarely dramatic.
   - **a.** VPA traditionally has been used, although the risk of hepatic failure is a concern in children younger than 2 years, whereas FBM also carries risk of hepatic and bone marrow toxicity; TPM and LTG are likely to be safer.
   - **b.** Clobazam has been FDA-approved for LGS and works on many seizure types, especially drop attacks.
   - **c.** RFA is another broad-spectrum agent also approved for the condition.
   - **d.** Other broad-spectrum agents such as LTG and TPM can also be helpful.
   - **e.** Narrow-spectrum drugs such as PHT and CBZ may be given for tonic–clonic seizures but can precipitate drop attacks.
2. There is considerable evidence that the ketogenic diet can be effective in LGS, with 30% to 50% reporting dramatic or convincing responses, and some children have been able to discontinue AEDs and show functional improvements that are maintained for a year or more.
3. For patients with potentially injurious drop spells, corpus callosotomy is an option, and VNS has shown efficacy against LGS in retrospective studies.
4. There are anecdotal reports of immune-modulating treatments such as ACTH, IV immune globulin, or plasmapheresis having at least transient efficacy in treating this and other severe and refractory pediatric epilepsy syndromes.

Febrile Seizures

Background

1. Febrile seizures (FS) constitute a provoked syndrome usually defined as the occurrence of brief convulsions in a neurologically normal child between 6 months and 5 years, in the setting of fever noted prior to the seizure and not attributable to CNS infection. If the seizure is focal, recurs within a day, or persists beyond 15 minutes, it is termed a "complex febrile seizure." Onset is most commonly between 18 and 22 months. This is a common syndrome, occurring in 3% to 4% of the population.
2. In certain children, the course is not benign, and genetic studies have identified rare variants in which afebrile seizures later develop, and this phenotype has been designated "generalized epilepsy with febrile seizures plus" (GEFS≤). Another epileptic syndrome that may present with prolonged FS is Dravet syndrome (severe myoclonic epilepsy of infancy), which is an epileptic encephalopathy usually caused by SCN1A mutations; the prognosis for this condition is not favorable.

Pathophysiology

FSs have a strong genetic component, and in GEFS≤, autosomal dominant mutations of the sodium channel genes SCN1A, SCN1B, and GABA-A receptor gene have been identified. It is likely that other channel abnormalities, perhaps with more complex inheritance, underlie the more common syndrome, and fever, which generally lowers the seizure threshold, "unmasks" the inherited tendency. The reasons for the strong relationship with age are not well understood.

Prognosis

1. The prognosis of simple FS is regarded as good, although 30% to 40% of children have a recurrence during subsequent febrile illness, especially if the index seizure occurs during the first year of life.
2. The prognosis for later development of epilepsy may be approximately 4 times that of the general population, but much of this risk corresponds to children who have had complex FS. An important subgroup comprises those with prolonged FS, an unknown number of whom will later develop the syndrome of mesial temporal sclerosis, usually diagnosed in the context of surgical treatment in adolescence or adulthood. At least some of these

patients have accompanying anatomic abnormalities that may have predisposed them to both prolonged FS and to later development of intractable epilepsy.

3. Prognosis for neurologic development after FS is excellent, as developmental delay not apparent before the first FS seldom occurs afterward, except in rare cases of SE.

Diagnosis

1. The diagnosis depends on the child meeting the criteria described previously and on ruling out a CNS abnormality as the cause of the seizure.
2. Lumbar puncture should be considered at initial presentation, since meningitis, especially in young children, may present with a paucity of other signs.
3. EEG is generally regarded as not useful because nonspecific abnormalities, such as posterior slowing, have no prognostic value, and even spike–wave complexes do not strongly predict later seizures (although they may reflect the inherited low threshold underlying the syndrome). Similarly, if the examination is normal, neuroimaging is not needed.
4. Other evaluations are aimed at identifying the cause of the fever, such as viral illnesses or otitis media, which are common in the affected age group.

Treatment

1. Preventive treatment with standard AEDs is no longer recommended for FS.
2. Aside from acetaminophen for fever control and treatment of the underlying illness, treatment options after a first FS include DZ given orally 0.3 mg/kg q8h at onset of subsequent fever or potential febrile illness; an alternative is rectal DZ gel dosed according to the age and weight per package insert.

Benign Epilepsy with Centrotemporal Spikes

Background

1. BECTS, also termed “benign rolandic epilepsy,” is the most benign focal epilepsy in childhood.
2. Seizures begin between 2 and 12 years, most commonly between 5 and 10, and consist of mainly nocturnal and infrequent generalized seizures as well

as frequent diurnal or nocturnal focal seizures without loss of consciousness involving the oral sensorimotor cortex; this location produces the characteristic symptoms of tingling or an electrical feeling in the cheek or mouth, often progressing to twitching of the face and less commonly the hand or arm. The child cannot speak but is fully conscious.

Pathophysiology

This syndrome has a genetic basis, with some families having mutations on chromosome 15; the EEG trait is more strongly penetrant than the epilepsy syndrome, which is present in only a minority of those with the characteristic EEG findings.

Prognosis

Seizures stop during adolescence, typically before age 16, and patients remain neurologically normal. Similar seizures with prognoses that are less benign have been reported in patients with focal lesions in the rolandic cortex or adjacent areas, and these should be considered in the differential diagnosis.

Diagnosis

Diagnosis depends on the clinical history and is established by the characteristic EEG finding of diphasic spikes and sharp waves in one or both centrotemporal regions, especially during light sleep. If the examination is normal and the history and EEG typical, neuroimaging is not necessary, although MRI should be pursued if seizures do not respond or other features are atypical.

Treatment

1. Because of the benign course, not all child neurologists treat patients with this syndrome, although most do if a secondarily generalized seizure occurs. Another treatment approach is to administer benzodiazepines as needed.
2. Any AED effective against focal seizures can be used. CBZ has been used traditionally.
3. Treatment can often be stopped after 1 to 2 years of seizure control, even if the EEG findings remain abnormal.

Childhood Absence Epilepsy

Background

CAE is a genetic generalized epilepsy that arises between age 3 and the onset of puberty, and it is characterized by very frequent (hence the previous term "pyknolepsy," from the Greek *pyknos*, meaning crowding) typical absence seizures and a characteristic EEG with normal background and 3-Hz spike–wave complexes. Absences may occur hundreds of times daily, and one-third to one-half of patients also have infrequent tonic–clonic seizures.

Pathophysiology

Inheritance may be autosomal dominant with incomplete penetrance (higher for the EEG trait than for clinical epilepsy); the associated mutation is unknown, although it most likely affects channels associated with the thalamocortical network underlying absence seizures.

Prognosis

1. Most patients respond completely to appropriate medication, and approximately two-thirds remit by puberty. Positive factors for remission include lack of tonic–clonic seizures (or, if present, onset after absence seizures have begun), negative family history, and no history of generalized nonconvulsive status epilepticus (NCSE).
2. If cognition, neurologic status, or EEG background is abnormal, prognosis is worse, and the possibility of an incorrect diagnosis must be considered.

Diagnosis

Diagnosis is often made clinically by having the patient hyperventilate for 3 to 4 minutes, which is a potent trigger for absences, and confirmed by EEG that also includes hyperventilation. If history and EEG are characteristic and the examination is normal, neuroimaging is probably not needed.

Treatment

ESX is the drug of choice for this condition and is superior to other medication options. VPA and LTG are second-line agents. If tonic–clonic seizures are present, VPA or LTG is preferable since ESX must be used with another AED, such as PHT, that will treat the tonic–clonic seizures. If ESX, VPA, or LTG

does not adequately control the absences, combinations of these may be used.

Juvenile Myoclonic Epilepsy and Related Syndromes

Background

1. JME is a genetic generalized epilepsy with onset during or after puberty (usually in the teenage years but possibly as young as 8 or as old as 30) and is characterized by myoclonic seizures, most often affecting the proximal upper extremities. It is the most common genetic generalized epilepsy, accounting for perhaps 5% to 10% of all adult epilepsy cases.
   - **a.** Myoclonic seizures usually occur within 1 to 2 hours of awakening but may also be experienced when falling asleep in the afternoon or at other times. Alcohol precipitates myoclonus or seizures in many affected children.
   - **b.** Approximately 90% of patients also have tonic–clonic seizures, and 10% to 30% have absences, which are much less frequent than in CAE and may also be incomplete, in that awareness may be partially preserved.
   - **c.** EEG shows 4- to 6-Hz spike–wave and polyspike–wave complexes, less regular than those in CAE.
2. The syndrome of JAE is similar to JME, but there are no myoclonic seizures and absences must be present. The syndrome of epilepsy with generalized tonic–clonic seizures on awakening lacks the absence as well as myoclonic seizures.
3. Seizures associated with all of these syndromes are very sensitive to sleep deprivation and alcohol withdrawal, which are frequent in the age group at risk.

Pathophysiology

JME and the related syndromes are genetic in origin with a site implicated on chromosome 6 in some ethnic groups; however, other genes are involved and account for the variability among patients with these syndromes.

Prognosis

The prognosis of the adolescent-onset syndromes is not as favorable as that for CAE, as 80% to 90% require lifelong treatment. However, most seizures respond well to treatment.

Diagnosis

Diagnosis depends on appropriate historic and EEG findings (often just polyspikes) and may be delayed because myoclonic jerks are often ignored. If clinical and EEG findings are typical, examination is normal, and response to medication is complete, neuroimaging is not needed; most patients, however, have had CT or MRI prior to diagnosis.

Treatment

1. VPA is still considered the first-choice drug, although in obese men or in women of childbearing age, it should be avoided if possible because of the risks of weight gain and teratogenicity. LTG is often effective, although in some patients, myoclonic seizures may not respond or may even worsen. (When PHT, or especially CBZ, is given, worsening of absence as well as myoclonic seizures is relatively common, although these may be useful adjuncts for tonic–clonic seizures.)
2. TPM, ZNS, PER, and LEV may be effective alternatives.
3. Finally, counseling on the need to obtain adequate sleep, avoid use of alcohol and other psychoactive substances, and maintain medication compliance is an important part of treatment.

Alcohol- and Drug-Withdrawal Seizures

Background

1. Alcohol-withdrawal seizures are an important cause of provoked seizures, accounting for a high proportion of cases of initial seizures and SE in susceptible populations. Seizures occur 7 to 48 hours after the last drink, most commonly between 12 and 24 hours, usually in association with other withdrawal symptoms such as autonomic arousal and agitation.
2. The timing of withdrawal seizures from other depressants, such as benzodiazepines and barbiturates, depends on the half-life of the relevant drug.

Pathophysiology

Alcohol and many other depressants potentiate GABA-mediated inhibition and may block excitatory neurotransmission; the compensatory receptor changes that occur with chronic use predispose the patient to neuronal hyperexcitability and seizures in the setting of abrupt withdrawal.

Prognosis

Withdrawal seizures, even in the rare cases that progress to SE, usually respond promptly to appropriate treatment, although patients may need to be observed for the later development of delirium tremens. The long-term prognosis depends on success in treating substance abuse.

Diagnosis

1. Diagnosis depends on an adequate history and is more obvious if alcohol is still present in the blood; physical examination directed toward signs of chronic alcohol abuse may be helpful.
2. The most important aspect of the evaluation is ruling out other metabolic and structural abnormalities associated with alcoholism, including hyponatremia, hypoglycemia, hypomagnesemia, and traumatic brain injury.

Treatment

1. Benzodiazepines are the mainstay of treatment for alcohol and benzodiazepine withdrawal, and they may be used, along with PHB, for barbiturate withdrawal. LZ 2 to 4 mg IV or IM can be given every 2 to 4 hours as needed to minimize withdrawal symptoms without causing excessive sedation. PHT is typically not helpful unless SE develops.
2. Referral to an appropriate substance abuse program should be attempted even if the chance of success is believed to be low.

“Lesional” Epilepsy

Background

1. Although structural lesions account for less than half of all cases of epilepsy, this proportion is far higher in patients with focal epilepsies and those with a later onset, especially after age 60.

a. At younger ages, pathologic specimens suggest that microscopic structural abnormalities, often disorders of cortical development underlie many cases of intractable partial epilepsy of adolescent or adult onset.

b. Other important causes:

1) Neoplasms, including benign brain tumors such as gangliogliomas, oligodendrogliomas, dysembryoplastic neuroepithelial tumors, and pilocytic astrocytomas. Metastatic cancer and higher grade gliomas account for a large proportion beyond the fifth decade.

2) Infections, particularly parasitic infections such as cysticercosis, but also long-term sequelae of bacterial and viral meningoencephalitis.

3) Traumatic brain injury, especially penetrating but also closed head injury if moderate or severe.

4) Stroke, both hemorrhagic and ischemic.

5) Congenital or acquired vascular anomalies, such as arteriovenous malformations or cavernous angiomas.

2. Clinical manifestations depend largely on the site of the lesion, although the correlation is far from perfect, since the ictal discharge may start adjacent to rather than in the lesion (depending on lesion type) and may produce no symptoms or signs until it spreads within the hemisphere or even to the contralateral hemisphere.

a. Lesions that produce either acute symptomatic seizures or later epilepsy are typically located cortically or subcortically rather than deeply.

b. Frontoparietal lesions near primary sensorimotor cortex typically produce contralateral somatosensory and motor phenomena, while other areas of the frontal lobe produce other manifestations: bilateral posturing if near the midline supplementary motor area, or vigorous automatisms and emotional experiences with orbitofrontal and/or cingulate involvement.

c. As a rule, frontal lobe epilepsies tend to produce frequent brief seizures that arise during sleep.

d. Temporal lobe epilepsies differ depending on whether the source is medial or lateral; medial temporal seizures are often characterized by a rising epigastric sensation or other autonomic disturbance as well as emotional or olfactory auras preceding focal dyscognitive seizures that progress from motionless staring to oral automatisms. These focal seizures often last 2 to 3 minutes and are followed by postictal confusion.

e. Lateral temporal lobe seizures are associated with auditory, language, or

sometimes visual phenomena.

f. Parietal and occipital lobe epilepsies may include focal seizures characterized by elementary or formed visual hallucinations or distortions of spatial perception, including vertigo.

Pathophysiology

The mechanisms by which structural lesions produce neuronal hyperexcitability are not well understood and likely vary for different types of lesions. Disorders of cortical development, for example, include neurons that may have abnormal receptors, channels, or connections, whereas foreign tissue and destructive lesions may injure specific neurons or neuronal populations to decrease inhibition or increase excitation on a neuronal or network basis. With hemorrhagic lesions, iron itself can be epileptogenic.

Prognosis

Prognosis for seizure control differs with lesion type and location. For example, mesial temporal sclerosis, a hippocampal lesion often associated with prolonged FS in childhood and onset of focal seizures in adolescence or early adulthood, is frequently refractory to medical management but amenable to surgical treatment. Among patients with neoplasms, overall prognosis depends on likelihood of growth or regrowth after resection, especially if recurrence is associated with malignant transformation, as can be seen with astrocytomas.

Diagnosis

The diagnosis of structural lesions has been revolutionized by MRI, which can reliably show not only neoplasms, abscesses, and vascular anomalies but also many disorders of cortical development and gliotic lesions such as mesial temporal sclerosis.

Treatment

1. Any of the AEDs effective against focal and tonic–clonic seizures can be used in patients with lesional epilepsy; no drug specificity related to location of the lesion has been demonstrated. The medications currently approved for monotherapy in new-onset focal epilepsy include OXC, TPM, FBM, and ESL. Older AEDs were grandfathered in by the FDA, while

newer drugs are used off label as monotherapy.

2. A significant proportion of those with lesional epilepsy will not respond to AEDs, and surgery should be strongly considered for any patient with a resectable lesion that can plausibly account for the epilepsy syndrome and whose seizures do not respond to two or more appropriate medications at reasonable doses. In many cases, complete resection of the lesion alone will render the patient seizure free, and many of these patients can eventually be withdrawn from medication; it is likely that in some cases, the outcome is better if surrounding electrically abnormal tissue is also removed.

Special Issues Related to Epilepsy in Women

Background

1. Approximately 40% of all cases of epilepsy, or almost 1,000,000 in the United States, occur in women of childbearing age. Issues that need to be considered include effects of hormones and pregnancy on epilepsy, influence of AEDs and seizures on pregnancy and pregnancy outcome, breast feeding, and other childcare issues.
2. It is important to recognize that the enzyme-inducing drugs CBZ, PHT, PHB, PRM, and to a lesser extent ESL, OXC, and TPM can increase metabolism of hormones and cause failure of oral contraceptives. If there is no other effective method available, oral contraceptives can still be used, but only medium- or high-dose pills, and failure rate is still above baseline.

Pathophysiology

1. Approximately one-third of women with epilepsy, especially those with focal and perhaps temporal lobe seizures, report increased seizures shortly before menses or at ovulation. These so-called “catamenial seizures” likely reflect the important effects of hormones on neuronal excitability.
   a. In general, estrogens increase excitability and progesterones (particularly allopregnanolone) have inhibitory effects. The ratio of rising and falling levels of these two hormone classes likely accounts for the menstrual variation, and it may affect seizure fluctuations during and after menopause.
   b. Occasionally, measurement of AED levels through the menstrual cycle

reveals changes in absorption or metabolism that can account for the exacerbations.

2. The mechanisms by which AEDs cause teratogenicity are not well understood, and these may be different for different AEDs.
   a. One hypothesis is that oxidative injury to fetal cells results from reactive AED metabolites.
   b. Folate deficiency is also associated with several AEDs and can adversely affect fetal cell division.

Prognosis

1. Women with catamenial epilepsy may experience fewer seizures after menopause, although some report exacerbation during the menopause. With respect to AED teratogenicity, monotherapy with the older drugs PHT, PHB, and VPA is associated with an approximate doubling of the rate of major congenital malformations from 2% to 3% at baseline to 4% to 7%. Medications with the lowest rate include LTG and LEV. There is also evidence for a favorable profile with low-dose CBZ (<400 mg). Data is lacking for a number of the newer medications.
2. Folic acid supplementation for women during pregnancy and especially prior to pregnancy has been shown to correlate with better childhood IQs.
3. During pregnancy, perhaps one-third of women experience an increase in seizures, and it is unclear whether this proportion has declined in recent years with increased awareness of the need to increase drug doses as pregnancy progresses. Seizures can adversely affect pregnancy either by causing falls and other accidents or, at least in the case of convulsive seizures, by producing fetal distress.

Diagnosis

The diagnosis of catamenial seizure exacerbations is established by keeping a careful diary of seizures and menses. Close neurologic and obstetric follow-up are needed to diagnose epilepsy-related pregnancy complications.

Treatment

1. Catamenial seizure exacerbations can be treated temporarily by increasing the baseline medication dose, using a short-term course of a benzodiazepine

or ACZ, or administering progesterone. The trial of progesterone versus placebo only showed efficacy for progesterone in a post hoc analysis of women with higher levels of perimenstrual seizures.

2. To minimize AED teratogenicity, an effective means of contraception must be used, and all women of childbearing age should be given supplemental folate; the optimal dose has not been determined, but at least 1 mg and perhaps as much as 4 mg should be given daily.
   - **a.** Polytherapy should be avoided whenever possible, and drug withdrawal prior to conception should be considered in women who have been seizure free for at least 2 years or in those for whom the diagnosis of epilepsy has not been established; in the latter case, vEEG monitoring can be decisive.
   - **b.** The most effective medication for an individual should be used at the lowest dose that controls seizures, especially the generalized tonic–clonic seizures that are most likely to put both mother and fetus at risk.
   - **c.** Knowledge of potential teratogenic effects of the newer drugs will be facilitated by encouraging pregnant women taking medications to contact the North American AED Pregnancy Registry, as early as possible in the pregnancy, by calling the toll-free number 1-888-233-2334 (1-888-AED-AED4).

3. Treatment during pregnancy should include measurement of drug levels every 1 to 3 months, including free levels of highly protein-bound drugs. Total and, to a lesser extent, free levels tend to fall as pregnancy progresses and doses usually need to be increased.
   - **a.** Vitamin K, 10 to 20 mg/d, is sometimes recommended during the last month of pregnancy, especially to mothers taking enzyme-inducing drugs, and vitamin K is routinely given to the baby to prevent neonatal hemorrhage.
   - **b.** Seizures during delivery, reported to occur in 1% to 2% of women with epilepsy, may be prevented by administering medications parenterally when absorption is in doubt; use of parenteral or sublingual LZ can also be considered, although neonatal sedation is a risk.
   - **c.** Following delivery, drug levels rise over a period of days to weeks and doses typically need to be decreased to avoid toxicity.

4. New mothers with epilepsy should be counseled to change the baby on the

floor, not to bathe the baby alone, and to take other reasonable precautions consistent with the nature of the mother's seizures. Although all medications can be found in breast milk, especially those that are not highly protein bound, specific risks have not been identified apart from sedation with barbiturates and benzodiazepines, and the benefits of breast feeding likely outweigh the risks.

Toxemia of Pregnancy

Background

1. Toxemia of pregnancy is a situation-related syndrome occurring in the second half of pregnancy and consisting of systemic alterations including hypertension with edema and/or proteinuria; coagulopathy and liver dysfunction are often present.
2. Cerebral involvement is similar to that associated with hypertensive encephalopathy and includes headache and cerebral edema, often causing visual phenomena and focal or tonic–clonic seizures.
3. Hyperreflexia is usually present.
4. The presence of coma or seizures indicates progression from preeclampsia to eclampsia.

Pathophysiology

The underlying mechanism of toxemia is not known but may reflect alteration in endothelial function; effects on the brain are similar to those of hypertensive encephalopathy and likely relate to loss of autoregulation of cerebral blood flow, especially in posterior cerebral regions.

Prognosis

Eclampsia has a maternal mortality rate of 1% to 2%, and there are fetal complications in one-third of cases.

Diagnosis

Eclampsia is diagnosed on the basis of clinical characteristics described previously, typically by the obstetrician.

Treatment

1. The procedure essential to reversing the underlying eclamptic process is delivering the baby.
2. Seizures must still be treated, however, and in some cases, preventative treatment is justified. Magnesium sulfate is preferred to treat eclamptic seizures, and in some cases, the addition of an AED is necessary. Magnesium sulfate may be given IV at 20 mg of a 20% solution (4 g) over 4 minutes, with maintenance of 1 to 3 g/h, or as 5 to 10 mg IM every 4 hours, titrating to a level of 3 to 5 mmol and monitoring for areflexia and weakness that could herald ventilatory compromise.

Seizures and Epilepsy in the Elderly

Background

1. The incidence of both acute symptomatic seizures and of epilepsy increase beyond age 60, and in the oldest, new seizures occur at annual rates exceeding 100/100,000.
2. The most common cause is previous stroke, both ischemic and hemorrhagic, but degenerative disorders including Alzheimer dementia and metastatic and primary brain tumors are important contributors.

Pathophysiology

The mechanisms by which the given processes cause seizures and epilepsy depend on the type of insult and are not well understood.

Prognosis

Overall, prognosis depends on the specific cause and on comorbid conditions, but in most cases, seizures respond to AED treatment at least as well, if not better, as in younger individuals.

Diagnosis

1. Differential diagnosis of transient neurologic dysfunction is similar to that previously outlined, but in the elderly, the likelihood of PNES is lower than in younger patients, and the risk of such physiologic causes as syncope or

TIA is higher.

2. Prolonged EKG or vEEG monitoring may be required. Among sleep disorders, REM behavior disorder is a parasomnia that is much more common in the elderly, and it is often associated with extrapyramidal movement disorders; polysomnography is required for diagnosis.

Treatment

1. Any of the traditional or newer AEDs discussed earlier may be used in the elderly population, but starting doses should be lower and doses should be increased more slowly.
2. In patients on anticoagulants or other drugs whose metabolism is altered by enzyme inducers, medications such as PHT and CBZ must be used with caution, particularly those with cardiac rhythm disturbances. Susceptibility to CNS adverse effects of barbiturates or benzodiazepines argues against using these agents when alternatives exist. In addition, medications which can worsen cognition such as CBZ and TPM should also be avoided.
3. In patients taking multiple drugs for other conditions, AEDs with minimal drug–drug interactions, such as GBP, LTG, PGB, or LEV, should be strongly considered; drugs such as GBP and LEV that are principally metabolized by the kidney should be dosed according to renal function.

Status Epilepticus

Background

1. SE is the most common neurologic emergency, affecting 50,000 to 200,000 in the United States annually.
2. While any type of seizure can evolve into SE, the most important and common type is generalized convulsive SE, in which the tonic–clonic seizures can be either primarily or secondarily generalized. Other important types include NCSE (absence SE or focal dyscognitive/complex partial), myoclonic SE, and epilepsia partialis continua (EPC).

Pathophysiology

1. SE reflects a failure of the usual seizure-terminating mechanisms. Why this happens only under some circumstances is not well understood.

a. Mechanisms of neuronal injury include hypoxia–ischemia and excitotoxicity. The latter can result in neuronal death even if oxygenation and blood flow are maintained; in animal models, a cascade of events culminating in neuronal loss occurs after 30 to 60 minutes of continuous seizures.
b. Systemic derangements that can predispose to neurologic injury include hypotension (usually following initial hypertension), combined lactic and respiratory acidosis, cardiac arrhythmia or infarction, hyperthermia, and renal injury from rhabdomyolysis.

2. Any of the causes of acute symptomatic seizures can lead to SE. These include drug withdrawal or intoxication, metabolic derangements, head trauma, CNS infection, cardiac arrest, or stroke.
a. SE can occur in patients with preexisting epilepsy of any cause, particularly if seizures are not well controlled or medications are not being taken or absorbed properly.
b. Especially in children, SE can be the first presentation of a genetic epilepsy.

Prognosis

1. The prognosis of generalized convulsive SE varies with age, etiology, and duration.
2. Mortality ranges from 2% to 3% in children to above 30% in adults, especially the elderly.
a. Anoxic injury carries the highest mortality and alcohol or AED withdrawal the lowest.
b. Duration of convulsive SE beyond 1 to 2 hours is associated with a mortality increase of approximately 20%.

3. Neurologic morbidity is more difficult to demonstrate than mortality but undoubtedly occurs in relation to etiology and probably duration of SE as well.

Diagnosis

1. The diagnosis of generalized convulsive SE should be suspected when any patient has a witnessed convulsion and does not begin to arouse within minutes, particularly when a subsequent convulsion occurs.

a. The condition should be distinguished from repetitive seizures, where the patient awakens between episodes. Although such seizure clusters may evolve into SE and need to be treated, urgency is less than with ongoing SE.

b. As convulsive SE progresses, motor activity can become attenuated, and diagnosis is then dependent on obtaining a history of earlier convulsions, supported by ictal EEG findings.

c. PNES can in some cases be prolonged and difficult to distinguish from generalized convulsive SE, but hypoxemia, rise in CPK level, and acidosis typically occur after convulsive seizures. Avoidance behavior or other signs of awareness should be sought on examination; EEG may be required in some cases.

d. In comatose patients, flexor or extensor posturing can occur, and paroxysmal sympathetic storm, sometimes called diencephalic seizures, also has a nonepileptic etiology and responds to opiates, dopaminergic agents, or autonomic blockers but not to AEDs.

2. EEG is commonly needed to diagnose less common forms of SE, such as absence or postanoxic myoclonic SE.

a. Focal dyscognitive/complex partial SE typically occurs in those with a preexisting history of partial epilepsy, but it may be the initial presentation of epilepsy or of an acute neurologic insult. Clinically, there is prolonged clouding of consciousness, usually with cycling over minutes corresponding to ictal and postictal phases of discrete focal dyscognitive seizures.

b. In absence SE, or spike–wave stupor, there is nearly continuously diminished responsiveness with bilaterally synchronous spike–wave discharges on EEG. Although the sensorium is clouded, the degree of impairment may be quite subtle. It may also present as an acute confusional state in adults or, rarely, as a psychotic disorder.

c. Myoclonic SE occurs most commonly and most ominously after a hypoxic–ischemic insult and can present as massive or more subtle, variably rhythmic jerks; EEG typically shows a relatively flat background with polyspikes and artifact corresponding to the jerks.

d. EPC is a form of focal SE without alteration in consciousness consisting of nearly continuous limb jerking that may be quite distal and subtle. It is

associated often with structural lesions, or in the specific pediatric syndrome of Rasmussen encephalitis, with a unihemispheric progressive inflammatory disorder.

Treatment

1. Because of the risk of significant morbidity and mortality with prolonged SE, a time-sensitive treatment protocol is recommended. The following incorporates elements of the American Epilepsy Society guideline:
   0 to 5 minutes (stabilization phase): Assess and support cardiorespiratory function. Give nasal oxygen (O_2) and insert airway if necessary. Obtain history (especially duration of seizures, prior seizures, drugs, etc.) and perform physical and neurologic examinations. Insert IV (normal saline) and draw blood for AED blood levels, toxic screen, CBC, glucose, electrolytes including calcium and magnesium, and hepatic and renal function tests. Give thiamine 100 mg and 50 mL of 50% glucose IV, if glucose <60 mg/dL. Call for EEG monitoring but do not delay treatment.
   5 to 20 minutes (initial therapy phase): Give LZ, 0.1 mg/kg, maximum of 4 mg per dose, may repeat dose once. Alternatively, IV DZ may be given at 0.15–0.2 mg/kg/dose up to 10 mg, may repeat dose once or IM midazolam 10 mg (if >40 kg), or 5 mg (if 13 to 40 kg). If none of the previous options is available, then IV PHB, rectal DZ, or intranasal midazolam are viable options. (Be prepared to assist ventilation immediately when administering IV benzodiazepines.)
   20 to 40 minutes (second therapy phase): If seizures continue, begin one of the following medications: fos-PHT 20 mg/kg (maximum dose: 1,500 mg), or VPA 40 mg/kg (maximum dose: 3,000 mg), or LVT 60 mg/kg (maximum dose: 4,500 mg), or PHB 15 mg/kg. In patients known or suspected to be on AEDs, do not wait for levels before beginning infusion. Monitor ECG and blood pressure. Treat fever with antipyretics and cooling.
   40 to 60 minutes (third therapy phase): If seizures persist, one option is to give a second IV antiseizure medication from the options listed earlier. Some would skip this step and, after intubation and while recording EEG, proceed directly to barbiturate anesthesia, midazolam, or propofol, all intravenously in amounts adequate to suppress convulsions and, equally important, electrographic seizures (continuous EEG monitoring is advised).

a. The barbiturate typically used is pentobarbital, 10 to 15 mg/kg load given at 25 mg/min until burst suppression appears or epileptiform activity is clearly suppressed. Maintain 0.5- to 5-mg/kg/h drip for at least several hours before tapering to look for seizure recurrence. If seizures recur, give 50-mg bolus and increase drip by 0.5 to 1.0 mg/kg/h. Alternatives include PHB in 5- to 10-mg/kg boluses given at 20-minute intervals.

b. Midazolam is given as a loading dose of 0.15 to 0.20 mg/kg followed by infusion of 0.05 to 0.30 mg/kg/h.

c. Propofol is given as a 1- to 3-mg/kg bolus over 5 minutes, repeated if necessary, and followed by maintenance infusion of 2 to 4 mg/kg/h, which can be increased as needed after boluses up to 15 mg/kg/h as blood pressure permits.

2. The drug used to induce coma should be weaned after 1 to 2 days while maintaining high therapeutic levels of PHT (18 to 30 mg/L) and/or PHB (25 to 50 mg/L) and/or VPA (70 to 120 mg/L) and/or LVT during anesthesia infusion to protect against recurrent seizures during taper. There is insufficient evidence for the use of other IV medications such as Lacosamide in this setting.
3. Hypotension during infusion of any of the aforementioned drugs should be treated by slowing or stopping the infusion and giving fluids and pressors as needed. Administration of sodium bicarbonate may be necessary to prevent circulatory collapse for severe acidosis, but overcorrection should be avoided because alkalosis renders neurons hyperexcitable and mild acidosis may be protective.
4. Thiopental (Pentothal) has also been suggested as an alternative to pentobarbital, but it may have more cardiovascular side effects and less predictable pharmacokinetics. Use of inhalation anesthetics (halothane, isoflurane) is controversial, and they should not be used without anesthesiology assistance.
5. Treatment for other forms of SE depends on the balance between risks of the specific seizure type and risks of treatment, especially if taken to the point of intubation and prolonged stay in the intensive care unit.

a. For focal dyscognitive SE and EPC, PHT, PHB, and VPA may be used, as can any of the other AEDs useful against focal seizures or the broad-spectrum AEDs; CBZ, OXC, GBP, and LEV in particular may be given

orally or through a nasogastric or gastric tube and built up to therapeutic doses relatively rapidly.

b. Drug-induced coma is typically not used unless the patient's level of consciousness continues to decline despite treatment.

c. For true absence SE, broad-spectrum drugs, particularly VPA, should follow benzodiazepines; drugs specific for focal seizures can be tried in adults without a history of generalized epilepsy, since a similar syndrome can sometimes represent a focal seizure with generalized spread.

d. EPC is often refractory to the aforementioned AEDs but may respond to FBM.

e. In the special case of Rasmussen encephalitis, case reports have shown at least transient benefit with immune globulin or plasmapheresis, but the surgical procedure of hemispherectomy may be needed, especially if function of the contralateral upper extremity has already been lost.

f. Postanoxic myoclonic SE may respond to benzodiazepines, LEV, or VPA, but there is little evidence that an already poor prognosis can be altered by AED treatment.

6. In general, proper diagnosis and treatment of SE offer both a challenge and an opportunity to avoid iatrogenic complications and improve patient outcome.

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3 Dizziness

Gregory T. Whitman and Robert W. Baloh

CLINICAL APPROACH TO DIZZINESS

Background

1. Dizziness is a sensation of altered orientation or motion in space.
2. Dizziness can be caused by many pathophysiologic mechanisms.
3. Dizziness is common in all settings and patient groups.
4. Dizziness tends to be more common in women than in men.
5. The prevalence of dizziness increases with age.
6. Presyncope and vertigo represent common dizziness subtypes, each occurring in about one-third of patients with dizziness.

History

1. Describe the sensation(s). Vertigo? Light-headedness? Imbalance?
2. How it began.
3. How long it lasts.
4. How frequently it occurs.
5. Circumstances that induce it. Is it induced by lying down? Prolonged standing? Bright light? Stress?
6. Associated symptoms, particularly asymmetric hearing loss. Recent changes in medications—remember, most medications can cause dizziness.

Pathophysiology

Varies with each disorder (discussed in the following sections).

Diagnosis

Localize one or multiple most likely site(s) of disease. Review the common types of dizziness below. Try to match the pattern(s) with that exhibited by your patient.

Treatment

Treatment depends on the underlying disorders. Avoid giving meclizine—for everything. It is most helpful for acute nausea and vertigo, and otherwise, it is not very helpful.

PRESYNCOPE

Background

Presyncope (near-faint dizziness): A light-headed sensation, the sensation one experiences before losing consciousness or fainting.

History

1. Light-headedness may be aggravated by prolonged standing, exercise, heat, reduced fluid consumption, and/or moving from the sitting to standing position.
2. Commonly associated with blurring or darkening of vision and difficulty concentrating
3. Use of multiple antihypertensive and/or diuretic medications increases the risk for presyncope.

Pathophysiology

1. The mechanism of presyncope is reduced blood flow to the entire brain. When cerebral blood flow is mildly reduced, patients report light-headedness, altered vision, warmth, a cold sweat, and postural instability; when there is a greater reduction in cerebral blood flow, syncope may occur.
2. Cardiac arrhythmias may produce spontaneous episodes of presyncope that

can occur in any position (e.g., lying down) and may be associated with chest pain or heart palpitations.

3. Orthostatic hypotension may be caused or aggravated by intravascular volume depletion and medications, particularly diuretics or antihypertensives. When the patient stands, gravitational pooling of blood occurs in the veins below the heart.
4. Vasovagal, also called neurally mediated presyncope, typically occurs when the patient is standing. However, unlike in orthostatic hypotension, the blood pressure is not necessarily reduced except in the last moments preceding syncope. The mechanisms are not fully understood but begin with afferent signals (e.g., from the arterial visceral mechanoreceptors). A cardinal sign is sudden decline in heart rate often in the setting of a stressor.
5. In postural orthostatic tachycardia syndrome (POTS), by definition, the heart rate rises 30 to 40 beats per minute within 10 minutes of standing or head upright tilt. This may be explained in part by a compensatory cardiac response to inadequate sympathetically mediated vasoconstriction and poor venous return to the heart.
6. Hyperventilation may cause presyncope, presumably at least in some cases by lowering the carbon dioxide content of the blood, thus producing constriction of the cerebral vasculature. However, hyperventilation as the sole contributor to dizziness is unusual. As an aside, we also note that respiration is under autonomic control. Thus, many people with various causes of presyncope may manifest a rapid respiratory rate—and therefore lowering of CO_2—on moving from the supine or sitting to standing position. As for many types of dizziness, this situation is a perfect setup for a vicious cycle of primary cerebral hypoperfusion that triggers hyperventilation, which in turn aggravates the cerebral hypoperfusion.

Prognosis

1. Often benign with appropriate treatment, although falls can lead to significant trauma, particularly in older people with orthostatic hypotension.
2. Some cardiac causes may be life threatening.
3. Orthostatic hypotension associated with degenerative neurologic diseases, such as Shy–Drager, Parkinson disease, and diffuse Lewy body disease, can be severely disabling.

4. POTS often begins in children and persists well into adulthood.

Diagnosis

1. Orthostatic hypotension: A documented drop in mean blood pressure of more than 10 to 15 mm Hg or a sustained drop in systolic blood pressure of 20 mm Hg or more within 3 minutes after the patient moves from a lying or sitting to a standing position. If the lowest sustained upright blood pressure is less than a diastolic of 60 mm Hg, or if baseline supine resting blood pressures are low, then the patient may experience symptoms of dizziness under certain circumstances, particularly with intravascular volume depletion.
2. POTS: Increase from baseline heart rate of more than 30 to 40 beats per minute within 10 minutes after the patient moves from a lying or sitting position to a standing position. In newly diagnosed POTS and orthostatic hypotension, in the absence of a clear and reversible cause, we may order blood tests similar to those for treatable causes of neuropathy, including, but not necessarily limited to, vitamin B_{12}, Lyme where endemic, thyroid-stimulating hormone (TSH), and antinuclear antibody (ANA), and tests for diabetes mellitus. Additional tests may be indicated in individual patients.
3. Vasovagal presyncope and vasovagal syncope. Characteristic history in a patient without pertinent neurologic or cardiovascular disease.
4. Cardiac arrhythmias: Any patient with episodic presyncope of unknown cause should undergo electrocardiogram (ECG) monitoring to search for sinus pauses, sinus bradycardia, atrial fibrillation, and sustained supraventricular tachycardia.
5. Hyperventilation: Characteristic-associated symptoms in the setting of anxiety and dyspnea. This is a diagnosis of exclusion; end-tidal CO_2 monitoring during tilt table tests may play a role in diagnosis especially when combined with transcranial Doppler ultrasound, but the application of these technologies to clinical autonomic function testing is in evolution.

Treatment

1. Orthostatic hypotension
   a. Removing offending drugs or correcting the causes of blood volume

depletion will often eliminate orthostatic presyncope. If there is no contraindication, patients should sip on water throughout the day.

b. In this as well as other forms of autonomic insufficiency, increased salt intake can increase blood volume but must monitor for hypertension, particularly supine hypertension.

c. Elastic stockings can prevent pooling of blood in the lower extremities. Thigh high stockings work far better than the knee high ones, and inclusion of an abdominal compression garment is even better.

d. In severe cases, the salt-retaining steroid fludrocortisone 0.1 mg p.o. daily can expand blood volume, and the α_1-adrenergic agonist midodrine 2.5 mg p.o. t.i.d. can increase vascular tone. Monitor for supine hypertension.

e. Avoid getting up quickly from bed.

f. Avoid taking hot showers first thing in the morning when symptoms may be more severe.

2. Vasovagal presyncope

a. An explanation of the benign nature of the disorder and the mechanism is usually all that is needed to reassure the patient.

b. Increase dietary salt and fluid intake and avoid conditions that predispose to hypotension or volume depletion.

c. A wide range of drugs including β-blockers, midodrine, pyridostigmine, serotonin reuptake inhibitors, and fludrocortisone have been used, but randomized placebo-controlled studies have not convincingly shown that any of these drugs are more effective than placebo. The effectiveness of placebo in controlling vasovagal presyncope and syncope in these studies indicates the importance of cortical inputs in the pathogenesis of vasovagal episodes.

d. If symptoms begin in a social situation, such as while out to eat, those predisposed to vasovagal and other types of presyncope should avoid jumping up quickly as often happens. It would be much better to sit or lie down.

3. POTS

a. The initial therapeutic approach to POTS is essentially the same as that for the other types of presyncope and autonomic dysfunction, as described earlier, except that if there is evidence of a hyperadrenergic element, for example, spikes in blood pressure, one should rule out a

pheochromocytoma usually starting with 24-hour urine fractionated catecholamines.

4. Cardiac disease
   a. Presyncopal dizziness associated with impaired cardiac output can be the warning sign of serious underlying cardiac disease, and there is a risk for sudden death if not appropriately treated.
   b. Management of cardiac arrhythmia obviously depends on the nature of the underlying heart disease, but many patients can be helped with the insertion of a pacemaker, even if the heart disease cannot be cured.
5. Hyperventilation
   a. Educating the patient on the vicious cycle nature of a hyperventilation episode and reassurance regarding the benign nature of the disorder is often effective treatment.
   b. A vigorous exercise program in conjunction with supportive psychotherapy is also helpful.
   c. Pharmacologic treatment with tricyclic amines or selective serotonin reuptake inhibitors may be indicated when there are associated symptoms of panic disorder. Long-term use of tranquilizers should be avoided because of the development of increased tolerance and dependency.

PSYCHOPHYSIOLOGIC DIZZINESS

Background

Psychophysiologic dizziness is typically described as a feeling of dissociation, as although one has left one's own body or a sense of "floating" or "swimming."

History

1. Symptoms are persistent and are not modulated much by position or type of activity.
2. Intensity increases with stress and may decrease with exercise. Many patients report onset of symptoms around the same time that they stopped a previously regular exercise routine.

3. Commonly associated with acute and chronic anxiety, panic, and agoraphobia
4. Patients may focus on the somatic symptoms, especially the dizziness and autonomic symptoms, rather than the intense anxiety associated with the attacks.
5. Patients may describe a sensation of spinning inside the head with the environment remaining stable.
6. Patients may describe aggravation of symptoms by complex visual environments that cause a lot of optic flow, such as grocery stores.

Pathophysiology

1. The mechanism of psychophysiologic dizziness is poorly understood, but it is believed—at least for some patients—to be related to impaired central integration of sensory signals.
2. Visual information may be overweighted resulting in excessive visual motion sensitivity that resembles the well-known illusion of feeling like one is moving backward, when a large nearby truck begins to slowly move forward. Consequently, it may feel overwhelming for the patient to walk in a visually rich environment.

Prognosis

1. With aggressive attention to exercise, and other nonpharmacologic and pharmacologic treatments, the prognosis is excellent.
2. Can recur after long periods of remission, sometimes in the setting of a life stressor such as loss of a loved one.

Diagnosis

Based on typical history and exclusion of other common dizziness subtypes.

Treatment

1. Patients with psychophysiologic dizziness need to understand that their symptoms are “real,” because of physiologic changes occurring in their bodies, and that the pattern of symptoms is commonly reported by other

patients. They are often convinced that they have a severe neurologic disorder and/or that the anxiety that they have recognized is secondary to a life-threatening physical disorder.

2. Three classes of medication are commonly used in the treatment of panic disorder (tolerance and dependency can occur with alprazolam, so this drug should be used cautiously).
   - **a.** Tricyclic amines (e.g., imipramine, desipramine, nortriptyline)
   - **b.** Benzodiazepines (e.g., alprazolam, clonazepam, and in more severe cases lorazepam)
   - **c.** Selective serotonin reuptake inhibitors (e.g., sertraline, citalopram)
3. Medications are used with supportive psychotherapy (psychiatry, psychology, and counseling). Patients with phobic features to their dizziness will often respond to behavioral therapies including some in which they are repeatedly exposed to the situations that evoke symptoms.
4. Exercise is often extremely beneficial.
5. Complementary and alternative medicine approaches particularly mindfulness meditation, yoga, and acupuncture are promising.

DISEQUILIBRIUM

Background

Subjective and/or objective imbalance or unsteadiness.

History

1. The core symptoms occur only when the patient is standing or walking.
2. Symptoms are related to control of posture and gait. They are for the most part unrelated to an abnormal head sensation, although there may be a vague feeling of difficulty with concentration.

Pathophysiology

1. Normal posture and gait requires the whole nervous system; thus, there are multiple mechanisms of disequilibrium involving all levels of the nervous

system including the neuromuscular system.

2. Loss of peripheral sensory input (e.g., peripheral neuropathy, vestibular ototoxicity, cataracts)
3. Central nervous system disorders (e.g., cerebellar ataxia, Parkinson-like syndromes, hydrocephalus, cerebral arteriosclerosis)
4. Mal de débarquement syndrome (MdDS)
   - **a.** In MdDS, often after exposure to motion (e.g., airplane, boat), or sometimes without an apparent risk factor, the person with MdDS develops a persistent feeling of rocking that improves or resolves while in a moving vehicle.
   - **b.** There is usually an associated instability of posture and gait. Patients describe that they feel like they are walking on a trampoline.
   - **c.** Presumed to involve abnormal processing of motion information by the brain. MdDS is similar to motion sickness as both are induced by unfamiliar forms of motion. In motion sickness, however, the patient feels worse while moving. In contrast, the person with MdDS feels better while in motion.
5. Superior semicircular canal dehiscence syndrome (SSCD)
   - **a.** In SSCD, there is a defect in the otic capsule, the bone that normally surrounds the inner ear, particularly the portion of bone covering the superior semicircular canal.
   - **b.** Sound waves are propagated through the inner ear abnormally. This results in abnormally sensitive perception of bone-conducted sound including abnormally loud perception of one's own voice (autophony) and vertigo induced by loud sound (Tullio phenomenon). Some patients can hear the sound of a tuning fork conducted through the skeleton from as far away as their lower extremities.

Prognosis

1. Disequilibrium related to peripheral sensory loss (vestibular, proprioceptive, or visual) tends to be mild, leading to a cautious gait, but patients remain mobile unless multiple senses are impaired.
2. Cerebellar infarction or degeneration leads to a more profound gait disorder that is only minimally compensated over time.
3. Disequilibrium because of severe confluent cerebral white matter

abnormalities may result in significant, although not always, severe impairment of cognitive and gait function.

4. MdDS may last for days to years, and there are no known ways to predict time to resolution.
5. SSCD symptoms may improve with careful avoidance of triggering factors such as straining and exposure to loud sounds.

Diagnosis

1. The broad-based ataxic gait of cerebellar disorders is readily distinguished from the milder gait disorder seen with peripheral vestibular hypofunction or other sensory loss. Cerebellar patients typically have gaze-evoked nystagmus and other oculomotor signs.
2. A Romberg sign suggests either myelopathy, peripheral neuropathy, or bilateral vestibular hypofunction.
3. Patients with bilateral vestibular hypofunction characteristically report bouncing, jumping, or oscillation of the visual scene called oscillopsia while riding in a moving vehicle or walking. The diagnosis rests on finding a decrease or absence of normal responses to caloric and rotational stimulation. The diagnosis can be strongly suspected at the bedside with a positive head thrust test or if a patient loses more than two lines of vision on a near card during 2 Hz passive head rotation in the horizontal (yaw) plane.
4. MdDS is recognized by the characteristic history. Neuroimaging and vestibular test results are normal or nondiagnostic.
5. SSCD can be investigated noninvasively with an audiogram that includes air and bone conduction; this will typically shows supersensitive bone conducted thresholds in the affected ear(s), resulting in an air-bone gap pattern with bone conduction acuities less than 0 dB—this is referred to as a "pseudoconductive" pattern. Vestibular evoked myogenic potential (VEMP) studies show abnormally low thresholds and large amplitudes. Diagnosis is confirmed by temporal bone computed tomography (CT), with special protocols specifically designed to detect SSCD.

Treatment

1. Physical therapy is reasonable for all patients with disequilibrium.

Management of patients with disequilibrium caused by sensory loss should improve sensory function when possible and train the brain to adjust to the sensory loss. Most patients can be helped by improving support with canes, walkers, and railings. Lights should be turned on for walking at night to help the patient make use of visual cues. Patients can be taught to acquire added sensory information by touching things around them as they walk (obtaining haptic cues), often with surprisingly good benefit.

2. Underlying treatable disorders that can contribute to abnormality of gait should be addressed. Although many causes of peripheral neuropathy are not easily reversible, some are, such as those associated with autoantibodies and vitamin deficiency.
3. Gentamicin is a remarkably selective toxin for the vestibular system so that monitoring hearing is of little use. When aminoglycosides are used, particularly gentamicin and tobramycin, the patient should be carefully monitored with frequent examinations of gait and balance.
4. Patients with alcoholic/nutritional cerebellar degeneration can stop the progression and may even show some improvement after stopping alcohol and improving nutrition.
5. Of the supratentorial causes of disequilibrium, Parkinson disease is often dramatically improved with L-dopa therapy, although gait may respond less than the other Parkinsonian features. Conversely, the gait of some patients with features of Parkinson disease but without the full syndrome has been noted to improve on L-dopa.
6. Hydrocephalus is reversed with placement of a shunt often with improvement in gait.
7. There is no proven treatment for MdDS, but new therapeutic approaches are rapidly evolving as follows.
   a. We have occasionally noted improvement or resolution of symptoms while using serotonin selective reuptake inhibitors (particularly citalopram), tricyclic amines, and various other migraine prophylactic medications. A practical approach is to simply treat any associated anxiety disorders, headache disorders, and any other brain-based disorders as one ordinarily would for a person without MdDS and monitor whether the MdDS symptoms improve.
   b. If patients must travel and are expected to be reexposed to provocative motion, we sometimes prescribe clonazepam 0.5 mg p.o. 30 minutes

before the trip begins; however, this requires a careful discussion about the risks and benefits.

c. Repetitive transcranial magnetic stimulation and vestibuloocular reflex (VOR) readaptation are new and promising treatments but so far have not been thoroughly tested in controlled treatment trials.

3. The treatment of SSCD is surgical.

a. When the diagnosis is made, best management involves follow up both by an experienced surgeon (otologist/neurootologist) to review the surgical options and a neurologist to oversee conservative efforts, such as treatment of associated migraine or other disorders that may be contributing to the patient's dizziness.

VERTIGO

Background

Vertigo suggests a disorder of the vestibular system (anywhere from the inner ear and vestibular nerve to the many central vestibular pathways).

History

1. Patients describe an illusion of movement of the environment or self, usually that of rotation, although patients occasionally describe a sensation of linear displacement or tilt.

2. The history is inextricably linked to pathogenesis and is discussed in the next section.

Pathophysiology

The pathophysiology of vertigo depends on the underlying disorder (see below). Vertigo suggests but is not specific for an imbalance in vestibular tone. Vertigo can result from loss of peripheral input caused by damage to the labyrinth or vestibular nerve, or it can be caused by a unilateral impairment of vestibular nuclear or vestibulocerebellar activity. As a rule, the more acute the lesion, the more likely that vertigo will occur; although in some cases, the mechanism appears to be acute on chronic loss of vestibular function. In some

cases, vertigo is caused by various disorders that cannot be easily tied to the vestibular system per se.

1. Benign paroxysmal positional vertigo (BPPV) (also called "benign positional vertigo") is by far the most common cause of vertigo. It results from free-floating predominantly calcium carbonate crystals (normally attached to the utricular macule) with the debris most commonly accumulating in the posterior semicircular canal. With positional change (e.g., lying down or turning in bed), the crystals move within the endolymph and displace the cupula, altering firing rates of primary afferents in the vestibular nerve and causing paroxysmal vertigo that ends after the debris settles into a new equilibrium position in the semicircular canal.
2. Acute peripheral vestibulopathy (vestibular neuritis or labyrinthitis) often occurs after a viral illness, and pathologic studies show atrophy of one or more of the vestibular nerve trunks, most consistent with an infectious or postinfectious process. The involvement of vestibular nerve inflammation is further supported by the occasional visualization on magnetic resonance imaging (MRI) of enhancement of the vestibular nerve on the affected side in the acute phase of vestibular neuritis. Typically, patients describe relentless vertigo and postural instability for days, followed by persistence and gradual improvement of symptoms over weeks to months. If the affected person's gait and balance return to normal within a few days, the diagnosis should be doubted.
3. Ménière syndrome: The principle pathologic finding is an increase in the volume of the endolymph associated with distention of the entire endolymphatic system (endolymphatic hydrops), although hydrops has occasionally been documented at autopsy of temporal bones of people who did not have documented clinical Ménière syndrome. Ruptures of the membranous labyrinth might explain the sudden episodes of vertigo that are characteristic of the syndrome. There is limited evidence suggesting viral, autoimmune, and/or allergic pathophysiology in some patients. The cardinal symptoms are prolonged episodes of vertigo (hours) with associated unilateral ear symptoms including acute feelings of pressure, change in hearing, or change in tinnitus.
4. Migraine: Although it has classically been suspected that vasospasm could explain the commonly associated episodic vertigo, the genetic findings of ion channelopathies in some families with migraine suggest that migraine-

associated vertigo may be related to electrochemical events at level of the neuronal cell membrane. People with migraine almost always have a family history of migraine. The core criteria for migraine may be found elsewhere in this book. Suffice it to say that at some point, the patient should have had either headache with photophobia, headache with nausea, or a typical migraine visual aura. About a quarter of patients with migraine describe recurrent or persistent episodes of dizziness without clearly associated changes in hearing or tinnitus. Spontaneous vertigo attacks may occur during the headache, before the headache, or more often, completely independent of headache. A brain-based pathophysiology may also be suggested by photophobia. The typical duration of the vertigo and/or other types of migraine-associated dizziness is minutes to hours, although it can wax and wane for days. We have noted that symptoms of migraine are often exacerbated in the setting of a bout of BPPV.

5. Other peripheral causes: Bacterial labyrinthitis can result from primary infection or secondary to meningitis. Autoimmune inner ear disease (AIED) can be part of a systemic autoimmune disease or selective to the inner ear; AIED is followed closely with audiograms and sometimes with the help of multiple specialists including otology and rheumatology. Perilymph fistula can result from trauma or heavy lifting or in association with cholesteatoma or stapes surgery. The most commonly used ototoxic drugs are aminoglycosides (particularly gentamicin and tobramycin).
6. Vertebrobasilar insufficiency (VBI) is usually caused by atherosclerosis of the subclavian, vertebral, and basilar arteries. Vertigo is common with both transient ischemic episodes and with infarction of the lateral brainstem or cerebellum (see Chapter 13).
7. Cerebellopontine angle (CPA) tumors—usually these are vestibular schwannomas (previously called acoustic neuromas) or meningiomas—grow slowly, allowing the vestibular system to accommodate; therefore, a vague sensation of disequilibrium is more common than acute vertigo. Typically, these patients present with unilateral tinnitus or hearing loss.
8. Other central causes: A seizure can include vertigo, but in almost all such cases, there are added neurologic symptoms or signs that betray the epileptic nature of the event (see Chapter 2). Inherited cerebellar ataxia syndromes and Chiari malformation can present with positional vertigo and static (nonparoxysmal) positional downbeat nystagmus. Vertigo may also occur

with multiple sclerosis and with tumors of the brainstem or cerebellum.

Prognosis

The prognosis of vertigo depends on the underlying disorder. Vertigo is acute or recurrent in episodes and typically not chronic or continuous. If the latter history is obtained, think of other types of dizziness.

1. BPPV is cured with a simple particle repositioning maneuver. If not treated, it will often remit spontaneously after weeks to months, but most patients will have recurrences. The incidence of BPPV increases with age.
2. Acute (nonbacterial) peripheral vestibulopathy, also called vestibular neuritis or if hearing is involved, labyrinthitis, is usually a monophasic illness with rapid improvement over days and a return to good function over weeks to months. Vertigo may increase within the first few days, but by day 5, it usually settles down and resolves into a syndrome of head motion intolerance and postural instability. During recovery, patients often note an increase in light-headedness and imbalance toward the end of the day. True recurrences of the full acute peripheral vestibulopathy syndrome are very rare. Thus, when recurrent acute vestibular neuritis is proposed, one should consider the possibility of other diagnoses.
3. Ménière syndrome is characterized by recurrent episodes of fluctuating hearing loss, tinnitus, and vertigo, typically lasting for several hours. The natural course is for a progressive unilateral loss of hearing over several years, often eventually reaching a "burnt-out" stage where the episodes of vertigo subside. Severe, bilateral hearing loss is unusual, but when it occurs, the patient may be a candidate for a cochlear implant; the role of cochlear implants for severe unilateral hearing loss remains to be fully outlined and may ultimately favorably affect the prognosis.
4. Migraine: Attacks will occur at irregular intervals over many years typically increasing during periods of stress and around menopause. Over the years, as patients learn to identify and avoid their symptom triggers, many are able to control symptoms with a reduced reliance on medications.
5. Vertebrobasilar transient ischemic attacks are typically abrupt in onset, usually lasting for several minutes and are usually associated with other neurologic symptoms. They can be the prodrome of infarction in the brainstem or cerebellum (see Chapter 13).

5. Tumors in the CPA are usually associated with mild dizziness and disequilibrium; symptoms are not often progressive unless the tumor becomes large enough to compress the brainstem or cerebellum. Treatment of vestibular schwannomas often requires transection of the vestibular nerve. The impact of this is likely often lessened by previous compensation because of slow growth of the tumor, but some patients take a long time to recover normal balance after surgery.

Diagnosis

1. BPPV: For the most common *posterior canal variant*, a burst of torsional vertical nystagmus is induced by rapidly moving the patient from the sitting to a head-hanging position (the Dix–Hallpike test). There are typically a few seconds of latency and fatigue with repeated positioning. There is accompanying paroxysmal distress and vertigo that follows the same temporal profile with latency, a finite duration and fatigue with repeated positioning. The head hanging right and left positions should be held for at least 10 seconds to allow for the possibility of BPPV with a longer than average latency. If the history is suggestive, and nystagmus is not elicited, the patient should be reexamined after a few minutes lying supine or at a later date (e.g., the next day). With the *horizontal canal variant*, a burst of horizontal nystagmus beating toward or away from the ground is induced by turning the head to the right and left with the patient in the supine position.
2. Vestibular neuritis: Characteristic clinical profile (spontaneous prolonged vertigo that gradually resolves over days into a syndrome of head motion intolerance and gait instability), examination findings consistent with a unilateral peripheral vestibular loss (spontaneous nystagmus and positive head thrust test). If in addition the patient has acute hearing loss in the same ear, the term “labyrinthitis” is used. Rarely, patients deny vertigo at onset but have prominent postural instability with all of the other expected signs and laboratory abnormalities. Vestibular testing typically shows a unilateral caloric paresis and multiple abnormalities on rotational testing in the dark.
3. Ménière syndrome: Fluctuating hearing levels occur (particularly in the low frequencies) in a patient with the characteristic prolonged (more than 20 minutes) episodes of vertigo. An audiogram is critical for the diagnosis. If there is no evidence of low-frequency hearing loss, the diagnosis of Ménière

syndrome should be questioned. Sometimes, development of interictal (between vertigo attacks) hearing loss is delayed, but if symptoms persist for more than a year with normal hearing, another diagnosis should be considered, and the most common differential diagnosis in this setting is migraine; also note that many patients will meet criteria for both migraine and Ménière.

4. Migraine: Diagnosis of exclusion in the patient with long-standing recurrent attacks of vertigo, normal hearing, and headaches that meet the International Headache Society (IHS) criteria for diagnosis of migraine. The diagnostic criteria for vestibular migraine are evolving but currently require a migraine-associated symptom (headache, light or sound sensitivity) with 50% of dizzy spells.
5. Vertebrobasilar transient ischemic attacks come abruptly without any apparent precipitating factor, last for a few minutes, and then end abruptly. There are nearly always associated symptoms and signs, such as visual loss, diplopia, dysarthria, weakness, or numbness. On neuroimaging, one should not forget to visualize the vertebral artery origins in the chest (see Chapter 13).
6. Brainstem infarction: Stroke syndromes involving the posterior circulation are usually easily identified on the basis of their characteristic combination of neurologic symptoms and signs and typical MRI findings.
7. Cerebellar infarction: Can masquerade as a more benign inner ear disorder, particularly if the damage is limited to the distribution of the medial branch of posterior inferior cerebellar artery (PICA). However, profound truncal ataxia with abnormal gait and a direction-changing, gaze-evoked nystagmus usually indicate a central lesion. MRI is the procedure of choice for viewing brain structures supplied by the vertebrobasilar system, although the intracranial large arteries and veins are usually better visualized with computed tomography angiography (CTA) compared to magnetic resonance angiography (MRA), necessitating a weighing of risks and benefits to select patients for use of contrast and x-rays.
8. CPA tumors: Detailed audiometric testing followed by neuroimaging—typically MRI of brain and internal auditory canals (IAC) with contrast—will usually lead to a diagnosis. Audiologists are trained to suspect a CPA tumor if speech discrimination (word recognition) is impaired out of proportion to abnormalities of pure tone threshold, as this suggests a

retrocochlear lesion such as a CPA tumor. The bedside version of this is to test whether patients can understand whispered speech well in both ears. MRI of the brain and IAC with contrast is the procedure of choice because it can identify small tumors confined to the internal auditory canal, tumors that are missed with CT scanning and by noncontrast MRI.

Treatment

Nonspecific Symptomatic Treatment

The best therapy for acute vertigo is to eliminate the underlying cause when possible (see the following section). When the pathophysiology is unknown, and definitive treatment is not available, and symptoms persist, symptomatic treatment with medication and physical therapy are indicated. Two general categories of drugs are used in the symptomatic treatment of vertigo and nausea: vestibular suppressants and antiemetics.

1. Vestibular suppressants act at the level of the neurotransmitters involved in propagation of impulses from primary to secondary vestibular neurons and in the maintenance of tone in the vestibular nuclei. When taken orally, they typically take about 20 to 30 minutes to have an effect and 2 hours or more before they have a peak effect. Therefore, with severe acute vertigo, a parenteral route is often preferable. Common side effects include dryness of the mouth and sedation, but all of these drugs have multiple side effects that should be reviewed before use.
   - **a.** Meclizine: 12.5 to 50 mg; oral, q 8 hours as needed.
   - **b.** Dimenhydrinate: 25 to 100 mg; IM, IV, oral, suppository, q 8 hours as needed.
   - **c.** Scopolamine: 1.5 mg; transdermal patch, q 3 days. We have found that to taper, these can be cut and a half or small fraction of a patch used.
   - **d.** Promethazine: 12.5 to 50 mg; IM, IV, oral, suppository, q 8 hours as needed.
   - **e.** Lorazepam: 0.5 to 2 mg; IM, IV, oral, q 8 hours as needed. Lorazepam can also be taken 0.5 mg sublingually at the onset of vertigo (e.g., in patients with recurrent attacks of vertigo in the setting of Ménière).
2. Antiemetic drugs have central dopamine and anticholinergic properties and are thought to prevent nausea and vomiting by inhibiting emetic centers.

Occasionally, these antiemetic drugs produce serious side effects, particularly in young patients. The major reactions can be categorized symptomatically as parkinsonism, akathisia, dystonia, and dyskinesia. The latter can be acute and reversible or subacute (tardive) and prolonged or permanent.

a. Prochlorperazine: 2.5 to 10 mg; IM, IV, oral suppository, q 8 hours as needed.

b. Metoclopramide: 5 to 10 mg; IM, IV, oral, q 8 hours as needed. We prefer to avoid this drug if possible because of a multiplicity of side effects, but it is occasionally useful.

c. Ondansetron: 8 mg; IV or oral, up to q 8 hours as needed.

3. Vestibular rehabilitation

4. After an acute peripheral vestibular lesion, compensation proceeds rapidly over several days and then slows down. Even if the vestibular loss (as measured for example by caloric testing) is permanent, most patients will recover reasonably well. Vestibular suppressants and antiemetics may impair the compensation process so they should only be used for the first few days. As soon as vomiting ceases, the medication should be gradually withdrawn, and this appears to stimulate normal compensation. Controlled studies in animals and humans have shown that an exercise program can accelerate the compensation process after an acute peripheral vestibular lesion. Sample exercises:

a. During the acute stage, when nystagmus is prominent, the patient should attempt to focus the eyes and hold them in the direction that provokes dizziness.

b. Once the nystagmus diminishes to the point that a target can be held visually in all directions (usually within a few days), the patient should begin eye and head coordination exercises. A useful exercise involves staring at a visual target while oscillating the head from side to side and up and down. The speed of the movement can be gradually increased, as long as the target can be kept in good focus.

c. Target changes using combined eye and head movement to jump quickly back and forth between two widely separated visual targets.

d. The patient should try to stand and walk while nystagmus is still present. It may be necessary to walk in contact with the wall or to use an assistant in the early stages. Slow supported turns should be made initially.

e. As improvement occurs, head movement should be added while standing and walking. At first, slow side-to-side and up-and-down movements and then fast head turns in all directions.

f. The compensation process occurs at a variable rate, dependent on multiple factors including age, but should be nearly complete within 2 to 6 months after an acute peripheral vestibular damage. Dizziness that persists beyond this time indicates either the presence of an ongoing vestibular disorder or poor central compensation.

Treatments for Specific Disorders

1. BPPV

a. Most patients with BPPV can be cured at the bedside with simple particle-repositioning maneuvers. The basic idea is to move the patient around the plane of the affected semicircular canal to allow the freely floating debris to rotate around the canal and out into the utricle. The maneuver to treat the most common *posterior canal variant* of BPPV is performed immediately after the diagnosis is confirmed by the Dix–Hallpike positioning test (Fig. 3-1).

b. Although many patients are cured with a single particle-repositioning maneuver, the cure rate is improved by repeating the procedure until no vertigo or nystagmus occurs on positional testing. Occasionally, vibration applied to the mastoid region is useful, particularly if the patient develops a slow, long duration nystagmus, rather than a brief burst of nystagmus with position change, or if the latency before the nystagmus begins is atypically long; the latter patterns of nystagmus suggest the debris is stuck to the wall of the semicircular canal or is attached to the cupula and not freely moving. For some patients, a series of particle repositioning maneuvers may be needed, in which case it may be helpful to enlist the help of a vestibular physical therapist.

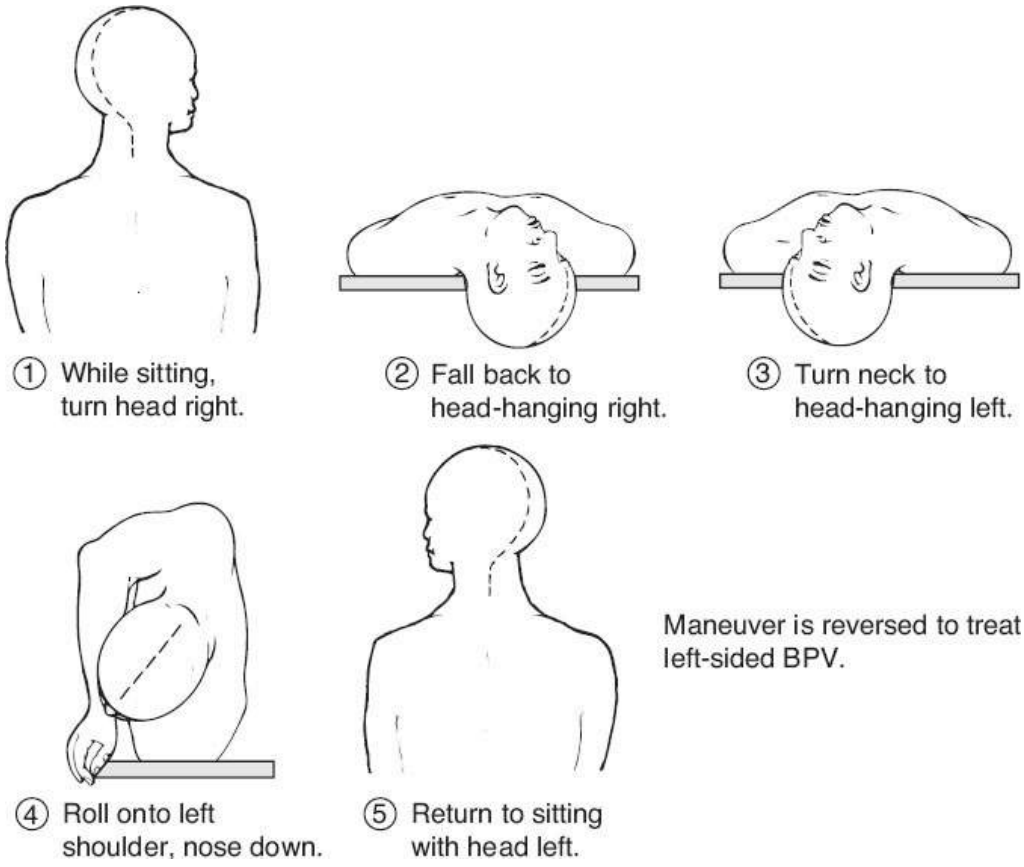

Figure 3-1. Maneuver for treating right-sided benign positional vertigo.

c. If the patient elevates the head during the movement from one head-hanging position to the other (e.g., right to left), the particles may move back in the opposite direction, away from the utricle defeating the effectiveness of the maneuver. It is critical that the head stays down during this phase of the positioning maneuver.

d. When returning to the sitting position at the end of the particle-repositioning maneuver, the patient may have a brief but violent burst of vertigo as late as a few minutes after assuming the sitting position. Presumably, this delayed vertigo occurs as the bolus of otolith debris drops out of the canal into the utricle.

e. For treating the *horizontal canal variant* of BPPV the patient is rolled in the plane of the horizontal semicircular canal while lying supine. The patient starts in the supine position and is rolled 90 degrees toward the normal side (the side with the lesser horizontal nystagmus), then in 90-degree steps to prone, to the abnormal side, and back to supine. Lying on

the side with the healthy ear down for several hours or even overnight is also effective. Horizontal canal BPPV tends to be more refractory than posterior canal, so persistence is critical until signs and symptoms resolve.

f. Patients who have multiple recurrences of BPPV can be taught to perform the particle-repositioning maneuver on their own. Some may benefit from premedicating themselves with meclizine or dimenhydrinate so that they feel more comfortable performing the maneuver in the controlled environment of their bedroom.

g. After a successful cure, patients may want to avoid extreme head-back positions (e.g., at the hairdresser or at the dentist's office), as these positions may allow any debris that happens to be present in the utricle to reenter the semicircular canal.

2. Acute peripheral vestibulopathy (vestibular neuritis and labyrinthitis)

a. Symptomatic treatment of vertigo

1) Vestibular suppressants and antiemetic drugs are effective in most patients with vestibular neuritis, but there have been few controlled studies available.

2) The response is clearly dose-dependent, so if the initial dose of vestibular suppressant or antiemetic drug is not effective, then higher doses should be tried.

3) All vestibular suppressant medications can be sedating; therefore, they should not be used when performing activities requiring a high level of alertness (e.g., driving, operating machinery, or performing athletic activities).

4) Less sedating drugs such as oral meclizine and transdermal scopolamine are useful for milder vertigo later in the course, but use of these should be minimized after the first few days. In our experience, many cases of prolonged recovery after vestibular neuritis have involved persistent use of meclizine.

5) Because of the multiple effects of each of these drugs, possible drug interactions should always be considered before use.

b. Vestibular exercises

1) Recovery from vestibular neuritis typically takes several weeks, although longer periods of recovery are not uncommon. The main goal of vestibular rehabilitation (see earlier) is to accelerate the vestibular

compensation process and improve the final level of recovery. Typically, patients know when it is appropriate to stop doing the home exercises that physical therapists typically dispense; if these are stopped prematurely, symptoms may increase. The necessary duration of exercises varies between individuals. Walking on uneven ground such as grass or sand may facilitate recovery of balance.

2) In animals, compensation after vestibular injury seems to be accelerated by stimulant drugs (e.g., amphetamine) and slowed by sedating drugs (e.g., diazepam).

c. Corticosteroids and antiviral drugs

1) One prospective randomized placebo-controlled study found that high-dose steroids but not valacyclovir was significantly better than placebo for recovery of peripheral vestibular function (caloric response) in patients with vestibular neuritis.

2) Until more data are available on risk/benefit, steroids can only be recommended for otherwise healthy individuals who present within a few days of onset. Suggested treatment regimen: methylprednisolone 100 mg initially and then tapered off by 20 mg every 3 days, or a similar course of prednisone starting at 60 mg. Individual factors often influence the treatment plan.

3) If the syndrome involves facial palsy as in the Ramsay Hunt syndrome, some prescribe a course of an antiviral medication such as valacyclovir 500 mg p.o. b.i.d. for 7 to 15 days, although admittedly the evidence base for this recommendation is limited.

3. Ménière syndrome

a. Management of dietary sodium

1) Medical management of Ménière syndrome typically begins with a sodium-restriction diet in the range of 1 to 2 g of sodium daily with a minimum therapeutic trial of 3 months to determine effectiveness. Patients should make an effort to spread out consumption of sodium over the course of each day. Fluid and food intake should be regularly distributed throughout the day, and binges (particularly food with high sugar and/or salt content) should be avoided.

2) If a good response is obtained, then the level of salt intake can in some cases be gradually increased while symptoms and signs are carefully monitored.

3) Occasionally, patients will notice that certain foods (e.g., alcohol,

coffee, chocolate) may precipitate attacks. We generally suggest no more than 1 dose of caffeine and/or alcohol per day.

b. Diuretics (hydrochlorothiazide 25 mg once or twice per day, triamterene 37.5 mg with hydrochlorothiazide 25 mg once or twice per day, or acetazolamide 125 to 250 mg p.o. b.i.d.) may provide additional benefit in some patients, although these drugs do not seem to fully replace a salt-restriction diet. Acetazolamide (250 mg once or twice a day) has been shown to decrease the osmotic pressure of the inner ear in experimental endolymphatic hydrops in guinea pigs, but there have been no controlled studies to see how acetazolamide compares with hydrochlorothiazide or other diuretics in the treatment of Ménière syndrome. Acetazolamide may also be beneficial for treatment of migraine, and it therefore is a reasonable therapeutic consideration for the patient with features of both migraine and Ménière syndrome.

c. Vestibular suppressants such as meclizine or promethazine are usually effective in aborting acute attacks of vertigo, nausea, and vomiting. These drugs should be taken as soon as possible, preferably during the prodrome if there are reliable warning symptoms. An antiemetic drug such as prochlorperazine or ondansetron may also be useful. One must balance the need to control vertigo against the need for the patient to maintain full mobility and function. In general, the stronger vestibular suppressants are more sedating and are reserved for the acute treatment of severe vertigo.

d. Surgical treatments: Although procedures aimed at the endolymph duct and sac (shunting and drainage) are logical based on the presumed pathophysiology of Ménière syndrome, in practice, these procedures have not been highly effective. Ablative procedures are most effective in patients with unilateral involvement who have no functional hearing on the damaged side. Vestibular neurectomy has the advantage of preserving hearing in a patient with residual cochlear function.

e. Gentamicin injection into the middle ear so that it enters the inner ear through the round window is a simple procedure that can be done on an outpatient basis and does not preclude later, more definitive surgical procedures. As noted earlier, gentamicin is remarkably selective in its vestibular ototoxicity.

l. Migraine

a. For less frequent acute episodes of dizziness and nausea: Antiemetics and antivertiginous vestibular suppressant drugs as discussed earlier.
   1) Promethazine (25 or 50 mg) is particularly effective for relief of vertigo and nausea. It has sedation as a side effect, but this is usually acceptable in a patient who is eager to sleep.
   2) Treatment of headache is dealt with in Chapter 12.

b. Nonpharmacologic interventions: Regular sleep, regular nutritious meals and avoidance of excessive caffeine, relaxation strategies.

c. Migraine prophylactic treatment: The mechanism of action of drugs for migraine remains speculative. A trial of a migraine prophylactic agent is warranted in any patient with episodic vertigo of unknown cause and a history of migraine headaches, or a strong family history of migraine. We begin with the lowest possible dose and gradually work up based on response and side effects.
   1) Tricyclic amines (e.g., nortriptyline 10 mg p.o. qhs)
   2) β-Blockers (e.g., propranolol 10 mg p.o. b.i.d.)
   3) Calcium channel blockers (e.g., verapamil 40 mg p.o. t.i.d.)
   4) Carbonic anhydrase inhibitors (e.g., topiramate 15 to 25 mg p.o. qhs, acetazolamide 125 mg p.o. b.i.d.)
   5) Selective serotonin reuptake inhibitors (e.g., sertraline 25 mg p.o. daily, citalopram 20 mg p.o. daily)

Other Peripheral Causes of Vertigo

I. Bacterial labyrinthitis

a. Any patient with acute or chronic bacterial ear disease associated with sudden or rapidly progressive inner ear symptoms should be hospitalized and treated with local cleansing and topical antibiotic solutions to the affected ear as well as parenteral antibiotics capable of penetrating the blood–brain barrier.

b. If the labyrinthitis is secondary to primary meningitis, it is best managed by treating the underlying meningitis (discussed elsewhere in this book). A resistant or recurrent meningitis may result from unrecognized posterior fossa epidural abscesses with dural perforation or from congenital direct communications with the cerebrospinal fluid.

c. Surgical intervention to eradicate the middle ear and mastoid infections is often required after a few days of antibiotic treatment.

2. Perilymph fistulas associated with head trauma, ear surgery, barotrauma, or sudden strain during heavy lifting, coughing, or sneezing.
   a. Bedrest, elevation of the head, and avoidance of straining.
   b. If symptoms persist despite bedrest, exploration of the middle ear for repair of the fistula may be considered.
3. AIED (either in isolation or as part of a systemic autoimmune process). Typically associated with subacute, bilateral sequential hearing loss that responds to treatment with a corticosteroid such as prednisone.
   a. High-dose steroids (60- to 100-mg prednisone, 12- to 16-mg dexamethasone) maintained for at least 10 to 14 days and then tapered slowly, monitoring with audiograms to ensure stability of hearing.
   b. If symptoms recur as the steroids are tapered, then more long-term immunosuppression with steroid-sparing drugs may be required, and assistance from a rheumatologist may be beneficial.
4. Ototoxicity
   a. Prevention is the key to management.
   b. Kidney function should be monitored when using any potentially ototoxic drug, and patients in high-risk groups such as those with kidney failure should probably not be given ototoxic drugs that are excreted by the kidney.
   c. Patients should be questioned on a regular basis during antibiotic administration to identify early symptoms of vestibular loss including dizziness and oscillopsia.
   d. When the earliest effects of ototoxicity are recognized, adjustments in the dose schedule or discontinuation of the ototoxic medication may reduce the likelihood of developing permanent symptoms. Often other drugs can be substituted that are less ototoxic. The ototoxic effects may be reversible if the drug is stopped early enough but reportedly there have been rare cases of ototoxicity after a single dose of an ototoxic medication. Nevertheless, courses of ototoxic medication should be kept as short as possible.
5. Vertebrobasilar transient ischemic attacks (see Chapter 13).
6. Labyrinthine infarction
   a. As with other unilateral peripheral vestibulopathies, symptomatic medications can help relieve the acute vertigo and nausea.

b. Vestibular rehabilitation exercises should be started as soon as the patient is able to cooperate.

7. Brainstem and cerebellar infarction

a. In select cases, intra-arterial thrombolysis or clot retrieval might be considered.

b. Unfortunately, antivertiginous medications are less effective for controlling central vertigo than for peripheral vertigo, and vestibular rehabilitation exercises are also usually less effective.

8. CPA tumors

a. Observation: One might follow a patient with a small tumor, particularly if the patient is older or has underlying medical problems. Serial MRI studies have shown that most vestibular schwannomas grow slowly, if at all.

b. Surgical approaches to the CPA: (1) translabyrinthine, (2) suboccipital, and (3) middle fossa. The translabyrinthine approach destroys the labyrinth but often allows complete removal of the tumor without endangering other nearby neural structures, particularly the facial nerve. The other approaches have the advantage of possibly saving residual hearing, but there is a greater risk of damage to the facial nerve. (4) Stereotactic radiosurgery provides another alternative for treating CPA tumors, particularly in high-risk patients. It may be ideal for managing acoustic neuromas associated with neurofibromatosis type II because eventually tumors will be bilateral in most cases; one drawback may be that subsequent conventional surgery may be made more difficult by the effects of previous radiation.

Other Central Causes of Vertigo

1. Tumors of the cerebellum and brainstem

a. Biopsy and surgical resection of the tumor when possible are the treatments of choice.

b. For metastatic tumors, the primary tumor can be biopsied if it can be found.

c. For unresectable tumors, radiation therapy is often beneficial. Prolonged survival is not uncommon with more benign astrocytomas. Medulloblastomas are very sensitive to radiation therapy.

2. Chiari type I and II malformations
   a. Suboccipital decompression of the foramen magnum region may stop the progression and occasionally lead to improvement in neurologic symptoms and signs, but patients should be chosen carefully for these neurosurgical procedures with every effort being made to exclude other more common causes of vertigo, which respond favorably to less invasive forms of therapy. Evidence for brainstem compression is sometimes evident from oculomotor testing (e.g., saccadic smooth pursuit in a younger patient).

3. Inherited and/or familial ataxia
   a. Patients are encouraged to use a cane or walker to improve sensory input and to avoid falls.
   b. Regular physical therapy to maintain range of motion about all joints is critical to avoid painful contractures.
   c. A diet low in long-chain fatty acids can be effective in controlling the progression of symptoms and signs in patient with Refsum disease.
   d. Acetazolamide is often remarkably effective in relieving the episodic symptoms in patients with episodic ataxia type II and is occasionally effective in patients with episodic ataxia type I. One typically begins with a low dose (125 mg/d) and then works up to an average effective dose of between 500 and 1,000 mg/d.
   e. Anecdotally, amantadine may improve motor function in some patients.

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4 Back and Neck Pain

Allan H. Ropper

LOW BACK PAIN

Background

1. Back pain is common in general and neurologic practice. Half of adults have experienced mild to moderate back pain at some time, many of whom were unable to work as a result.
2. Prior to being seen by a neurologist, most patients have seen other practitioners, making the neurologist an arbiter of previously provided information.
3. The majority of chronic low back pain has a mechanical basis in degenerative spinal disease of the joints, discs, and bones.
4. The examination for back pain infrequently reveals a specific diagnosis. The history often exposes the more serious causes.

History

1. Chronic back pain
   - **a.** The typical symptom is chronic "aching" in the low back, most often in the region of the lower lumbar spine, across the posterior waist, in the upper ramus of the iliac crests, or over the sacrospinal ligaments or sacroiliac joints.
   - **b.** Aching pain may be worse on awakening or increase through the day with activity or after prolonged sitting. Both are characteristic of benign "arthritic" causes.
   - **c.** Chronic low back pain from degenerative disease displays little limitation of motion, but there may be broad areas of tenderness over the muscles,

ligaments, and joints throughout the low back.

d. Severe osteoporosis or osteopenia gives rise to vague, relatively constant low back pain, but the majority of patients with these processes do not have pain.

e. Nocturnal pain, especially awakening the patient in the middle of the night, suggests metastatic disease in the spinal column and should not be attributed to arthritic back pain without further investigation.

f. A history of known active cancer, fever, night sweats, weight loss, recent bacteremia, HIV, or pulmonary tuberculosis suggests infectious or neoplastic infiltration of the spine.

g. Lumbar stenosis (see further on) is a disease of the older population, mainly men, characterized by aching back pain and claudication-type sciatic and leg pain that is induced by walking and relieved with rest.

h. Leg weakness, sensory changes in the legs or trunk, and bladder dysfunction indicate compression of the spinal cord or cauda equina and are not consistent with the nondescript types of back pain discussed here.

i. Persistent and increasing lumbar pain of recent onset without a history of recurrent discomfort earlier in life, compels consideration of retroperitoneal disease including renal cell cancer, pancreatic cancer, duodenal ulcer, abdominal aortic dissection, and retroperitoneal hematoma.

2. Acute back pain

a. Sudden mechanical injury from awkward positioning, being thrown or falling, lifting, and trauma elsewhere in the body are the main causes of acute back pain, called “strain.” Pain may be delayed by hours after the inciting event.

b. Lumbar disc rupture may cause acute back pain at the time of the event. The pain is often lateralized.

c. In acute low back strain, there is a disinclination to bend, twist, or extend the lower torso and the paraspinal muscles, accompanied by the assumption of protective postures of the trunk, and there may be palpable muscle spasm.

d. In adolescents, acute low lumbar pain after minor injury may indicate spondylolysis, a congenital weakness of the pars interarticularis that is prone to fracture usually at L5.

e. Focal thoracic or lumbar back pain may be the result of a compression fracture. Usually there has been a fall on the buttock or back, but major injury is not necessary if the bones are osteopenic.

f. Severe pain after direct trauma to the spinal column or head is a more serious matter of specialized nature because of potential disruption of the ligaments and supporting bony structures that result in instability of the spinal column.

g. As with chronic back pain described earlier, leg weakness, sensory changes in the legs or trunk, and bladder dysfunction indicate compression of the spinal cord or cauda equina and are not consistent with the nondescript types of back pain discussed here.

h. Disc rupture causes projected pain along the distribution of the adjacent nerve root: For example, L5 rupture is perceived as sciatica; there may also be acute pain over the L5–S1 facet joint.

Pathophysiology

1. The pain-sensitive structures that generate low back pain include free nerve endings in the periosteum, capsule of the facet joints, and annulus surrounding the disc.
2. The origin of most chronic low back pain is osteoarthritis involving the facet joints, discs, and degeneration of the spinal ligaments. A role of inflammation in these structures has not been established, but some treatments are oriented to that component.
3. Degenerative arthritic changes lead to hypertrophy of the bone surrounding the facet joints and, in advanced cases, loosening of the structural elements that maintain alignment of the spine.
4. The resultant instability may lead to spondylolisthesis, or slippage of one vertebral segment upon an adjacent one. This results in narrowing of the spinal canal and compression of the cauda equina roots that may itself cause pain.
5. Pain referred to a distant site from bony or disc disease is termed "sclerotogenous" and has a distribution that approximates neurogenic "referred" pain from root compression, but it tends to be less severe, fluctuates more, and is vaguer in localization.
6. Much back pain is described as "muscular" and is located in the paraspinal

muscles; it has been presumed that pain receptors in the muscle contribute to discomfort.

7. A relationship of chronic low back pain with posture, abdominal girth, and fatigue of muscles has long been proposed but without definite basis.

Prognosis

1. Most nonmalignant acute back pain is self-limited, but certain individuals are prone to repeated acute injury and chronic discomfort.
2. Most studies show about 50% improvement in acute pain level by 1 month, continued slower improvement over the following 2 months, and persistent pain in those who have not improved by that time.
3. The risk of recurrence of acute back pain within 3 months of an episode is about 25% and within a year is about 75%.
4. The prognosis of infectious, inflammatory, or malignant low back pain is determined by the nature and treatment responsiveness of the underlying process.

Diagnosis

1. Straight leg raising and derivative maneuvers and the motor, reflex, and sensory examination are most useful in detecting lumbar root compression as described further on.
2. Sharp percussion of the spine may disclose tumor infiltration or compression fracture of a vertebral body.
3. Imaging of the lumbar spine with x-ray, computed tomography (CT), or magnetic resonance imaging (MRI) is not required in cases that conform by history to musculoskeletal or acute mechanical low back pain.
4. Plain films of the lumbar spine have limited value but may demonstrate degenerative arthritis and may reveal metastatic disease to spinal bones. Views in flexion and extension are useful in detecting instability of lumbar segments as the source of back pain.
5. Degenerative changes of the joints and disc spaces on imaging studies are common with aging. Their presence does confirm that these changes are the cause of low back pain.
6. Pain that persists for more than several weeks and is not explained by

preceding bouts of acute injury should have imaging to detect cancer, fracture, and osteomyelitis.

7. In cases of otherwise unexplained deep lumbar pain or flank pain, imaging of the retroperitoneal space, abdomen, and sometimes the pelvis, is advisable.
8. Sedimentation rate, C-reactive protein, blood cultures, and immunoelectrophoresis are useful to exclude infection, cancer, and myeloma in appropriate cases.

Treatment

1. Many symptomatic treatments, particularly acetaminophen and nonsteroidal anti-inflammatory agents, but also stretching of low back muscles, heat applied externally or through diathermy, and massage are used for acute low back pain with no clear superiority of one over the other.
2. Muscle relaxants and diazepines have an ambiguous role and have not been shown to be particularly effective.
3. Patients with painful low back strain may be obliged to rest in bed or easy chair, but beyond symptomatic relief, there is no evidence that rest speeds improvement. The patient can determine the most comfortable position—lying with pillows under or between the knees or decubitus position may reduce pain.
4. Chiropractic adjustment may speed the return to functional capacity after low back strain. Low-velocity distraction and ballottement administered by qualified physical therapists are also helpful. Compression fracture, cancer, or infection are reasons to avoid adjustments.
5. Instructions in proper biomechanics of sitting, lifting, bending, and carrying are appropriate for individuals with recurrent or postural low back pain. Weight support belts for workers may reduce injury.
6. Changes in mattress firmness and automobile seats that provide back support are found to be helpful for some patients.
7. Patients with chronic low back pain as part of a depressive–chronic pain syndrome may respond to antidepression medications. This diagnosis should be made sparingly.
8. Back pain from bulging but non-ruptured discs alone is not aided by surgery.
9. In the special circumstances of degenerative spondylolisthesis, pain may be

improved by surgery with fusion, but cases must be selected with care. More harm than good is done by ill-considered surgery (see later sections).

SCIATICA

Background

1. Sciatica refers to sharp and aching pain that originates in the buttock or gluteal fold and radiates down the back or lateral aspect of the thigh. The term has been used for other nondescript back and leg pains but then loses its utility as a sign of nerve root compression.
2. Unlike the types of low back pain described in earlier sections, sciatica usually indicates L4, L5, or S1 nerve root compression.
3. Bilateral sciatica usually signifies severe degenerative spinal disease.

History

1. The patient describes pain beginning in or around the buttock on one side and radiating to the posterior or posterolateral thigh. Radiation below the knee or into the foot occurs but is uncommon.
2. Most sciatica does not have acute precipitating events, but lifting, twisting, or back injury may precede the symptom. The combination of paraspinal lumbar pain followed in hours or days by sciatica is most characteristic of lumbar disc rupture.
3. The severity of sciatic pain varies, but at its extreme, it is very disabling and prevents either sitting, standing, or walking.
4. A few patients with sciatica have additional neurologic symptoms: numbness in the foot, foot drop, or weakness of foot plantar flexion.
5. Chronic low back pain and limitation of lumbar motion when associated with sciatica suggest lumbar stenosis (see later section).
6. Bilateral sciatica with either leg weakness or urinary incontinence with indicates compression of the cauda equina, an urgent condition.

Pathophysiology

1. Compression of one L4, L5, or S1 is the usual source of sciatica; the pain is

a neurogenic referred pain.

2. The common causes are disc rupture and spondylitic bony overgrowth within the spinal canal; less common are synovial cyst and benign nerve sheath tumors.
3. The sciatic nerve may be compressed or injured within the gluteal muscle because of injection hematoma or trauma and infrequently, by entrapment under the piriformis muscle (piriformis syndrome).

Prognosis

1. Sciatica most often improves with time. One-third of patients improve within 2 weeks and three-quarters within 3 months, but the remainder continues to have pain at variable levels.
2. The duration or severity of sciatic pain can represent unacceptable disability and loss of work time for certain individuals. Treatment is then directed at the underlying cause of nerve root compression (see later section).
3. Recurrent and intermittent sciatica occurs in half of patients.

Diagnosis

1. The straight leg raising test indicates root compression if pain radiates from the buttock to below the knee when the angle of the leg is between 30 and 70 degrees. Sensitivity of the test for disc herniation is approximately 90%, but specificity is low. A positive test (Lasègue sign) requires the elicitation of sciatica, not simply hamstring tightness.
2. Sciatica in the opposite leg is 90% specific sign for root compression by disc on the side of pain (crossed straight leg raising, Fajersztajn sign).
3. The motor, sensory, and reflex features of the major disc syndromes causing sciatica are listed in Table 4-1.
4. Imaging of the lumbar spine can be delayed for several weeks unless there are unusual features such as severe and intractable low back pain, considerable leg or foot weakness, or bladder difficulty that may mandate surgical treatment. Plain x-rays are least informative. I perform MRI if sciatica has not resolved in several weeks and surgical or other invasive treatment is contemplated.

Table 4-1 Lumbar Root Syndromes

Root/Disc Level	Pain Distribution	Muscle/Weakness	Reflex Loss	Sensory Loss
L3/(L2–L3)	Anteromedial thigh, over knee	Adductor longus—hip adduction Partial quadriceps (shared L3 and L4)—knee extension	Reduced knee jerk	Medial thigh
L4/(L3–L4)	Anterolateral thigh	Partial quadriceps (shared L3 and L4)—knee extension	Reduced or absent knee jerk	Medial malleolus
L5/(L4–L5)	Sciatica—posterior thigh	Tibialis anterior—foot drop Extensor hallucis longus—toe extension	None or reduced medial hamstring reflex	Lateral lower leg and great toe
S1/(L5-S1)	Sciatica—posterior thigh into ankle	Gluteus medius—hip abduction Hamstrings—knee flexion Gastrocnemius—ankle flexion Flexor digitorum brevis—toe flexion	Reduced or absent ankle jerk	Lateral foot and sole

5. Hip disease may be difficult to distinguish from sciatica. The Patrick test (downward pressure on the knee of the leg crossed over the opposite one with the foot placed on the opposite knee) and external rotation of the hip with the knee flexed do not elicit sciatica but may elicit hip pain from osteoarthritis.
6. Other causes of sciatica are infrequent but include the preeruptive phase of shingles in a lumbar or sacral root, metastases to the spine, inflammatory radiculitis (mainly Lyme; Bannwarth syndrome, or recurrent herpes simplex type 2 [Elsberg syndrome]), neurofibroma, synovial facet cyst, and carcinomatous meningitis.

Treatment

1. As with nondescript musculoskeletal low back pain, there is no evidence

that bed rest, traction, heat, chiropractic manipulation, or physical therapy aids the resolution of sciatica. The effects of various exercise and musculoskeletal programs have been difficult to determine, and no program seems more effective than another.

2. Several randomized trials have demonstrated that sciatic pain that has persisted for 6 to 12 weeks improves faster with surgery than with conservative treatment, but by 1 year, there are few differences in pain or disability with and without surgery. In these trials, almost half assigned to conservative treatment nevertheless eventually chose to have surgery for symptom relief.
3. I counsel patients to stay active within the limits of pain tolerance and to take nonsteroidal pain medications for several weeks, if tolerable to the patient, before advising surgery. I counsel that pain from disc herniation can be rapidly eliminated by surgery, but that waiting is a reasonable option and the choice is based on lifestyle, job, and personal needs.
4. Sciatica that is severe, bilateral, or associated with severe foot or leg weakness or bladder or bowel dysfunction is an indication for surgery. Nevertheless, patients with tolerable foot drop or regional sensory loss alone may be offered the option of waiting for spontaneous improvement.
5. Sciatica in the absence of well-defined disc herniation or spondylosis that compresses the neural root foramen on imaging studies does not respond well to surgery.
6. Epidural steroid injection and similar procedures help some patients but have failed to demonstrate sustained benefit in controlled trials. Patients with disabling pain who do not wish to, or are unable to, have surgery (see below) are referred for one of these procedures. If there is no improvement after one or two treatments, I do not recommend subsequent injections.
7. Oral glucocorticoids, antiepileptic medications, muscle relaxants, and antidepressants have no firm basis for use.

LUMBAR STENOSIS

Background

1. This term applies to degenerative narrowing of the lumbar spinal canal with

compression of lumbosacral roots.

2. The most characteristic feature is progressive posterior leg or calf pain with increasing walking distance.
3. Signs and symptoms are exaggerated or more likely to arise in individuals with congenitally narrow canal, either in the anteroposterior or in the lateral dimensions.

History

1. Typical of lumbar stenosis is chronic generalized low back pain, intermittent sciatica, and most characteristic, posterior leg pain or sciatica that is induced by walking, termed "neurogenic claudication," which is improved by brief rest and by leaning forward in a "bicycle posture," which reduces the lumbar lordotic curvature.
2. The main distinction is from vascular claudication because of iliofemoral arterial occlusion.

Pathophysiology

1. Stenosis usually affects several adjacent lumbar levels but may be most severe at one level or be caused by a single large disc.
2. The spinal elements that produce narrowing of the lumbar canal in varying proportion are (a) disc protrusion or rupture, (b) hypertrophy of bone at the facet joints, (c) hypertrophy of the ligamentum flavum, (d) spondylolisthesis, and, in some instances, (e) a spondylitic bar consisting of a bony ridge at the disc space. The last of these is more characteristic of cervical spondylosis (see further on).
3. All of these changes are degenerative in the sense that they occur increasingly with age, activity, and minor physical trauma. Certain individuals and families have a tendency to spinal stenosis.

Prognosis

1. Lumbar stenosis is typically gradually progressive and becomes disabling when pain greatly limits walking.
2. In some patients, the condition stabilizes and allows for reasonable function but surgery can be curative (see below).

Diagnosis

1. The history is stereotyped and can be differentiated from vascular claudication by focusing on the sciatic distribution of most of the pain and the normality of distal arterial pulses (unless there is concurrent vascular disease).
2. The ankle-brachial arterial index and other ultrasound or vascular imaging tests may be needed to affirm that claudication is not vascular.
3. Among the most certain signs of neurogenic claudication is loss of ankle jerks after prolonged walking, coincident with leg pain. Return of reflexes after several minutes of rest is further confirmatory.
4. Straight leg raising tests usually cause some degree of sciatica.
5. There is often limitation of low back flexion and extension.
6. X-ray images may show a spondylitic bar and spondylolisthesis but do not allow appreciation of the extent of canal narrowing. Instability of the lumbar spine at sites of spondylolisthesis, often with worsening canal narrowing, can be demonstrated by flexion-extension views.
7. CT and MRI scans demonstrate a narrowed canal at one or more levels, bunching of nerve roots at lower lumbar levels, and spondylolisthesis.
8. Electromyography (EMG) can be helpful in demonstrating fibrillation potentials in muscles innervated by the lower lumbar and first sacral root. Some practice guidelines do not include the use of this study.

Treatment

1. Back exercises and stretching under the guidance of a therapist may improve symptoms and forestall surgery. Exercises and positions that increase the canal diameter by reversal of the lumbar lordosis can be somewhat effective. This can be accomplished by having the patient sit or use a stationary bicycle or lean forward over a chair while kneeling.
2. Surgical decompression relieves pain and prolongs walking distance, and this improvement is sustained for at least 2 years in randomized trials, but at later periods, there is less difference in overall disability.
3. There are several surgical approaches for severe lumbar stenosis. Most include multiple-level laminectomies and fusion of adjacent lumbar segments with the use of facet screws and small stabilizing rods. There is controversy regarding the need for fusion in the absence of instability.

4. The need for repeat surgery to further decompress the canal or repair previous work can be anticipated in 5% of patients.
5. Recuperation after surgery is generally 6 to 12 weeks but depends on the extent of surgery. Claudication pain is usually relieved immediately after surgery. During this time, patients may drive and walk.
6. There is limited evidence that epidural or other injections, chiropractic manipulation, or other forms of therapy are helpful in the long-term treatment of lumbar stenosis and associated pain.

Facet Syndrome

1. This is a less well-defined syndrome of focal back pain directly over one of the lumbar or cervical facet joints.
2. The patient is able to point to the region of pain, and there is tenderness over the same area. Rotation of the torso away from the affected side usually exaggerates pain.
3. Injections of the facet joints with local analgesics and steroids are confirmatory of the diagnosis but are controversial as ongoing treatments.

NECK PAIN, CERVICAL RADICULOPATHY, AND CERVICAL MYELOPATHY

Background

1. Nondescript, aching musculoskeletal neck pain, like low back pain, has predominantly degenerative causes and precedents.
2. The neurologist should search for signs of root compression and cervical cord compression.
3. Crepitus is a common complaint with changes in neck position but has an inconsistent relationship with pathologic changes in the spine.
4. Whiplash represents a controversial category of neck pain that is the result of rapid forward and backward rotation of the head on the neck, usually from a sudden stop in a vehicle.
5. Fibromyalgia–chronic fatigue syndrome involves ill-defined pain and tenderness in the cervical, trapezius, and adjacent muscles.

5. Polymyalgia rheumatica affects the shoulder muscles, sometimes with aching in the neck and other proximal muscles.

History

1. Sleeping in an awkward position, extreme rapid turning of the head to avoid objects, and direct injury, all may cause acute severe but self-limited neck pain.
2. Radiating sharp or aching pain down one arm usually indicates root compression from disc rupture or spondylitic change.
3. Imbalance, hand numbness ("like wearing gloves"), and sphincter dysfunction are signs of cord compression from cervical spondylosis.
4. Torticollis occasionally begins with neck aching.
5. Pain originating in the upper cervical spine may be referred to the occiput, and that originating in the thoracic spine may be felt in the interscapular area, shoulders, or across one side of the upper chest.
6. There is sparse evidence supporting a connection between vertigo or dizziness and cervical spine disease.
7. In the case of acute neck pain, alternative diagnoses include vertebral artery dissection, meningitis, and cervical epidural abscess.

Pathophysiology

1. All of the factors contributing to spinal degeneration, namely arthritis, and repeated minor injury that cause lumbar pain, also apply to cervical syndromes.
2. Pain radiating down the brachium or more distally and paresthesias or numbness in a hand indicate root compression most often from a ruptured disc or spondylitic change that compresses the root as it exits the neural foramen.

Prognosis

1. This depends on the underlying cause, but musculoskeletal neck pain resolves spontaneously in weeks. Muscle tears may take months to improve, and cervical disc disease has a variable course.
2. Reinjury of neck musculoskeletal structures is common and tends to affect

the same regions of the neck with each subsequent event.

Diagnosis

1. The motor, sensory, and reflex changes corresponding to root compression at cervical levels are given in Table 4-2. Sensory loss is infrequent in cervical root compression but when present, conforms to the expected dermatomal distribution.
2. Cervical MRI resolves most important causes of neck pain, but, as with lumbar pain, it is usually unnecessary for the diagnosis of nondescript musculoskeletal aching of the neck.
3. EMG is helpful in focusing attention on a specific level of nerve root compression.
4. Brachial neuritis is frequently mistaken for cervical root disease, but pain in the former tends to be more severe, burning, over the deltoid or in the axilla, and worse at night. Weakness with atrophy appears days to weeks after the pain.
5. Injury of the shoulder, particularly fragmentation of the labrum, may also imitate cervical spine disease.
6. Systemic symptoms or signs such as fever, night sweats, weight loss, adenopathy, active cancer, or connective tissue disease prompt caution in the diagnosis of degenerative diseases of the cervical spine.

Treatment

1. Nondescript neck aching may be treated by stretching, heat, massage, and gentle traction. The emergence of radicular features or worsening pain with these maneuvers justifies reexamination. Acetaminophen and nonsteroidal analgesics may be helpful.
2. Facet joint and epidural injections have not provided sustained relief in most clinical trials but may be tried in treatment-resistant cases.

Table 4-2 Cervical Root Syndromes

Root/Disc Level	Pain Distribution	Muscle/Weakness	Reflex Loss	Sensory Loss
C5/(C4–	Over scapula	Deltoid, biceps,	Mildly reduced	Over

C5)	and posterior shoulder, lateral arm to elbow	brachioradialis—shoulder abduction, elbow flexion Infra- and supraspinatus—shoulder abduction and external rotation	biceps; deltoid and pectoralis reduced	shoulder; lateral deltoid area
C6/(C6–C7)	Lateral arm and forearm to thumb and index fingers	Biceps—forearm flexion	Biceps and brachioradialis loss	Lateral arm and forearm; thumb and index fingers
C7/(C7–C8)	Lateral arm and forearm to middle finger	Triceps—elbow extension Extensor carpi radialis—radial wrist extension	Lost or reduced triceps jerk	Second, third, and fourth fingers; lateral forearm
C8/(C8–T1)	Medial forearm and hand	Long flexors, extensors, and abductors of wrist and fingers	Reduced or normal triceps jerk	Fifth and ring fingers; medial forearm above hand
T1/(T1–T2)	Medial arm	Intrinsic hand muscles (most shared with C8)	None or Horner syndrome	Medial arm

3. Wearing a soft collar, particularly when driving, is favored by some clinicians.
4. A "cervical pillow" that is hollow in the center and restricts movement laterally may be used during sleep.
5. Chiropractic adjustments inconsistently benefit cervical pain and neurologists have expressed concern about vertebral artery dissection after the use of high-velocity movements. Many patients will have already seen a chiropractor by the time they consult the neurologist.
6. Surgical consultation is appropriate in cases of disc protrusion or spondylitic change that produces sustained or intractable radicular pain for

many days or weeks (see below). The pain tends to be less well tolerated than is sciatica.

7. As with lumbar disease, operation without a firm anatomic basis for neck and root pain usually does not lead to improvement.
8. When one or two roots are involved clinically and by EMG, and there is no myelopathy (see below), a limited surgical approach with foraminotomies may be helpful.

CERVICAL SPONDYLOSIS

Background

1. Narrowing of the cervical spinal canal by degenerative changes in joints, bones, discs, and ligaments, comparable to lumbar stenosis, compresses the cervical cord.
2. Symptoms and signs are greatly exaggerated or more likely to arise in individuals with congenital narrow spinal canal, most often in the anteroposterior dimension.
3. Male predominance is not as prevalent in this disease as in the lumbar stenosis.

History

1. Two constellations of complaints occur, sometimes overlapping. The first is symmetric sensory complaints in the hands with “thickness” or “glove” feeling, imbalance, urinary incontinence, and proximal leg weakness, indicative of cervical myelopathy.
2. The second, the result of associated root compression discussed earlier, is sharp or aching neck and brachial pain, with radiation down one arm, and variable sensory symptoms in the hand on that side. The intrinsic hand muscles may atrophy in both conditions.

Pathophysiology

1. Degenerative processes affect facet joints, disc space, and ligaments, narrowing the cervical canal and leading to stenosis of the neural foramina

and nerve root compression, usually in the mid or lower portions of the canal.
2. Spondylolisthesis may be prominent at sites of spinal instability and contribute to narrowing of the spinal canal.

Diagnosis

1. The physical signs are either hyper- or hyporeflexia in the arms, depending on the level of cord compression and the presence of root compression (explaining hyporeflexia), Romberg sign, variable Babinski signs, Hoffman signs, asymmetric atrophy of hand muscles, and inconsistent and mild pinprick loss over the upper arms and hands.
2. The combination of upper and lower motor neuron signs simulates amyotrophic lateral sclerosis.
3. MRI demonstrates spondylitic "bars" of bone at the levels of protruded discs, spondylolisthesis, and ligamentous hypertrophy that together produce canal narrowing. CT and plain x-rays demonstrate aspects of spondylosis less completely and are less reliable in gauging compression of the cord.
4. The presence of signal change on MRI within the spinal cord at or near the level of maximal narrowing is a sign of underlying spinal cord damage.
5. EMG may be confirmatory by demonstrating a pattern of motor root compression.

Treatment

1. Stabilization and gentle stretching by wearing a cervical collar may ameliorate radicular pain.
2. Evidence for benefit from epidural injections and other nonsurgical procedures is limited.
3. MRI signal changes within the cord, or signs of all but the mildest myelopathy (e.g., Babinski signs alone), are among the best relative indications for surgical decompression.
4. Surgical approaches to cervical spondylosis have changed in the last decade. Canal narrowing isolated to one or up to two (in some cases three) levels can be approached anteriorly with fusion to maintain spinal stability (anterior cervical discectomy).

5. Laminectomy or laminotomy is still favored by some surgeons and may be preferable if more than two or three levels are involved or there is a severely narrow canal on a congenital basis.
6. If radicular pain and motor symptoms predominate, it is possible to perform only foraminotomies as discussed earlier for cervical radiculopathy, but any myelopathy is not addressed.

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5 Sleep Disorders

Milena Pavlova

EXCESS DAYTIME SLEEPINESS

Background

Nearly a quarter of healthy adults have excessive daytime sleepiness (EDS). There are many causes including insufficient or ill-timed sleep (i.e., jet lag or voluntary sleep restriction), primary sleep disorders, as well as medical and neurologic disorders that disrupt sleep or produce pathologic sleep states.

History

1. The typical complaint is of falling asleep unintentionally, causing embarrassment, loss of productivity, and sometimes being hazardous (e.g., while driving).
2. Excessive sleepiness should be distinguished from fatigue and abulia, which have a much wider range of causes. A sleepy patient actually falls asleep rather than feels unwilling or too weak to engage in activities.

Pathophysiology

1. The causes of daytime sleepiness can be categorized in the following:
   - **a.** Insufficient or fragmented amount of sleep the night before
   - **b.** Disorders in sleep drive
2. The intrinsic drive to sleep is dependent on two main factors: (a) homeostatic, determined by prior wakefulness, and (b) circadian, determined by the individual's current phase of the circadian rhythm. Under normal conditions, these two factors function synchronously to ensure continuous alertness during the "biological day" and continuous sleep during

the "biological night." The precise timing of sleep in relation to these idealized periods is modulated by ambient light, environmental conditions that promote or impede sleep, medications, and elective or forced wakefulness.

3. Insufficient sleep is the most common cause of excess daytime sleepiness among both adults and children. It can be because of self-inflicted sleep restriction in order to increase productivity or other environmental factors or because the time allotted for sleep is not the time when the drive to sleep is high (circadian misalignment because of jet lag, shift work, or other circadian rhythm disorders). It can lead to both sleepiness, and to other serious consequences, including poor concentration, lack of productivity, as well as putative impairments in immune and metabolic functions.
4. Sleep fragmentation can be caused by environmental factors, medical or neurologic disease, and primary sleep disorders.
5. Physiologically, most adults need between 7 and 9 hours of sleep. If sleepiness is present even after an adequate amount of sleep, and in the absence of any sleep fragmenting disorders (sleep apnea, movement disorders, etc.), there may be an abnormally high sleep drive. This can be caused by (a) medications, (b) medical or neurologic disorders, (c) circadian misalignment (e.g., jet lag), or (d) primary disorders of sleep drive (such as narcolepsy and idiopathic hypersomnia).

Table 5-1 Epworth Sleepiness Scale

In the last 30 days, how likely were you to doze off or fall asleep in the following situations (in contrast to just feeling tired)	High Chance (3)	Moderate Chance (2)	Slight Chance (1)	Never Doze (0)
1. Sitting and reading				
2. Watching TV				
3. As a passenger in a car for an hour without a break				
4. Sitting inactive in a public place (e.g., theater, church)				
5. Lying down to rest in the afternoon when circumstances permit				

6. In a car while stopped for a few minutes in traffic
7. Sitting quietly after lunch without alcohol
8. Sitting and talking to someone

Total score of more than or equal to 10 indicates clinically important daytime sleepiness.

Diagnosis

1. Sleep quantity is determined by history, sleep logs, and actigraphy. Polysomnography (PSG) is indicated if a primary sleep disorder is suspected.
2. The Epworth sleepiness scale (Table 5-1) can help quantify the complaint.
3. Sleepiness can be measured by the multiple sleep latency test (MSLT), in which the patient is allowed five nap opportunities, each 2 hours apart, beginning 2 hours after awakening. An average latency to sleep onset of less than 8 minutes across the five naps is considered indicative of pathologic daytime sleepiness. The appearance of more than one rapid eye movement (REM) period during the MSLT naps or during the overnight PSG indicates REM dysregulation, a result of either sleep loss or narcolepsy.

Table 5-2 Stimulant Medications

Medication	Daily Dose Range (mg)
Methylphenidate (Ritalin)	5–80 (divided doses)
Methylphenidate (Ritalin-SR)	20–60 daily
Methylphenidate (Concerta, Metadate, Focalin)	18–54 daily
Dextroamphetamine (Adderall)	5–60 (divided doses)
Dextroamphetamine (Adderal-XR)	20–60
Modafinil (Provigil)	100–400 (daily or twice a day)
Armodafinil (Nuvigil)	20–250

Treatment and Prognosis

1. Treatment depends on establishing the underlying cause.
2. When sleepiness persists after the underlying cause had been adequately addressed, wake-promoting medications (Table 5-2) can be used.

3. The clinician should discuss the hazards of drowsy driving and other situations for which alertness is crucial for safety. Even healthy individuals often underestimate their degree of sleepiness.

EXCESS DAYTIME SLEEPINESS AS A RESULT OF MEDICAL AND NEUROLOGIC DISEASE

Background and Pathophysiology

Numerous neurologic, medical, and psychiatric states and diseases cause sleepiness, either by disrupting the mechanisms involved in sleep homeostasis or by disrupting nighttime sleep. The major causes are:

1. Neurologic causes of sleep fragmentation
   - **a.** Abnormal movements: Tremor and inability to shift positions in bed in Parkinson disease, other neurodegenerative conditions.
   - **b.** Seizures: Either as a cause or as a consequence of fragmented sleep.
   - **c.** Spasticity: As a result of stroke, spinal cord lesion, multiple sclerosis (MS), or other conditions.
   - **d.** Nocturia: In MS, diabetes, and other conditions.
   - **e.** Comorbid primary sleep disorder: Examples include REM behavior disorder, seen in more than one-third of the patient with synucleinopathies. Periodic limb movement disorder (PLMD) is commonly seen among patients with peripheral neuropathy, with spinal cord lesions, and with Parkinson disease. Obstructive sleep apnea (OSA) is particularly common in stroke patients, with amyotrophic lateral sclerosis (ALS), and after cervical spinal cord lesions. Patients with postpolio syndrome have an increased risk for both OSA, as well as central sleep apnea (CSA).
2. Medical conditions that prevent or disrupt sleep
   - **a.** Medications: A detailed description can be found in Table 5-3.
   - **b.** Pain: Virtually all forms of acute and chronic pain are responsible for poor sleep and subsequent sleepiness. The pain produced by cancer, spondylosis, rheumatologic conditions, fracture, and the postoperative state is common and may not be revealed without careful acquisition of the patient's history. Certain nocturnal pains are, of course, characteristic of

serious conditions such as spinal and brain tumor. Skin diseases with itching and gastroesophageal reflux are derivatives of this category.

c. Nocturia: Independent of neurologic conditions, the common problem of prostatism causes frequent nocturnal arising from bed.

d. Cardiopulmonary failure: Disrupts sleep as a result of dyspnea, especially if there is orthopnea.

e. Psychiatric disorders

1) Anxiety states: Both acute situational and chronic anxiety associated with depression are highly likely to change sleep, mostly with insomnia.

2) Mania: Usually associated with reduced need for sleep but not typically causing secondary daytime sleepiness.

Table 5-3 Medications Associated with Excessive Daytime Sleepiness

Class of Medication	Common Agents	Notes
Antidepressant	Tricyclic antidepressants (amitriptyline, doxepin, etc.)	Less common with SSRIs
Antihistamines	Brompheniramine, diphenhydramine, hydroxyzine, chlorpheniramine	Less common with second-generation agents
Anxiolytics	Benzodiazepines (diazepam, clonazepam flurazepam, temazepam, etc.)	Longer acting agents associated more with daytime sedation
Antihypertensives	α-2 agonists (clonidine), α-1 antagonists (prazosin)	Sedation can be transient
Antiepileptics	Gabapentin, topiramate, phenytoin, phenobarbital, clobazam, pregabalin, zonisamide	Rates have varied in different studies
Antipsychotics	Thioridazine, chlorpromazine, quetiapine, clozapine, olanzapine	May be transient

SSRIs, selective serotonin reuptake inhibitors.

Prognosis

Prognosis depends on the underlying cause. It is best for remediable pain, anxiety states, and circadian and environmental disruption that are amenable to

simple rectification.

Diagnosis

Diagnosis is made by history of one of the described disturbances and by confirming the presence of sleepiness by observation or multiple sleep latency testing.

Treatment

The first step of treatment is control of sleep disrupting factors. In patients in whom sleepiness persist thereafter, wake-promoting medications (modafinil, armodafinil, stimulants) can be helpful to control residual sleepiness with minimal side effects. Counseling about driving may be appropriate as well because episodes of irresistible sleepiness may occur, not preceded by obvious warning.

PRIMARY SLEEP DISORDERS LEADING TO EXCESSIVE SLEEPINESS

Sleep Disordered Breathing

Background

1. Major subtypes include:
   - **a.** OSA: Characterized by repetitive episodes of pharyngeal collapse during sleep.
   - **b.** CSA: Characterized by periods of absent respiratory effort. These may occur sporadically or in a cyclic pattern (e.g., Cheyne–Stokes respiration).
   - **c.** Sleep-related hypoventilation syndromes: Periods of decreased ventilation with profound hypercapnia, most commonly associated with neuromuscular weakness or chest wall abnormalities.
2. Sleep disordered breathing causes daytime sleepiness secondary to fragmentation of sleep and intermittent hypoxia.

History

The patient may present with excessive sleepiness, sleep fragmentation, or in some cases a complaint of insomnia. A bed partner may report snoring, pauses in breathing, or apparent arousals, manifesting with motor restlessness. Many patients complain of difficulty with concentration and memory, or mood disturbance. Less common complaints include morning headache and sexual difficulties.

Pathophysiology

1. In OSA, there is respiratory obstruction, leading to partial or complete cessation of breathing despite present effort to breathe. The pharyngeal dilator muscle is less active during sleep, and the uvula or tongue or both fall and either partially or completely occlude the airway. Risk factors include obesity, advanced age, male gender, and anatomical features, such as a small airway, retrognathia, and macroglossia.
2. CSA presents with episodes of absent effort to breathe. There are two basic mechanisms that trigger central respiratory events: (a) posthyperventilation central apnea, which may be triggered by a variety of clinical conditions, and (b) central apnea secondary to hypoventilation, which can be because of medications that affect the respiratory drive (particularly opioids) or pathology that affects the medulla (such as a Chiari malformation), or idiopathic conditions.
3. CSA of the Cheyne–Stokes type is most commonly seen in patients with systolic congestive heart failure (CHF) but may occur with neurodegenerative disorders.
4. Sleep-related hypoventilation in patients with neuromuscular weakness is exacerbated by sleep-related changes in muscle activation especially during REM sleep when ventilation is primarily maintained by diaphragm activation.

Prognosis

1. The prevalence and severity of OSA increases with age. Increasing data suggest that OSA is also independently associated with cardiovascular diseases such as myocardial infarction and stroke.

2. Prognosis for idiopathic CSA is less well defined.
3. Cheyne–Stokes respirations in patients with CHF are an independent predictor of mortality.
4. Sleep-related hypoventilation in patients with neuromuscular disease is a precursor to daytime respiratory failure.

Diagnosis

The gold standard for diagnosis is overnight attended PSG. However, in many cases, a home sleep apnea test can be used as a more cost-effective measure. It is important to note that a home sleep apnea test (a) does not typically include any central nervous system (CNS) measures (i.e., it cannot determine reliably the amount of sleep), (b) may in some cases underestimate severity and thus a normal home test does not rule out presence of sleep apnea, and (c) there is no measure of motor activity. The severity of disease is quantified by the apnea–hypopnea index (number of abnormal respiratory events per hour of sleep) or AHI. By current criteria, an AHI index of more than 5 per hour is considered abnormal and warrants treatment in the presence of clinical symptoms, while an AHI of greater than 15 per hour warrants treatment even in the absence of clinical symptoms because OSA may increase risk of major comorbidities, such as hypertension, type 2 diabetes, myocardial infarction, and stroke.

Treatment

1. OSA

   Conservative measures that may improve OSA include weight loss and avoidance of alcohol and sedative medications.

   a. In some patients, respiratory events occur primarily while sleeping supine. For them, the use of wedge pillows or similar shaped objects in the nightshirt/ gown can be used to limit sleep in this position.

   b. *Positive airway pressure* (PAP) therapy applied via a nasal mask is the primary modality of therapy. It works as a pneumatic splint, preventing airway collapse. It can be delivered continuously (continuous positive airway pressure [CPAP]) or as bilevel (bilevel positive airway pressure [BiPAP]), which provides a lower pressure on expiration from inspiration. It may lead to decreased daytime sleepiness and improved overall function and quality of life, and in some studies, it shows lower

blood pressure in comparison to placebo.

c. Required PAP is determined during a "titration" study that can often be performed during the same night as the diagnostic polysomnogram (split-night study).

d. *Oral appliances* are custom-made mouthpieces that function by advancing the mandible, thus enlarging the pharyngeal airway. They are effective for patients with mild-to-moderate OSA, and efficacy ranges from 60% to 80%. Many patients prefer these devices to PAP because of ease of use.

e. *Surgical therapy* of OSA includes minimally invasive procedures (such as radiofrequency uvular ablation) and more invasive procedures such as uvulopalatopharyngoplasty (UPPP).

f. Success rates for surgery vary depending on the procedure, but for UPPP, the success rates are approximately 40% to 50%.

g. In a minority of patients whose apnea is adequately treated, EDS remains a significant problem. In these patients, the addition of wake-promoting medications has been shown to improve symptoms while not substantially reducing CPAP compliance.

2. CSA

a. Treatment of CSA is substantially more difficult than OSA. Careful review of contributing medications and limiting use of opiates and alcohol are imperative.

b. Options for idiopathic CSA include the use of respiratory stimulants such as medroxyprogesterone and BiPAP.

3. Cheyne–Stokes respiration

a. If associated with CHF, optimizing therapy for heart failure is the primary therapy (after load reduction, diuretics, β-blockers, etc.). A follow-up study is recommended to confirm that measures have been effective.

b. Other available treatments include supplemental oxygen and nasal PAP.

4. Adaptive servoventilation (ASV)

a. ASV is a new method of treatment that uses an automatic, minute ventilation–targeted device that performs breath-to-breath analysis and adjusts its settings accordingly. It is a promising treatment option for patients with CSA. It can also be helpful in treating patients with OSA, who also have central apneas or Cheyne–Stokes respiration. However, ASV should be considered with caution in patients with a decreased

ejection fraction because a recent analysis demonstrated an increased risk of cardiac mortality in patients with a left ventricular ejection fraction (LVEF) of ≤45%. As a result, current guidelines do not recommend use of ASV in these patients.

NARCOLEPSY

Background

Narcolepsy is present in 0.05% of adults (prevalence similar to that of MS). Onset is usually in the second decade of life, but initial appearance of symptoms in the 30s is not uncommon. The mean time between symptom onset and diagnosis is frequently prolonged because of misdiagnosis.

History

Narcolepsy is characterized by excess daytime sleepiness and dysregulation of REM processes. The classic tetrad includes:

1. Sleepiness: Patients describe episodes of irresistible need to fall asleep (sleep attacks) or a general tendency to fall asleep in any passive situation. Ironically, nocturnal sleep is often fragmented. Naps are typically short and refreshing.
2. Sleep paralysis: The appearance of REM atonia in early stages of sleep or wakefulness, leading to brief (seconds to minutes), usually frightening, inability to move voluntary musculature in the presence of full alertness, either upon awakening or at the transition from wake to sleep. Concomitant paralysis of the accessory muscles of inspiration may result in the sensations of dyspnea.
3. Cataplexy: Episodes of transient loss of muscle tone, stimulated by emotions, most commonly laughter or telling a joke. The episodes are brief (<2 minutes) and usually bilateral. There may be transient loss of deep tendon reflexes. Based on the presence or absence of cataplexy, narcolepsy is classified as narcolepsy type 1 (with cataplexy) or type 2 (without cataplexy).
4. Hypnagogic (at sleep onset) or hypnopompic (at sleep offset) hallucinations: It is the appearance of the hallucinatory phenomena of dreams during

wakefulness. Usually these are fragmentary and brief (hearing the telephone or one's voice being called) or seeing a shadow of a person, although rarely they may be more elaborate.

a. Sleep paralysis and hypnagogic hallucinations are occasionally reported in isolation by individuals without narcolepsy.

b. Narcolepsy is currently classified as existing with or without cataplexy. The exact percentage of individuals with the excess daytime sleepiness of narcolepsy with cataplexy is unclear, but it is thought to be 50% to 80% of cases.

Pathophysiology

Progress in understanding the pathophysiology of narcolepsy has been made in the past 10 years, stimulated by findings that HLA genotype DQB1*0602 is much more common in individuals with the disease (85% of narcoleptics vs. 25% of the general population). Knockout mice for the hypothalamic peptide hypocretin (orexin) exhibit behavioral states consistent with narcolepsy. In human narcoleptics, a reduction in the number of hypothalamic neurons responsible for the production of hypocretin (orexin) and the absence of this ligand in the cerebrospinal fluid (CSF) confirm the importance of hypocretin in narcolepsy with cataplexy.

Prognosis

Narcolepsy is a chronic, but nonprogressive, disorder. Some individuals will have the onset of cataplexy a number of years after the onset of daytime sleepiness.

Diagnosis

The clinical description by the patient and observers of cataplexy is nearly pathognomonic. The MSLT provides objective confirmation and at this time is the gold standard. Criteria include:

1. Mean sleep latency of less than 8 minutes
2. Presence of *two or more* sleep-onset REM periods (REM occurring within 15 minutes of falling asleep during a nap opportunity). The sleep onset REM periods may be seen either during the daytime sleep opportunities or during the preceding PSG.

a. For narcolepsy type 1, hypocretin-1 (Hct-1) in CSF levels can be used diagnostically. The diagnosis is supported by Hct-1 less than or equal to 110 pg/mL, or one-third of mean normal control values.

Treatment

The importance of adequate nocturnal sleep and the value of daytime napping should be stressed as means of minimizing daytime sleepiness in narcolepsy.

The first-line pharmacologic treatment of narcoleptic daytime sleepiness typically include modafinil (at doses 200 to 400 mg/d) or armodafinil (typically effective at 100 to 250 mg). Its common limiting side effect is headache, and there are several drug interactions. Modafinil affects the P450 system enzymes, inducing 1A2 and 3A and inhibiting 2C19. Patients taking oral contraceptives, benzodiazepines, and other substances metabolized by P450 systems should be warned of the interaction.

Alternatively, stimulant medications, such as methylphenidate or amphetamine derivatives can be used. Controlled-release preparations of methylphenidate and amphetamines have been developed, allowing once to twice per day dosing. However, concerns persist regarding their potential for abuse and the relatively common side effects of headache, anorexia, mood alterations, and blood pressure and pulse elevations. Amphetamine derivatives should be used with caution in patients with epilepsy, while modafinil has been confirmed efficacious and safe in these patients.

Women who are planning pregnancy may present a particular challenge, as none of the currently available stimulant medications are confirmed as safe in pregnancy. Optimal sleep hygiene and planned/scheduled naps may be a reasonable alternative.

Treatment of *cataplexy* is achieved with REM suppressants. The former role of tricyclic antidepressants has been replaced by better tolerated and safer selective serotonin reuptake inhibitors (SSRIs) (Table 5-4). Both of these classes of medications suppress cataplexy, sleep paralysis, and hypnagogic hallucinations.

Cataplexy, as well as daytime hypersomnolence, may be also successfully treated with sodium oxybate (Xyrem). It is typically taken twice per night. Because of powerful sedating effect, use of this medication should be carefully monitored, and patients should be cautioned against concomitant use of other sedative medications or alcohol.

Table 5-4 Medications for Cataplexy

Medication	Daily Dose Range
Clomipramine (Anafranil)	25–75 mg
Imipramine (Tofranil)	75–150 mg
Protriptyline (Vivactil)	15–20 mg
Fluoxetine (Prozac)	20–40 mg
Paroxetine (Paxil)	20–40 mg
Sertraline (Zoloft)	50–200 mg
Venlafaxine (Effexor)	75–150 mg
Sodium oxybate (Xyrem)	3–9 g (given in two evenly divided doses at night)

IDIOPATHIC HYPERSOMNIA

Background

Idiopathic hypersomnolence shares the excess daytime sleepiness of narcolepsy but does not have any of the REM-related symptoms. Individuals report normal nocturnal sleep (in distinction to narcolepsy), but severe difficulty arousing from sleep in the morning or from daytime naps. These naps are longer than the ones in patients with narcolepsy and may take 2 to 3 hours. Even after these long naps, patients are only partially refreshed.

Diagnosis

Diagnosis is made by PSG and MSLT. Overnight PSG demonstrates high sleep efficiency and pathologically shortened sleep latency on MSLT (<8 minutes) but without the appearance of REM periods during daytime naps. As medical and neurologic (see earlier) disorders can lead to excess daytime sleepiness, this is generally a diagnosis of exclusion. As suggested by its name, the cause of idiopathic hypersomnolence is unknown.

Treatment

Treatment is targeted to symptomatic relief of the daytime somnolence.

Modafinil (at doses 200 to 400 mg/d) can be used as well as armodafinil (typically effective at 100 to 250 mg), or stimulants (amphetamine, dextroamphetamine, etc.). However, response is usually limited.

KLEINE–LEVIN SYNDROME

Background

The Kleine–Levin syndrome (KLS) is characterized by periodic and prolonged episodes of hypersomnia and various behavioral disturbances including compulsive hyperphagia, lasting from a few days to weeks, and complete remission with normal behavior in between.

Pathophysiology

The cause and pathogenesis of KLS are unknown. It is more common in males, but female cases have been described as well, and the ratio is 4:1. When seen in young women, it can have a catamenial pattern. There are symptomatic forms because of acquired hypothalamic lesions, but the similarity to idiopathic KLS is limited.

Diagnosis

Diagnosis is made by the presence of the prolonged episodes of sleepiness and excluding other causes of excessive sleepiness.

Treatment

Treatment can include stimulants or modafinil for hypersomnolence and possibly lithium salts.

INSOMNIA

Background

Insomnia is the description given to the complaint of difficulty falling or

staying asleep. It affects about one-third of the general population and persists in close to 12% to 15% of adults. The disorder is more common in women and increases with advanced age until about 60 years.

Pathophysiology

The timing and duration of sleep are primarily determined by underlying "homeostatic" sleep drive (duration of prior wakefulness) and circadian (internal clock) processes. Insomnia results either by impaired response to the homeostatic drive or by distorted phase relationships between the allocated sleep time and the circadian sleep drive.

Acute insomnia is usually produced by a defined precipitating event. All of the mundane medical causes of sleep disruption listed in earlier sections, particularly pain and anxiety, are seen in practice.

Prognosis

Adjustment (acute) insomnia is self-limited. The prognosis of comorbid insomnia depends on the underlying cause. Insomnia can be associated with cognitive and attention difficulties, increased health care utilization, and increased risk of developing mood or anxiety disorders, or alcohol or substance abuse.

Diagnosis

Diagnosis is based on history. If a primary sleep disorder is suspected, PSG or home apnea test may be valuable.

Treatment

Depends on the underlying cause and the duration of the symptom.

SHORT-TERM INSOMNIA (ACUTE INSOMNIA, ADJUSTMENT INSOMNIA)

Background

Usually 1 day to 3 weeks in duration.

Pathophysiology

Associated with unfamiliar sleep environment, situational stress, acute medical illness or pain, shift work, or caffeine or alcohol use.

Prognosis

Generally time-limited.

Diagnosis

Available from history.

Treatment

1. If insomnia is limited to 1 or 2 days, treatment is usually unnecessary.
2. Relief from the underlying cause of the insomnia should be sought.
3. Insomnia beyond a few days can be treated with medications (Table 5-5).
   a. Benzodiazepine receptor agonists (BzRAs) are first-line agents *for short-term use*, given their efficacy, tolerability, and the wide range of half-lives available.
   b. Alternative agents to BzRAs should be prescribed to individuals with a history of substance or alcohol abuse or dependence. For patients who also have OSA, it is best to use medications without muscle-relaxant properties.

Table 5-5 Commonly Used Pharmacologic Treatments for Insomnia

Generic Name	Trade Name	Common Dose Range (mg)	Half-Life, Including Active Metabolites (h)
Benzodiazepine receptor agonists			
Clonazepam	Klonopin; others	0.5–1.0	30–60
Flurazepam	Dalmane; others	15–30	20–60
Temazepam	Restoril; others	7.5–30	6–18

Lorazepam	Ativan; others	1–2	12–18
Alprazolam	Xanax; others	0.25–1.0	6–20
Triazolam	Halcion; others	0.125–0.25	2–3
Zolpidem	Ambien	5–10	2–3
Zaleplon	Sonata	10–20	1–1.5
Eszopiclone	Lunesta	1–3	6
Zolpidem sublingual	Intermezzo	1.75–3.5	1.4–3.6
Melatonin receptor agonists			
Ramelteon	Rozerem	8	1–1.5
Tasimelteon	Hetlioz		(approved for non–24-h circadian rhythm disorder, not insomnia)
Sedating antidepressants and other sedating			
Amitriptyline	Elavil; others	25–100	10–50
Doxepin	Sinequan; others	25–100	6–10
Trazodone	Desyrel	25–150	5–9
Mirtazapine	Remeron	7.5–30	20–40
Gabapentin	Neurontin	300–1,200	5–9
Orexin antagonist			
Suvorexant	Belsomra	5–20 mg	10–22

CHRONIC INSOMNIA (PRIMARY INSOMNIA PSYCHOPHYSIOLOGIC [CONDITIONED] INSOMNIA, IDIOPATHIC INSOMNIA)

Background

Criteria for diagnosis include reported difficulty initiating and/or maintaining sleep, or waking up earlier than desired, which results in either fatigue/malaise, or attention, concentration, or memory impairment, or other daytime disturbances, such as impaired social, family, occupational, or academic performance, mood disturbance/irritability, or behavioral problems

(e.g., hyperactivity, impulsivity, aggression). The reported sleep–wake complaints cannot be explained purely by inadequate opportunity (i.e., enough time is allotted for sleep) or inadequate circumstances (i.e., the environment is safe, dark, quiet, and comfortable). The diagnosis of chronic insomnia requires that the disturbances occur at least three times per week and have been present for at least 3 months.

Reports of difficulties initiating sleep, difficulties maintaining sleep, or waking up too early can be seen in all age groups. Resistance going to bed on an appropriate schedule and difficulty sleeping without parent or caregiver intervention is seen most commonly in children and older adults who require the supervision of a caretaker because of a significant level of functional impairment (e.g., those with dementia).

Medical and psychiatric disorders can lead to comorbid insomnia, and thus, appropriate questions to elicit a story compatible with these disorders should be asked during the history.

Pathophysiology

Insomnia is considered to be caused by cognitive and physiologic hyperarousal. Chronic insomnia is often a symptom of an underlying problem rather than a disorder itself and typically the result of the combined effect of predisposing, precipitating, and perpetuating factors (the 3 *P*'s model).

In the prior (International Classification of Sleep Disorders [ICSD]-2) classification, several subtypes were delineated.

1. Psychophysiologic insomnia usually begins with insomnia from another cause but then develops into a chronic condition, as a cycle of worsening anxiety regarding sleeplessness produces worsening insomnia. Patients often report an excessive focus on and heightened anxiety about sleep, difficulty falling asleep in bed during planned time, but ability to fall asleep during monotonous activities, and/or sleeping better away, outside of home.
2. Idiopathic insomnia is usually lifelong. It starts without any identifiable precipitating cause, often in infancy or childhood. It has a persistent course without periods of remission.
3. Paradoxical insomnia is a disparity between polysomnographic recorded sleep and patient perception of inadequate sleep.

Although helpful from pathophysiologic perspective, these types are often difficult to distinguish in clinical practice, and treatment remains similar.

Prognosis

The complaints are chronic and may lead to impaired quality of life and mood disturbance. Course may be waxing/waning or persistent without periods of remission.

Diagnosis

Diagnosis is based on history. Identifying comorbidities is helpful. PSG is usually not of diagnostic value, except to diagnose sleep-state misperception or to exclude other disorders.

Treatment

Instructions of optimal sleep hygiene may be helpful for most of the patients and for some may be sufficient even without added mediation therapy.

1. Sleep hygiene measures are essential for all individuals with insomnia.
   - **a.** Regular wake times
   - **b.** Determine time in bed—most need 7 to 9 hours of sleep, do not stay in bed longer
   - **c.** Allow ample amount of light during the day
   - **d.** Allow less light in the evening
   - **e.** Avoid late afternoon naps
   - **f.** Avoid afternoon caffeine—last intake ideally at noon
   - **g.** Avoid alcohol close to bedtime—last intake ideally more than 5 hours before habitual bedtime
2. Cognitive-behavioral techniques have demonstrated the best long-term efficacy.
   - **a.** Stimulus control: Limits negative association of bed and sleep-onset period. This is counterintuitive to many with insomnia. Additional recommendations are:
     - **1)** Use bed for sleep only
     - **2)** Turn clock, so it is not visible from the bed
   - **b.** Sleep restriction therapy: Restricts time in bed to the amount the patient reports sleeping (usually 5 to 6 hours). Produces short-term sleep deprivation, promoting easier time falling and staying asleep, and subsequent increased confidence and reduced anxiety regarding sleep.

Once sleep improves, expansion of time in bed by 30 minutes per night per week achieves more normal total sleep duration. Sleep diaries and regular appointments are valuable.

c. *Relaxation procedures*: Progressive muscle relaxation, biofeedback, yoga, and meditation. Mastery of technique and daily use are essential.

3. Hypnotic and anxiolytic medications may be helpful (Table 5-5). If long-term medication use is expected, it is prudent to use ones that are not likely to lead to tolerance. For patients who also have OSA, it is best to use ones without muscle-relaxant properties.

4. Melatonin agonists, an orexin antagonist, and other medications can be used as well. The typical dose used for ramelteon (melatonin agonist) is 8 mg, higher doses have not shown to be effective. Suvorexant, an orexin antagonist, is usually started at 10 mg.

RESTLESS LEGS SYNDROME

Background

Restless legs syndrome (RLS) is a sensory phenomenon, referring to an uncomfortable sensation that leads the patient to move limbs. It is closely related to periodic leg movements of sleep (PLMS). Frequency increases with age. Additionally, RLS is more frequent during pregnancy.

History

Patients complain of uncomfortable sensations in the extremities, usually legs. They may describe tingling, "creepy-crawly" sensation, electrical feeling, pain, or simply state the sensation is indescribable.

Pathophysiology

RLS is seen with chronic renal failure, iron deficiency, rheumatoid arthritis, antidepressant use, and pregnancy.

1. Approximately one-third of primary RLS is familial, with early-onset (before age 30 years) cases possibly having an autosomal dominant mechanism. There are at least two RLS susceptibility genes, but autosomal

dominant pattern of inheritance can occur without any of the known genes.

2. Serum and/or CSF ferritin levels may be low, indicating a possible role of iron (through its involvement in dopamine production) in pathophysiology of RLS.

Prognosis

RLS can have waxing–waning course. It can resolve when the underlying condition (e.g., anemia) is treated.

Diagnosis

Diagnosis is made by clinical history, including the typical symptoms.

1. Dysesthesia and restlessness in the legs (or arms) that are relieved by movement.
2. Symptoms are exclusively present or worse in the evening or at night compared to the daytime.
3. Symptoms are exacerbated by sleep deprivation.
4. PSG is not needed for diagnosis, but if performed, it shows PLMS in 80% of the patients.
5. Laboratory evaluation to assess ferritin level.

Treatment

1. A ferritin level less than 50 μg/L indicates a need for iron supplementation.
2. Dopaminergic agents are extremely effective in relieving symptoms of RLS and decreasing PLMS.
   - **a.** Pramipexole (0.25 mg starting dose, increase by 0.25 mg every 3 days to effective dose, usually 0.25 to 1.0 mg)
   - **b.** Ropinirole (0.25 to 2.0 mg) 2 hours before symptom onset; if needed before 6 to 8 PM may also need to be given before bed to relieve symptoms all night.

     The patients may experience "augmentation": earlier appearance of symptoms during the day, which can then worsen with earlier dosing of medication, leading to refractory symptoms. This is more common with L-dopa than with dopamine agonists.

     Common side effects of dopaminergic agents include nausea, insomnia,

and fatigue. Rare side effects include peripheral edema, orthostasis, compulsive behaviors, and sleep attacks. They should be avoided in individuals with history of, or current, psychosis.

c. Gabapentin. Although it is generally not as effective as an opioid, there are less concerns with its use. Usual effective dose ranges from 300 to 1,800 mg. It can be given in divided doses in the evening and before bed. Common side effect is sedation. It should be used at lower doses cautiously in those with renal insufficiency or failure. The patients should be warned to not stop the medication abruptly, if higher doses are used.

d. Opioids may be less effective than dopaminergic agents and have the potential for misuse. Oxycodone or codeine in small doses is very effective in relieving RLS symptoms, particularly in those with painful dysesthesia.

PERIODIC LIMB MOVEMENT DISORDER

Background

PLMS are commonly recorded movements during sleep, consisting of repetitive dorsiflexion of the foot and/or lower leg. Movements are generally subtle and may not be recognized by a bed partner, although in more severe forms they are gross. Other limbs can be affected, including arms and rarely trunk. PLMS may or may not be associated with arousals from sleep, and indices of the number of movements with and without arousal per hour of sleep are derived. The term PLMS derives from the periodicity of movements, which occur at 15- to 30-second intervals during sleep. Movements are roughly 2 seconds in duration. When a sleep complaint occurs in the presence of PLMS, absent other known causes of sleep disruption, a diagnosis of PLMD is given.

History

PLMS are commonly recorded on overnight PSG, and population estimates of the prevalence of PLMS exceeding 5 per hour range from 11% to 58%. PLMS are more commonly recorded in the elderly, in those taking antidepressants, and in a number of medical (end-stage renal disease, CHF, diabetes) and neurologic or sleep disorders (OSA, narcolepsy, Parkinson disease, MS).

Although roughly 80% of individuals with RLS will demonstrate PLMS, only a small proportion of those with PLMS will describe symptoms of RLS. Controversy exists regarding the clinical importance of PLMS for sleep quality or daytime alertness, with some studies showing a lack of correlation of PLM index with subjective or objective sleep quality or daytime sleepiness, and others showing limited associations.

Pathophysiology

PLMS are associated with dopaminergic dysregulation at either the spinal or higher CNS levels. Dopaminergic antagonists can produce PLMS, whereas dopaminergic agonists are extremely effective in reducing them. Disorders characterized by dopaminergic deficiency (e.g., narcolepsy, sleep REM behavior disorder) show high rates of PLMS. Functional imaging of the brain has demonstrated small, but consistent, reductions in dopaminergic function in PLMS. Finally, correlations of dopaminergic metabolites are observed with the number of PLMS. The presence of PLMS in quadriplegics suggests that the motor program for these movements exist in the spinal cord and are somehow disinhibited in patients with excessive movements during sleep.

Prognosis is similar to RLS.

Diagnosis

PLMD is suspected if an individual (or their bed partner) reports kicking or jerking of the legs during sleep and has a complaint of sleep disruption or excess daytime sleepiness that cannot be accounted for by another cause. PSG confirms the diagnosis of PLMD, both to document the PLMS and to exclude other causes of repetitive leg movements, most prominently OSA. In an adult, a frequency of more than 15 leg movements per hour of sleep is consistent with the current definition of PLMD. In addition to the PLMS, the diagnosis of PLMD requires presence of daytime sleepiness or sleep disturbance, which cannot be better explained by another disorder (such as sleep apnea, anxiety, narcolepsy, etc.). It is important to note that may times PLMS can be asymptomatic or associated with another disorder. For example, five or more PLMS per hour occur in 80% to 90% of patients with RLS, in about 70% with REM sleep behavior disorder (RBD), and in 45% to 65% with narcolepsy.

The differential diagnosis of nocturnal leg movements in the sleep period includes RLS (in which leg restlessness is reported prior to sleep onset),

anxiety (in which leg movements will be observed during waking, not sleep), nocturnal seizures (which will demonstrate abnormal electroencephalogram [EEG] changes), OSA (in which characteristic respiratory abnormalities are observed), or REM sleep behavior disorder (in which movements are dream enactments, occurring during REM sleep, and are not periodic).

Treatment

Treatment of PLMD begins with eliminating precipitating or exacerbating agents (e.g., antidepressants). PLMS can be dramatically reduced with the addition of dopaminergic agents, especially if there is concurrent RLS. However, EEG arousals may persist even with elimination of the manifest motor activity. Additionally, dopaminergic agents may be associated with augmentation. Coadministration or substitution by a benzodiazepine has also been advocated. Use of clonazepam, in small numbers of patients, was effective in improving both the number of PLMs as well as sleep continuity measures. Benzodiazepines should be used cautiously in older patient because of the risk of falls, those with cognitive complaints, and comorbidities, particularly in patients with epilepsy.

DISORDERS OF THE CIRCADIAN RHYTHM

Background

Multiple normal neurophysiologic functions are affected by the circadian system independently of sleep–wake state and time awake. Subjective alertness, cognitive performance, and short-term memory are lowest close to the time of the temperature minimum, or the "biological night." The timing of other body functions also has circadian or day/night variability, independently of the state of sleep or wakefulness. Examples include the morning peak in cortisol secretion, preserved even in conditions of continuous wakefulness, nocturnal peak of gastric acid secretion, melatonin secretion, and others. These functions have tightly established phase relationships (e.g., the time when cortisol secretion reaches peak level is also the time when melatonin secretion decreases).

Pathophysiology

When the times of sleep and wakefulness change on a consistent basis, other body rhythms follow, and normal phase relationships are eventually reestablished. However, these phase relationships can be changed either temporarily (during jet lag) or longer period of time (advanced and delayed sleep phase syndromes [DSPS]) and as a result, the patient may experience difficulty with sleep onset at the desired time, sleepiness, poor concentration, lack of productivity, and other symptoms.

Prognosis

Jet lag is self-limited. DSPS (see the next section) is sometimes self-limited, improving in older age.

Delayed Sleep Phase Syndrome

DSPS is a disorder of the phase relationships between the desired sleep times and the circadian system, manifesting as a tendency to fall asleep much later than desired and awakening later than the times typical for the general population. As a result, these patients frequently come to medical attention with complaints of insomnia. DSPS is especially frequent cause of insomnia in young adults.

Advanced Sleep Phase Syndrome

Similar to DSPS, in advanced sleep phase syndrome (ASPS), the "biological night" of the patient is "locked" at an adverse time relative to the desired bedtime, occurring hours earlier. This disturbance is more frequent among older individuals. There are familial forms of the disorder.

Diagnosis

The ICSD has established the following "minimal criteria" for diagnosis of DSPS: (a) inability to initiate sleep at the desired time and difficulty awakening; (b) delayed timing of the habitual sleep episode; (c) presence of symptoms for 1 month or more; (d) when constraints permit (e.g., when not working or attending classes), the patient opts for delayed timing of the major sleep episode, which is felt to be of good quality and quantity, and can awaken

from this sleep episode without difficulty, and remains on this delayed sleep–wake schedule without difficulty; and (e) 2 weeks or more of subjective sleep data (e.g., sleep–wake diary) verify the presence of the delayed, habitual sleep–wake schedule.

For both DSPS and ASPS, diagnosis is made based on clinical history and can be confirmed by sleep diary or objective measures, such as wrist actigraphy. Circadian phase markers (usually serum melatonin or core body temperature) can confirm the diagnosis but are not routinely recommended. PSG or MSLT is not indicated unless another sleep disorder is suspected.

Treatment

The most powerful factors that entrain the circadian rhythm are (a) light—giving information about the time of the "day" and (b) melatonin—giving information about the time of "night." Based on these, several approaches have been proposed for treatment of DSPS.

1. Chronotherapy: The patient is advised to delay sleep times by 3 hours every 24 hours until the desired sleep time is reached. In a case report, this treatment was successful in a 10-year-old and resulted in improvement of sleep and attention.
2. Phototherapy (light treatment): Bright light can "shift" the "biological night" of individuals (as measured by major physiologic parameters, e.g., core body temperature) in experimental conditions. The rapidity and degree of change depends on the intensity of the stimulus, and its timing relative to the subject's core body temperature minimum at the start of the treatment. Thus, the "ideal" treatment starts with measurement of the patient's physiologic "night" (from the time of the temperature minimum or melatonin secretion) in a constant routine protocol, described earlier. Such measures are expensive, cumbersome, and not considered cost-effective for clinical purposes. However, bright light can be used for treatment of DSPS, empirically administered in the hours between 6 and 9 AM at 2,000 to 2,500 lux, with reasonable success. The optimal duration of therapy is not established, although treatment lasting 2 weeks for 2 hours every morning has been successful. As bright light is safe and relatively easy to administer, it is an approved treatment for DSPS.

   Treatment options for ASPS are similar to DSPS. Phototherapy, as evening bright light at 2,500 to 4,000 lux in the hours between 8 and 11 PM for 2 to 3 hours can be used.

3. Melatonin: It can be used to shift circadian rhythm and is a reasonable alternative treatment. Administration of 5 mg at 10 PM has been successful and well tolerated. Unlike some hypnotics, treatment is not associated with "hangover effect," but some patients have reported morning fatigue. Given that the effects on the reproductive system development are not fully known, caution has been advised in younger patients.

   Other reported treatment options include B_{12} supplementation. In a two-patient report of adolescents who did not have B_{12} deficiency, administration of high doses B_{12} was successful. However, no randomized studies have been performed.

4. Blue light may be more effective than bright light in adjusting circadian rhythms.

   None of the above approaches have been compared and none is established as superior. Furthermore, patients vary widely on compliance and thus any one of the above or a combination can be used, depending on the circumstances.

Jet Lag

Desynchronization between the environmental and the biological "night" occurs during travel across time zones in a short period of time, commonly known as "jet lag." Similarly to the earlier described sleep phase disruption syndromes, it can cause insomnia, difficulty with concentration, or sleepiness and could be logically expected to modify disorders that have a circadian pattern. Typically, adjustment to eastbound travel is more difficult than for travel westbound. Treatment can include phase advance prior to travel, use of bright light during the anticipated daytime at the arrival destination, or melatonin.

PARASOMNIA

Parasomnias are divided into those arising from non-REM sleep (also known as confusional arousals) and those occurring during REM sleep. These two types of parasomnias can often be distinguished by their distinctive time of occurrence, presence of dream recall upon awakening during the behavior, mental status upon awakening, duration, degree of amnesia for the event, and associated autonomic activation.

Non–Rapid Eye Movement Parasomnias

Background

Behaviors or affective expression partially divorced from full awareness can occur during full or partial sleep states. Most common are motor activities (walking, eating, sexual behavior) or emotional responses (fear, anger, sexual excitement), usually occurring in brief episodes. Complex mentation and sound judgment, and feedback from the environment are suppressed. These disorders are more frequent in children, are associated with amnesia, and occur in the first 1 to 2 hours of sleep, usually arising from slow wave sleep.

History

Confusional arousals are usually brief, simple motor behaviors, which occur without substantial affective expression. Mental confusion with automatic behavior, indistinct speech, and relative unresponsiveness to the environment are hallmarks of a confusional arousal. Sitting up in bed with simple vocalization and picking at bedclothes are common examples. If interrupted by family members, responses may be momentarily absent, incomplete, or inappropriate.

Sleepwalking involves more elaborate behaviors, usually without substantial emotional involvement. Common examples include attempts to use the bathroom, go to the kitchen, eat or even cook, or, in some cases, leave the home. Although the walker's eyes are open, behavior may be clumsy. Dreaming is usually not present, and individuals (if awakened) will report only simple mentation (a fragment or feeling). Patients typically return to sleep and are amnestic for the event the next morning.

Sleep terrors (pavor nocturnus) have many of the properties of other non-REM parasomnias but are characterized by more intense autonomic, motor, and affective expression (and experience). In children, sleep terrors may be heralded by a scream, followed by displays of extreme fear, crying, and inconsolability. In adults, agitation is common, frequently with the belief that there is an imminent threat, with behavior of escape or defense. For this reason, sleep terror sufferers may cause injury to themselves, others, or to property, in their highly agitated state. As in sleepwalking, dreaming is usually not reported, but simple thoughts are present ("the room is on fire," or "I am being attacked"), which can be difficult to dispel, even after the sufferer has

awakened.

Non-REM parasomnia variants have also been identified in adults: excessive sleep inertia (or "sleep drunkenness"), abnormal sleep-related sexual behavior ("sex-somnia"), sleep-related eating disorder, and sleep-related violence.

Sleepwalking occurs in 10% to 20% of children and 1% to 4% of adults. Sleep terrors are less common than sleepwalking, with roughly 5% of children, and 1% to 2% of adults reporting a history of such events. Roughly 80% of adults with sleepwalking have it as a continuation of a childhood behavior, although many will not come to medical attention until their 20s to 30s.

Pathophysiology

The expression of all non-REM parasomnias appears to depend on a genetic predisposition combined with a precipitating event, which may be endogenous (e.g., respiratory obstructive event, pain, leg movement of sleep) or exogenous (e.g., forced awakening or environmental disruption). In predisposed individuals, sleep deprivation, medications, sleep disorders, stress, and circadian misalignment may all aggravate or expose an underlying parasomnia. It is unclear why such partial arousals are more common in children.

In a predisposed individual, parasomnias can be triggered by

1. Medications (sedative antidepressants, hypnotics such as zolpidem)
2. Stress
3. Sleep deprivation
4. Erratic sleep schedule
5. Most instances are idiopathic

Prognosis

As described earlier, for children, episodes tend to become less frequent or often stop in adulthood. For adults, there is usually a waxing/waning course.

Diagnosis

Diagnosis is made by history. A clear description of the events, the timing, and any associated behaviors is useful, although sometimes difficult to obtain. Polysomnogram is indicated if the clinician suspects that the events are triggered by arousals from another sleep disorder (sleep apnea or PLMS). The distinction from focal (especially frontal lobe) epileptic events is key and

sometimes difficult, thus evaluation with an EEG (full 16 channel montage) is helpful.

Treatment

The decision to treat non-REM parasomnias is based on the frequency of the event, the risk of associated injury to self or others, and the distress the behavior is causing the patient or family members. Fortunately, for the majority of adult sufferers, parasomnias occur infrequently, but their appearance is unpredictable.

For most children, parasomnias do not require medication treatment unless there is risk of harm. Regularization of the sleep–wake cycle and avoidance of sleep deprivation will reduce the frequency of events. For those children and young adults who do sleepwalk, enhancing the safety of the sleeping environment, such as locking doors and windows and keeping hallways and stairs well lit, is essential.

When treatment of sleepwalking or sleep terrors in an adult is warranted, a three-step approach is used:

1. Modification of predisposing and precipitating factors
2. Enhancing safety of the sleeping environment
3. Pharmacotherapy

There are no specific medications targeting parasomnias. In most cases, medications that improve sleep continuity also lead to a decrease in the number of events. Clonazepam (0.5 to 1.0 mg qhs) has been used successfully for sleepwalking and sleep terrors for extended periods without the development of tolerance in most patients. If the parasomnia occurs within the first half of the sleep period, short-acting BzRAs such as triazolam (0.125 to 0.25 mg qhs) are recommended to minimize daytime carryover effects. Other treatment options include imipramine and amitriptyline.

Rapid Eye Movement Sleep Behavior Disorder

Background

RBD is characterized by pathologic appearance of the features of REM sleep. In RBD, the usual atonia of REM sleep is absent, allowing the patient to enact dreams, which, when agitated or violent, can result in injury to the sleeper or

bed partner.

History

The patient presents with various dream-enactment behaviors, including kicking, hitting, screaming, and others. The individual is unresponsive to the environment until awakened, at which point they will achieve rapid and full alertness and report a dream which usually corresponds to the exhibited behavior. Episodes of full-blown RBD are intermittent, but sleep talking, shouting, vivid dreams, or fragmentary motor activity may occur between such events. It is this agitation and/or injury that bring the patient for consultation, usually at the behest of the bed partner.

Pathophysiology

An animal model of RBD, in which lesions around the locus coeruleus produced "REM sleep without atonia," was developed well before the discovery of RBD, and it implicates these brainstem areas in the control of motor activity in REM sleep. In patients with RBD, dopamine transporter abnormalities in the nigrostriatal system have been demonstrated. Similarly, a reduction in neurons in the peri locus coeruleus has been seen. However, more widespread CNS dysfunction is suggested by data showing slowing of the EEG during wake as well as subtle neuropsychologic dysfunction in patients with idiopathic RBD.

RBD can be triggered by medications, most commonly SSRIs.

Prognosis

RBD is a chronic disorder, usually observed in males above age 50 years, and in individuals with certain neurologic disorders. In particular, RBD is often present in individuals with α-synucleinopathies (Parkinson disease, dementia with Lewy bodies, and multiple system atrophy). RBD may also be a heralding symptom of neurologic illness: In one study, two-thirds of patients with RBD followed for 10 years developed Parkinson disease. RBD may also be precipitated by treatment with serotonergic antidepressants.

Diagnosis

The diagnosis of RBD is made by PSG, which demonstrates elevated muscle tone or excessive phasic muscle activity in the submental and anterior tibialis

electromyogram during REM sleep. At times, body movements are manifest during REM on sleep study. Excess periodic limb movements of sleep may also be observed during both REM and non-REM sleep.

Treatment

First-line treatment of RBD consists of BzRAs. Options include:

1. Clonazepam (0.5 to 1.0 mg). Because of the long half-life of clonazepam, excess daytime sleepiness and/or cognitive impairments may be seen.
2. Shorter acting benzodiazepines (e.g., lorazepam 1 to 2 mg) allow less sedation.
3. Melatonin (3 to 15 mg qhs).

Removal of potentially offending medications such as antidepressants should be attempted as is clinically possible.

Safety of the sleeping environment for both the patient as well as the bed partner is essential.

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6 Cancer Neurology

Eudocia Quant Lee and Patrick Y. Wen

PRIMARY BRAIN TUMORS

Background

Primary brain tumors (PBTs) are a heterogeneous group of neoplasms arising from the central nervous system (CNS) with varied outcomes and management strategies.

Epidemiology

1. Approximately 77,000 PBTs are diagnosed annually in the United States, of which approximately 25,000 are malignant.
2. There has been a steady rise in incidence of PBTs during the last two decades, in part because of increased sensitivity of imaging modalities.
3. Incidence of PBTs is 22/100,000 persons per year and increases with age.
4. PBTs are the most common cancer in children and the second leading cause of cancer death under the age of 19 years.
5. In adults (age 20≤ years), the most common tumor types (in decreasing order of frequency) are meningioma (36.4%), pituitary tumors (such as pituitary adenoma) (15.5%), nerve sheath tumors (such as vestibular schwannoma) (15.5%), and glioblastoma (GBM) (15.1%).
6. In children (age 0 to 19 years), the most common tumor types in decreasing frequency are pilocytic astrocytoma (15.5%), malignant glioma (11.7%), and embryonal tumors (such as medulloblastoma) (11.4%).

Genetic Factors

One percent to 5% of patients with brain tumors have an underlying genetic syndrome that increases their risk of developing a brain tumor (Table 6-1).

Environmental Factors

There are only two unequivocal risk factors for PBTs:

1. Cranial irradiation is associated with an increased risk for meningiomas (10-fold risk) and gliomas (three- to sevenfold risk) with a latency period of 10 to 20 years after exposure.
2. Immunosuppression is associated with an increased risk for CNS lymphoma.
3. The association between PBTs and other forms of radiation, such as electromagnetic radiation and radiofrequency radiation (from portable cellular phones with antenna) is less clear.

Pathophysiology

1. Gliomas arise from cells of neuroglial origin, whereas meningiomas arise from meningothelial (arachnoidal) cells.
2. Exact cell of origin in gliomas is uncertain, but there is increasing evidence that gliomas arise from neural stem cells or progenitor cells.

Table 6-1 Genetic Syndromes Associated with Brain Tumors

Neurofibromatosis type 1: Autosomal dominant (loss of gene encoding neurofibromin on chromosome 17)	
Associated with	Schwannomas Astrocytomas (including optic nerve gliomas) Neurofibromas Neurofibrosarcomas
Neurofibromatosis type 2: Autosomal dominant (mutation of *NF2* gene on chromosome 22)	
Associated with	Bilateral vestibular schwannomas Schwannomas of other cranial nerves Multiple meningiomas Spinal tumors such as Ependymomas
von Hippel–Lindau syndrome: Autosomal dominant (mutation of *VHL* gene on chromosome 3)	
Associated with	Hemangioblastomas Pancreatic cysts, retinal angiomas, renal carcinoma, pheochromocytoma
Li–Fraumeni syndrome: Autosomal dominant (germline mutation of *p53*)	
Associated with	High-grade gliomas and choroid plexus carcinomas Sarcomas, breast cancer, and leukemias

Turcot syndrome: Cancer syndrome characterized by familial polyposis and brain tumors. It may be associated with familial adenomatous polyposis (FAP) (autosomal dominant, mutation in *APC* on chromosome 5) or hereditary nonpolyposis colorectal cancer (HNPCC) (mutation in mismatch repair gene)	
Associated with	Gliomas, usually GBM in HNPCC Medulloblastomas in FAP Polyposis coli
Basal cell nevus syndrome (Gorlin syndrome, nevoid basal cell cancer syndrome): Germline mutations of the patched (*PTCH*) gene	
Associated with	Medulloblastoma
Familial meningiomas	
Familial gliomas	

GBM, glioblastoma.

Molecular Genetics

1. Familial syndromes account for less than 5% of CNS tumors. The genetic syndromes associated with brain tumors are listed in Table 6-1.
2. Brain tumors result from a multistep process driven by the sequential acquisition of genetic alterations. These include loss of tumor suppressor genes (e.g., *p53* and *PTEN*) and amplification and overexpression of protooncogenes such as the epidermal growth factor receptor (EGFR) and the platelet-derived growth factors (PDGFs) and their receptors (platelet-derived growth factor receptor [PDGFR]). The accumulation of these genetic abnormalities results in uncontrolled cell growth and tumor formation.
3. Glioma: The primary classes (astrocytoma, oligodendroglioma, GBM) have traditionally been based on histopathology although the field is moving toward molecular classification. Primary (arising *de novo*) GBMs differ from secondary (arising from lower grade glioma) GBMs based on molecular features. GBMs in pediatric patients are also vastly different from GBMs in adult patients with regard to their mutation and gene expression profiles. This may have implications in the selection of targeted molecular therapies for these tumors.
   a. Gliomas with isocitrate dehydrogenase (*IDH*) 1 and 2 mutations
      1) Low-grade oligodendrogliomas (World Health Organization [WHO] grade 2)

a) Codeletion of chromosome arms 1p and 19q
b) Telomerase reverse transcriptase (*TERT*) promoter mutations
c) Mutations in the homolog of Drosophila capicua gene (*CIC*) or far-upstream binding protein 1 gene (*FUBP1*)
d) *Notch1* mutations

2) Anaplastic oligodendrogliomas (AOs) (WHO grade 3): In addition to aforementioned mutations
a) *CDKN2A*
b) Phosphatidylinositol-3-OH kinase (PI3K) subunit mutations including *PIK3CA* and *PIK3R1*

3) Low-grade astrocytomas (WHO grade 2)
a) *TP53* mutations
b) Alpha thalassemia/mental retardation syndrome X-linked (*ATRX*) mutations

4) Anaplastic astrocytoma (WHO grade 3): In addition to the aforementioned mutations
a) *CDK4* and *CDKN2A*
b) *MDM2* amplification
c) Loss of heterozygosity (LOH) of chromosome 10q

5) Secondary adult GBM (WHO grade 4 astrocytoma arising from lower grade glioma): In addition to the aforementioned alterations (including *IDH1*, *TP53*, and *ATRX*)
a) *PDGFRA* amplification

b. Gliomas without *IDH1* or *IDH2* mutation

1) Primary adult GBM (arising *de novo*): Vast majority of GBMs are primary (90% to 95%)
a) Receptor tyrosine kinase alterations including *EGFR* amplification, *PTEN* deletion/mutation, PI3K subunit mutations, *PDGFRA* amplification, and *NF1* mutation
b) Retinoblastoma (*RB1*) alterations including *CDKN2A/p16* mutation/deletion, *CDK4* amplification, *RB1* mutation/deletion
c) p53 alterations including *CDKN2A/ARF* mutation/deletion, *MDM2* amplification, and *TP53* mutation/deletion

2) Pediatric GBM: Nearly always arise *de novo*
a) *H3F3* mutations
b) Death-domain associated protein (*DAXX*) mutations

c) *TP53* mutations
d) *ATRX* mutations

4. Medulloblastoma: Four molecular subtypes characterized by one of the following:
   a. Alterations in the sonic hedgehog (SHH) pathway
   b. Alterations in the Wingless (WNT) pathway
   c. High-level amplification of *MYC*
   d. Amplification of *MYCN* and cyclin-dependent kinase 6 (*CDK6*)

Prognosis

1. The prognosis of brain tumors is determined by tumor type, grade, and location and by patient's age and functional status (Karnofsky performance status [KPS]).
2. As a result of this marked heterogeneity, the prognostic features and treatment options must be carefully reviewed for each patient.
3. The feasibility of resection is a key determinant of prognosis and depends on the location and the invasiveness of the neoplasm.
4. Histologic grade of the tumor is important and clearly dictates the survival, but care must be taken because sampling errors may underestimate the grade. Furthermore, low-grade neoplasms can transform to higher grade neoplasms.
5. Advances in surgery, radiation therapy (RT), and chemotherapy have led to improvement in prognosis for some low-grade gliomas, AOs, and GBMs.

Diagnosis

Location

1. The frequency of tumors at a location depends on age and type of tumor.
2. In adults, 70% of tumors occur in cerebral hemispheres; and in children, 70% of tumors occur in posterior fossa.

Clinical Presentation

1. Symptoms are caused by variety of effects caused by brain tumors including pressure against adjacent structures, elevated intracranial pressure (ICP),

and seizures.

2. Symptoms can be acute or subacute but generally are progressive and depend on the size, location, and growth rate of tumor and peritumor edema.
3. Acute symptoms can result from seizures, intratumoral hemorrhage, or rapid growth or edema in eloquent areas.
4. Among patients with new-onset seizures, 5% are found to have a brain tumor.
5. Generalized and focal seizures occur in 15% to 95% of patients with supratentorial tumors and are more common in low-grade tumors and meningiomas.
6. Can present with generalized or focal signs.
7. Increased ICP symptoms include change in mental status, headache, nausea, vomiting, drowsiness, and papilledema.
8. Headache is the presenting feature in 35% of patients and develops in up to 70% during the course of the disease. They are often indistinguishable from tension headaches or migraines. It should be borne in mind that the vast majority of headaches seen in unselected populations are benign. As headache is a nearly universal phenomenon, its actual relationship to tumor is often tenuous. They are usually bilateral, diffuse, and typically worsened with Valsalva maneuvers and lying down.
9. Focal signs include hemiparesis, sensory loss, ataxia, aphasia, memory loss, neglect, and visual loss.

Diagnostic Tests

1. Magnetic resonance imaging (MRI) enhanced with gadolinium is the test of choice for diagnosis of brain tumors.
2. Sometimes, computed tomography (CT) with contrast is the only choice in patients with pacemakers or metallic implants.
3. Tumor cells have been found in the peritumoral edema, which corresponds to the T2-weighted MRI abnormalities.
4. Other modalities such as magnetic resonance spectroscopy (MRS), perfusion and permeability imaging, positron emission tomography (PET), and single-photon emission computed tomography (SPECT) may be helpful in distinguishing tumor from radiation necrosis or inflammation.
5. Functional MRI can be used to define eloquent areas to assess risk of

surgery.

6. The presence of multiple lesions on a contrast-enhanced study favors a metastatic process, but metastases can present as a solitary lesion in up to 30% of patients.
7. Lumbar puncture (LP) for routine cerebrospinal fluid (CSF) studies, cytology, and flow cytometry is useful to rule out leptomeningeal involvement of tumors, especially in the case of lymphoma, medulloblastoma, pineal tumors, and germ cell tumors. LP is generally contraindicated if elevated ICP is suspected or if there are large mass lesions. CSF studies are unlikely to diagnose gliomas involving only the parenchyma.
8. In cases of suspected metastatic disease, a full workup to search for a primary tumor should be undertaken and includes ocular, testicular, breast (mammogram in females), and prostate examinations (males) and urinalysis, complete blood count, peripheral smear, stool guaiac testing, body CT, bone scan, and, increasingly, PET scan.
9. Stereotactic biopsy or preferably craniotomy with resection of the mass allows histologic diagnosis and should be performed in most patients.

Pathology

1. The classification, prognosis, and treatment of brain tumors are ultimately dependent on the histopathologic features of the surgical specimen and the clinical context.
2. Errors can occur when a small sample is taken for biopsy in a heterogeneous tumor and does not reflect the biology of the entire tumor.
3. Unlike other types of cancers, gliomas are not staged and instead classified according to grade. Glial tumors are graded on the basis of cellularity, nuclear atypia, mitoses, microvascular proliferation, and necrosis according to the WHO system.
4. Grading for astrocytoma
   a. WHO grade I (pilocytic) astrocytoma is very slow growing.
   b. WHO grade II (low grade) astrocytoma shows relatively homogenous appearance, hypercellularity, nuclear atypia, and ill-defined tumor margins. Pleomorphic xanthoastrocytoma (PXA) is a more benign variant.
   c. WHO grade III anaplastic astrocytoma (AA) shows high cellularity,

mitosis, and pleomorphism.

d. WHO grade IV (GBM) not only shows features of grade III but also has necrosis and endothelial proliferation.

5. As genotyping of tumors becomes increasingly more common and shown to be of prognostic value, the classification of tumors will evolve.

Differential Diagnosis

1. A wide differential diagnosis must be kept in mind during the initial evaluation of a brain mass as many treatable conditions can mimic brain tumors.
2. The differential includes other PBTs, metastases, lymphoma, abscesses, viral infections, encephalomyelitis, demyelination, stroke, vascular anomaly, vasculitis, and granulomatous and inflammatory disease.

Treatment

Treatment of patients with brain tumors requires close cooperation of a multidisciplinary team of physicians including neurologists, neurosurgeons, radiation therapists, oncologists, neuroradiologists, neuropathologists, and psychiatrists.

Supportive Care

1. **Corticosteroids**
   - **a.** Used to reduce symptomatic vasogenic edema surrounding tumors, which lowers ICP and mass effect. Clinically, improvement begins within 12 to 48 hours with maximum improvement by fifth day.
   - **b.** Response is independent of type of corticosteroid used (dexamethasone, methylprednisolone, prednisone, hydrocortisone) in equivalent doses.
   - **c.** Dexamethasone is used widely because of low mineralocorticoid (salt-retaining) side effects.
   - **d.** Dexamethasone usually given as bolus of 10 mg and then 16 mg/d by mouth (p.o.) or intravenous (IV).
     - **1)** Oral absorption is excellent.
     - **2)** Half-life of oral dexamethasone is long enough for it to be given once or twice daily.
   - **e.** Higher doses (up to 40 mg) can be given to critically ill patients until

definitive treatment (surgery, radiation) is undertaken.

f. Side effects include glucose intolerance, oral candidiasis, opportunistic infections including *Pneumocystis jiroveci* pneumonitis (PJP), gastric irritation, adrenal suppression, steroid myopathy, osteoporosis, and psychiatric problems.

g. Patients may need glucose monitoring and H_2 blockers or proton pump inhibitors to reduce gastric irritation.

h. Patients who are likely to remain on steroids for prolonged periods should have PJP prophylaxis (e.g., 160 mg of trimethoprim plus 800 mg of sulfamethoxazole [Bactrim DS] 3 d/wk) and prophylactic therapy for osteoporosis (calcium and vitamin D supplements and bisphosphonates).

i. Steroids should be tapered to the lowest dose possible to avoid complications.

j. Patients who are on steroids for prolonged periods may need adjustments to control edema perioperatively and during chemotherapy and radiation treatments.

2. Anticonvulsants

(a) Prophylactic antiepileptic drugs (AEDs) are not recommended for patients unless they have history of seizures. There is no evidence that patients with brain tumors who have never had a seizure benefit from prophylactic anticonvulsants.

(b) Prophylactic AEDs should be given to patients undergoing craniotomies but can be tapered off 1 to 2 weeks after the procedure.

(c) Cytochrome P450 enzyme-inducing antiepileptic drugs (EIAEDs), such as phenytoin and carbamazepine, increase the metabolism of many chemotherapeutic agents and reduce their efficacy.

(d) More than 20% of brain tumor patients receiving phenytoin or carbamazepine develop drug rashes.

(e) The newer AEDs, such as levetiracetam, that do not induce cytochrome P450 enzymes, have less drug interactions and are better tolerated.

Prevention of Venous Thromboembolism

Patients with brain tumors have an increased risk of developing venous thromboembolism (VTE) (30% lifetime risk in patients with GBM). Extra care must be taken to prevent VTE in the perioperative period. When a patient develops VTE, anticoagulation is usually safe after the perioperative period

and is more effective than inferior vena cava filtration devices. Low molecular weight heparin may be safer and slightly more effective than warfarin.

Supportive Care

Many patients with brain tumors benefit from physical and occupational therapy, psychiatric consultation, visiting nurses, social services, patient support groups, and brain tumor organizations (American Brain Tumor Association [2720 River Rd, Des Plaines, IL 60018, Phone: (847) 827-9910 or patient line: (800) 886-2282, e-mail: info@abta.org;wwwabta.org]; the National Brain Tumor Society [East Coast Office: 124 Watertown Street, Suite 2D, Watertown, MA 02472, Phone: (617) 924-9997; West Coast Office: 22 Battery Street, Suite 612, San Francisco, CA 94111-5520, Phone: (415) 834-9970, e-mail: info@braintumor.org, www.braintumor.org]).

Therapy

Surgery

1. Decisions regarding aggressiveness of surgery for a PBT are complex and depend on the age and performance status of the patient; the feasibility of decreasing the mass effect with aggressive surgery; the resectability of the tumor (including the number and location of lesions), and, in patients with recurrent disease, the time since the last surgery.
2. Biopsy or surgical resection is performed on most patients to obtain histologic confirmation of the type and grade of tumor and provides information on prognosis and treatment.
3. Biopsy is performed using stereotactic devices or intraoperative MRI. Biopsies are performed for tumors that are deep or in eloquent areas where surgical resection is contraindicated.
4. Because of heterogeneity in the tumor, a small biopsy sample may be nondiagnostic or not representative of the whole tumor.
5. Appropriate localization of biopsy to obtain the highest grade area is important.
6. Extensive tumor resection is the surgical procedure of choice for most tumors and improves neurologic function and survival. This can be achieved for many extra-axial tumors, but few intra-axial tumors can be resected

completely.

7. Partial resection can be palliative by improving neurologic function and improving survival when total resection is not possible.
8. Repeated partial resections may be beneficial, especially for benign tumors.
9. Patients who develop hydrocephalus (usually because of tumors that obstruct the third or fourth ventricles) require a ventriculoperitoneal (VP) shunt to reduce ICP.
10. Some tumors such as brainstem gliomas have characteristic imaging features. Although pathologic confirmation is preferred, biopsy is sometimes avoided because of the high risk of neurologic deficits and patients might be treated without tissue diagnosis.
11. Intraoperative MRI can help in clarifying normal and abnormal tissue, thereby allowing for more complete resection.
12. A postoperative MRI, with and without contrast, should be performed within 24 to 48 hours after surgery to document the extent of disease following surgical intervention.

Complications of Surgery

1. The standard risks of anesthesia and neurosurgery include hemorrhage, stroke, increased edema, direct injury to normal brain, infection, and VTE.
2. Postoperative cerebral hemorrhage may require evacuation if producing focal deficits.
3. Cerebral edema is usually present preoperatively and may be exacerbated during surgery by mechanical retraction, venous compression, brain manipulation, and overhydration. Generally, steroids are given for several days prior to craniotomy.
4. Risk of cranial infection is increased with length of operation and introduction of foreign materials (shunt tubing, clips, chemotherapy polymers), and most infections are caused by cutaneous and airborne pathogens. Most patients are given perioperative prophylactic antibiotics.
5. Communicating hydrocephalus can occur transiently postoperatively.
6. Neuroendocrine disturbances such as syndrome of inappropriate secretion of antidiuretic hormone (SIADH) can occur after surgery, and electrolytes and fluid balance should be carefully monitored to prevent hyponatremia and cerebral edema.

7. Surgery of the hypothalamic–pituitary axis can result in various degrees of panhypopituitarism and diabetes insipidus (DI).

Radiation Therapy

1. RT for patients with PBTs usually involves a limited field encompassing the tumor volume (commonly defined as the region showing T2-weighted abnormalities on an MRI scan plus a 1- to 2-cm margin).
2. Usual dose is 6,000 cGy for high-grade PBT such as GBM; 5,000 to 5,400 cGy for low-grade PBT such as low-grade astrocytoma and 3,600 cGy for spinal tumors in 180- to 200-cGy fractions over approximately 6 weeks. A common scheme for whole brain radiation therapy (WBRT) in the management of brain metastases (BMs) is 3,000 cGy in 10 to 15 fractions.
3. Several different treatment approaches are used to treat brain tumors including conformal external beam (most common), stereotactic radiosurgery (SRS), and stereotactic radiotherapy (SRT).
4. Increasingly sophisticated techniques are available to administer conformational irradiation, including intensity-modulated radiation therapy (IMRT), which allows variation of radiation dose in different parts of the radiation field.
5. SRS involves the treatment of small intracranial targets (such as BMs) using a large, single fraction of ionizing radiation in stereotactically directed narrow beams. It allows a high dose of radiation to be delivered to the tumor while relatively sparing surrounding brain. SRS can be administered using x-rays from stereotactic linear accelerators, γ-irradiation from cobalt sources in Gamma Knife radiosurgery, and protons from cyclotrons (proton beam therapy). Radiation necrosis is relatively common. Risk increases with dose and volume treated; 5% to 10% of patients require surgical resection of necrotic area for symptomatic relief.
6. SRT is stereotactic radiation administered in multiple fractions to reduce risk of radiation injury to surrounding structures. It tends to be used for larger tumors.

Chemotherapy

1. The blood–brain barrier (BBB) provides the CNS with a privileged environment and consists of the cerebrovascular–capillary endothelium.

Only physiologically small, lipid-soluble drugs or actively transported drugs can cross the BBB.

2. Chemotherapy is useful for primary central nervous system lymphoma (PCNSL), anaplastic and low-grade oligodendrogliomas, anaplastic and low-grade astrocytomas, and medulloblastoma. Temozolomide has modest efficacy in GBM.

NEUROEPITHELIAL TUMORS

Pilocytic Astrocytoma

Background

1. The most common noninfiltrative, focal astrocytoma in childhood.
2. Mainly in children and adolescents but 25% in patients older than 18 years.
3. Also seen in individuals with neurofibromatosis type 1 (NF1).

Pathophysiology

1. Nearly all pilocytic astrocytomas have alterations in the *BRAF* oncogene leading to its activation, primarily by fusion with the *KIAA1549* gene.
2. Mostly sporadic, but deletions of 17q (NF1) are associated with 15% of optic gliomas in patients with NF1.

Prognosis

1. Indolent course, often surgically resectable, and rarely transforms to malignant tumor.
2. Greater than 90% 10-year survival for supratentorial lesions after total resection.
3. A 95% 25-year disease-free survival for cerebellar pilocytic astrocytoma after total resection.
4. A 74% to 84% 10-year survival for subtotal resection.
5. In children, 75% stable at 4-year follow-up after surgery and chemotherapy (vincristine and actinomycin D) when too young to receive radiation.

Diagnosis

Location

1. In children, it occurs in the cerebellum, optic pathway, and hypothalamus.
2. In young adults, it arises in cerebrum, brainstem, optic nerve, thalamus, and hypothalamus.

Clinical Presentation

Clinical features depend on location. Cerebellar lesions produce symptoms secondary to obstruction of CSF flow or pressure on cerebellum leading to headaches and ataxia.

Diagnostic Tests

MRI with gadolinium typically shows a cyst with mural nodule that enhances or a nodule alone.

Pathology

1. WHO grade I, grossly well-circumscribed, and gelatinous appearance.
2. Two microscopic patterns: A tightly packed parallel array of well-differentiated astrocytes with Rosenthal fibers (globular, refractile, homogenous, eosinophilic bodies) and a loose matrix of astrocytes, long slender piloid "hairlike" cells, and amphophilic granular bodies.

Differential Diagnosis

Low-grade diffuse astrocytoma, dysembryoplastic neuroepithelioma, ependymoma, and ganglioglioma.

Treatment

1. Some tumors in surgically inaccessible areas (e.g., optic nerve glioma) grow very slowly and may be observed for many years before definitive therapy is required.
2. Surgically curable if complete resection is possible.
3. Conformal radiation or SRT is helpful if resection is not possible or for recurrent tumor.
4. Chemotherapy with agents such as carboplatin and vincristine is useful in young children.

Pleomorphic Xanthoastrocytoma

Background

Rare focal astrocytoma with characteristic clinical, imaging, and pathologic features.

Pathophysiology

1. Believed to originate from subpial astrocytes because of its superficial location with attachment to the leptomeninges.
2. *BRAF* (*V600E*) mutations occur in approximately 60% of PXAs.

Prognosis

1. Indolent lesions.
2. Good with resection, 76% 10-year survival.
3. Rare anaplasia (15% to 20% of patients) associated with poor prognosis.

Diagnosis

Location

Predilection for superficial temporal and parietal lobes involving the leptomeninges and, rarely, the dura.

Clinical Presentation

1. Most common in children and young adults (second and third decade of life).
2. Usually have a long history of seizures before diagnosis.
3. Occasionally causes headaches and focal deficits.

Diagnostic Tests

MRI shows a heterogenous, superficial meningocerebral nodule, often associated with a cyst, iso- to hypointense on T1-weighted images and enhancing.

Pathology

1. Typically WHO grade II; enlarged, lipid-laden astrocytes; inflammation; extreme pleomorphism; cellular atypia; and spindle and multinucleated giant cells. No necrosis or vascular hyperplasia.
2. Undergoes anaplastic transformation in 15% to 20% of patients.

Differential Diagnosis

Can be mistaken histologically for fibrous histiocytoma of the meninges, giant cell astrocytoma with histiocytic infiltration, and lipidized giant cell GBM multiforme. Must also be differentiated from other forms of gliomas and dysembryoplastic neuroepithelial tumor (DNT).

Treatment

1. Surgical resection.
2. RT and chemotherapy may be considered for recurrent tumor.
3. Case reports suggest a potential role for *BRAF* inhibitors in PXAs with *BRAF* (*V600E*) mutations.

Subependymal Giant Cell Astrocytoma or Subependymal Giant Cell Tumor

Background

1. Rare low-grade glioneuronal tumor.
2. Found in children and young adults.
3. Almost exclusively associated with tuberous sclerosis complex (TSC) and present in 15% of patients with TSC.

Pathophysiology

1. Associated with neurocutaneous disorders such as TSC and nevus sebaceous syndrome.
2. Partial loss of chromosome 22q.

Prognosis

1. Slow growing and benign.
2. Rarely malignant degeneration.

Diagnosis

Location

Arises in the wall of the lateral ventricle, attached to caudate head.

Clinical Presentation

1. Often diagnosed incidentally in TSC patients, as part of surveillance.
2. May obstruct CSF flow at the foramen of Monro and cause obstructive hydrocephalus producing headache and visual disturbance.

Diagnostic Tests

MRI shows an intraventricular enhancing mass.

Pathology

1. WHO grade I, giant astrocytes with glassy, eosinophilic cytoplasm, without significant anaplasia. May express neuronal markers.
2. Lesion represents neoplastic transformation of "candle guttering" subependymal nodules in TS.

Differential Diagnosis

Choroid plexus tumors, ependymoma, subependymoma, and astrocytoma.

Treatment

1. Surgical debulking for symptomatic (especially obstructive symptoms) or growing lesions. Complete resection may be curative.
2. Mechanistic target of rapamycin (mTOR) inhibitor everolimus for TSC-associated subependymal giant cell astrocytoma (SEGA), especially if contraindication exists for surgery, total resection not possible, or bilateral SEGAs.
3. Occasional role for SRS or SRT.

Diffuse Astrocytoma

Background

1. Low-grade diffuse astrocytomas (LGA) are slow-growing tumors.
2. Although referred to as "low-grade," these tumors grow and gradually evolve to higher grade astrocytomas, ultimately causing morbidity and reduced survival.
3. Early diagnosis is difficult because of nonfocal findings with these tumors.

Epidemiology

1. LGAs comprise 10% of all adult PBTs.
2. Incidence rate is 0.5/100,000 and peaks in the third and fourth decades.
3. In adults, most arise in the cerebral hemispheres, and in children, most arise in the posterior fossa.

Pathophysiology

1. Usually sporadic.
2. Associated with characteristic molecular abnormalities including *TP53* and *ATRX* mutations (see "Molecular Genetics" section).

Prognosis

1. Highly variable and depends on age and amount of residual tumor after surgery.
2. All LGAs eventually progress to higher grade tumors.
3. Positive prognostic factors include long duration of symptoms, complete resection, excellent postoperative neurologic status, low MIB-1 proliferation index (<3% to 5%), age <40 years, and presence of *IDH1/2* mutation.
4. Median overall survival with maximal therapy can be 10 to 15 years.

Diagnosis

Clinical Presentation

Usually present with new-onset seizures (50% to 70%). Less commonly, they present with headaches, focal deficits, or subtle neurobehavioral changes. Some patients may be asymptomatic.

Diagnostic Tests

1. MRI typically shows a nonenhancing white matter mass, hypointense T_1, hyperintense T_2, and fluid-enhanced inversion recovery (FLAIR) with ill-defined borders and little or no edema.
2. Histologic diagnosis ultimately depends on obtaining tissue via biopsy or surgical resection.

Pathology

1. WHO grade II, low-grade glioma.
2. Hypercellular, well-differentiated fibrillary or gemistocytic neoplastic

astrocytes; may be cystic, infiltrative; moderately increased cellularity, occasional nuclear atypia.

3. Diffuse variants include fibrillary, protoplasmic, and gemistocytic.
4. Biopsy results can be misleading because gliomas often have varying degrees of cellularity, mitoses, or necrosis from one region to another.

Differential Diagnosis

Includes high-grade astrocytoma, oligodendroglioma, ganglioglioma, DNT, infarction, demyelination, progressive multifocal leukoencephalopathy (PML), and vasculitis.

Treatment

1. Treatment may depend on molecular features and prognostic factors.
2. Maximal safe resection of tumor improves neurologic deficits and results in prolongation of survival.
3. For select patients with LGA (such as age <40 years who undergo complete resection and whose tumor has favorable molecular features), observation with serial imaging until progression may be a reasonable approach.
4. For those requiring treatment, options may include radiation alone, radiation combined with chemotherapy, or (rarely) chemotherapy alone.
   - **a.** Involved field RT is a standard component of treatment, which may ameliorate symptoms, improve survival, and reduce seizure frequency in LGA.
   - **b.** Timing of irradiation (upfront after surgery vs. at recurrence) is controversial. Upfront irradiation delays recurrence, but overall, survival similar to patients who do not receive irradiation until there is evidence of recurrent disease.
   - **c.** Patients with a greater likelihood of rapid disease progression (age ≥40 years, large preoperative tumor ≥5 cm, incomplete resection, absence of *IDH1/2* mutation) or ongoing tumor-related symptoms are more likely to benefit from radiation.
   - **d.** Radiation combined with chemotherapy may be beneficial in select "high-risk" LGA patients (age ≥40 years and/or incomplete resection). In this select subgroup, RT followed by procarbazine, lomustine (CCNU), and vincristine (PCV) was associated with longer overall survival compared to RT alone (13.3 years vs. 7.8 years). This study was performed prior to

U.S. Food and Drug Administration (FDA) approval of temozolomide so unclear if combining RT with temozolomide (as per GBM standard of care) would have similar results.

e. For LGA, chemotherapy may be combined with radiation (as earlier) or given at recurrence. There is currently no Class I evidence to support chemotherapy alone for previously untreated LGA, although some advocate chemotherapy alone in select young patients with favorable tumor types (*IDH1/2* mutant) who may live long enough to experience the long-term cognitive toxicity of radiation.

f. Chemotherapeutic regimens used for LGA include temozolomide and PCV.

Anaplastic Astrocytomas

Background

1. Incidence rate is 0.5 per 100,000 and is less common than GBM.
2. Peak age incidence is 35 to 50 years.
3. Male-to-female ratio is 3:2.

Pathophysiology

1. Usually sporadic.
2. Associated with characteristic molecular abnormalities (see "Molecular Genetics" section).

Prognosis

1. AA eventually progress to GBM.
2. Uniformly fatal despite aggressive therapy. Occasional long-term survivors.
3. Factors that portend a poor prognosis: Older age, less than gross total resection, poor functional status (KPS <70).
4. Molecular features associated with a better prognosis: *IDH1* or *IDH2* mutation.
5. Median overall survival with maximal therapy is 2 to 3 years.

Diagnosis

Location

Cerebral hemispheres, especially frontal (40%) and temporal (30%) lobes, and rarely in adults' brainstem, cerebellum, and spinal cord.

Clinical Presentation

1. Patients often present with symptoms of increased ICP (headache, nausea, vomiting), seizures, or focal neurologic findings related to the size and location of the tumor and associated peritumoral edema.
2. Can have symptoms up to 2 years before diagnosis in AA.

Diagnostic Tests

1. CT and MRI can show T2/FLAIR hyperintense lesions with vasogenic edema, mass effect, and variable enhancement.
2. Histologic diagnosis ultimately depends on obtaining tissue via biopsy or surgical resection.

Pathology

1. Diffusely infiltrating and characterized by nuclear atypia, increased cellularity, and significant proliferative activity.
2. May arise from LGA or *de novo* as AA.

Differential Diagnosis

Includes other PBTs, metastases, lymphoma, and abscess.

Treatment

1. Maximal safe resection of tumor improves neurologic deficits and quality of life and results in modest prolongation of survival.
2. If resection is not possible because the tumor is in eloquent area, it should be biopsied to obtain histologic diagnosis. Every effort should be made to obtain tissue from area of actively growing tumor (usually enhancing area) to avoid undersampling.
3. After surgery, the standard of care for AA is less well defined than GBM, although options could include radiation combined with temozolomide, radiation alone (with temozolomide at recurrence), or temozolomide alone (with radiation at recurrence). Treatment may be individualized based on clinical and molecular prognostic factors. Randomized studies to determine best treatment options for AA are ongoing.
   a. Combined radiation and temozolomide similar to GBM standard of care

(discussed in the following text) may be considered in patients with poorer prognostic factors such as older age and wild-type *IDH1/2*.

b. A randomized study comparing chemotherapy treatment with temozolomide or PCV (with radiation at recurrence) or radiation (with chemotherapy at recurrence) showed no difference in time to treatment failure.

c. Results from an international, phase III randomized trial (CATNON) of 1p/19q non-deleted grade 3 gliomas comparing at radiation with or without temozolomide are pending, but preliminary results suggest survival benefit with the addition of adjuvant temozolomide to radiation. The benefit of adding concurrent temozolomide to radiation is still unknown as results are not known.

Glioblastoma

Background

1. GBMs are the most common malignant PBT (46%).
2. Incidence rate is 3 to 4/100,000.
3. Peak age incidence is 60 years.
4. Male-to-female ratio is 3:2.

Pathophysiology

1. Usually sporadic.
2. Associated with characteristic molecular abnormalities (see "Molecular Genetics" section).

Prognosis

1. Uniformly fatal despite aggressive therapy. Occasional long-term survivors.
2. Factors that portend a poor prognosis: Older age, less than gross total resection, poor functional status (KPS <70).
3. Median overall survival with maximal therapy is 15 to 18 months.

Diagnosis

Location

Cerebral hemispheres, especially frontal (40%) and temporal (30%) lobes, and rarely in adults' brainstem, cerebellum, and spinal cord.

Clinical Presentation

1. Patients often present with symptoms of increased ICP (headache, nausea, vomiting), seizures, or focal neurologic findings related to the size and location of the tumor and associated peritumoral edema.
2. Can have symptoms for several months with GBM.

Diagnostic Tests

1. CT and MRI can show heterogeneous enhancing lesions with vasogenic edema, mass effect, and frequently, tracks along white matter paths including the corpus callosum (butterfly glioma). Occasionally have associated hemorrhage or calcification. GBM usually also has ring enhancement and central necrosis.
2. MRS shows elevated choline peaks (reflecting active membrane synthesis) and decreased *N*-acetyl aspartate peaks (reflecting neuronal loss).
3. Histologic diagnosis ultimately depends on obtaining tissue via biopsy or craniotomy.

Pathology

1. Pseudopalisading areas of necrosis, endothelial vascular proliferation, pleomorphism, and mitosis.
2. Most arise *de novo* as primary GBM, although some may arise from lower grade gliomas (secondary GBM).
3. Histologic variants include giant cell GBM (large bizarre cells), small cell GBM, GBM with oligodendroglial features, and gliosarcoma (spindle cell component).

Differential Diagnosis

Includes other PBTs, metastases, lymphoma, and abscess.

Treatment

Surgery

1. Maximal safe resection of tumor improves neurologic deficits and quality of life and results in modest prolongation of survival.

2. The extent of tumor debulking should be documented with an immediate postoperative MRI scan performed with and without contrast.
3. Not curative even with apparent gross total resection as infiltrative microscopic disease inevitably remains in surrounding brain.
4. If resection is not possible because the tumor is in eloquent area, it should be biopsied to obtain histologic diagnosis. Every effort should be made to obtain tissue from area of actively growing tumor (usually enhancing area) to avoid undersampling. PET and perfusion MRI may help direct biopsy.

Radiation Therapy

1. Involved field RT is standard component of treatment. Ameliorates symptoms and improves survival.
2. Because RT can produce additional BBB dysfunction, corticosteroid requirements may increase and scans may look worse during the first 3 months after completion of RT (especially when RT was combined with chemotherapy), even though there is no actual tumor progression (pseudoprogression).
3. Despite RT, most tumors recur within primary site of disease.
4. Repeat radiation is considered in special circumstances.
5. Other radiotherapy methods such as brachytherapy, hyperfractionation, radiosurgery, and radiosensitizers have not significantly improved survival.

Chemotherapy

1. In newly diagnosed GBM, the standard of care is radiation combined with temozolomide (an alkylating agent).
   a. Overall, the addition of temozolomide produces an approximately 2 to 3 months increase in median survival and a small increase in percentage of long-term survivors. Benefit greater for young patients and patients with methylation of the methylaguanine DNA methyltransferase (MGMT) gene promoter.
   b. Temozolomide is given concurrently with RT (75 mg/m^2 p.o. daily for 6 weeks with RT), followed by 4 weeks off treatment, and then adjuvantly as 150 to 200 mg/m^2 p.o. days 1 through 5 every 28 days for six cycles. Toxicities include nausea, fatigue, and marrow suppression. Use of prolonged low-dose temozolomide increases risk of PJP. Patients receiving this regimen often receive PJP prophylaxis.

c. The addition of bevacizumab (discussed in the following text for recurrent GBM) to radiation and temozolomide did not extend survival over standard of care.

d. The addition of tumor treating fields (a locoregionally delivered antimitotic treatment worn as a device on patient's head) to adjuvant temozolomide after radiation may extend survival over standard of care.

2. Studies performed before temozolomide became the standard of care showed that slow-release polymer wafers impregnated with BCNU (Gliadel wafers) placed in the wall of the surgical cavity at time of debulking improves survival in newly diagnosed and recurrent GBM by approximately 2 months. BCNU wafers have largely fallen out of favor because temozolomide became standard of care.

3. For recurrent GBM, options include lomustine (CCNU) and/or bevacizumab.

a. Bevacizumab is a humanized monoclonal antibody that binds vascular endothelial growth factor (VEGF). May have antitumor activity and helps reduce peritumoral edema and corticosteroid use. Standard dose is 10 mg/kg intravenously every 2 weeks. Toxicities include hypertension, proteinuria, and rarely serious hemorrhage (including CNS) and thromboembolism (including stroke, deep vein thrombosis [DVT], pulmonary embolism [PE]). Studies of bevacizumab have not demonstrated a survival benefit compared to lomustine. Retrospective data and anecdotal evidence suggests that bevacizumab improves quality of life because in part of its steroid-sparing effects.

b. Lomustine (CCNU) is an alkylating agent and is dosed as 90 to 130 mg/m^2 p.o. once every 6 weeks for six cycles total. Toxicities include nausea, fatigue, and marrow suppression (more severe than temozolomide).

Experimental Therapies

Targeted molecular therapy (e.g., inhibitors various signal transduction molecules), viral gene therapy, tumor vaccines (dendritic and peptide), immunotherapy, and inhibitors of tumor invasion are being evaluated in clinical trials.

Gliomatosis Cerebri

Background

1. Characterized by widespread dissemination of neoplastic astrocytes, involving at least three cerebral lobes, often contiguously, with or without discrete mass lesions.
2. Often bilateral involvement of the cerebral hemispheres and/or deep gray matter and frequent extension to the brain stem, cerebellum, and even spinal cord.
3. These tumors are rare. Peak incidence is 40 to 50 years of age.

Pathophysiology

Molecular genetic alterations in gliomatosis cerebri resemble those in diffuse astrocytoma.

Prognosis

Prognosis is variable but often similar to GBM.

Diagnosis

Location

Diffuse infiltration without discrete tumor masses, usually deep in thalamus and basal ganglia.

Clinical Presentation

Cognitive/neurobehavioral changes, headaches, seizures, and papilledema.

Diagnostic Tests

MRI shows homogenous hypodense areas, loss of gray-white junction, swollen hemispheres, diffuse increase in T2 and FLAIR signal, and minimal to no enhancement.

Pathology

1. Grossly diffuse enlarged brain, microscopically extensive gray-white matter infiltration of tumor cells.
2. Graded from low grade to high grade (WHO grades II to III).
3. Mostly astrocytic histology, although oligodendroglial components have been reported.

Differential Diagnosis

Inflammatory, infectious, or demyelinating process in the appropriate clinical context.

Treatment

1. Stereotactic biopsy needed for diagnosis; usually not resectable.
2. Some patients respond temporarily to radiotherapy.
3. Occasional response to temozolomide and nitrosoureas (lomustine and carmustine).

Brainstem Glioma

Background

1. In children, brainstem gliomas account for 15% of PBTs and include diffuse pontine glioma (80%), cervicomedullary glioma, dorsally exophytic glioma, tectal glioma, and focal glioma.
2. In adults, brainstem gliomas are uncommon and account for less than 3% of gliomas.

Pathophysiology

Usually astrocytic in origin. Its prognosis is generally worse than the pathology would suggest because of its location.

Prognosis

Diffuse pontine glioma has a poor prognosis with a median survival of only 1 year despite aggressive therapy. Intrinsic focal low-grade brainstem gliomas have a better prognosis: 80% 5-year survival.

Diagnosis

Clinical Presentation

Brainstem gliomas present with cranial nerve (CN) palsies, ataxia, weakness, and numbness.

Pathology

Diffuse brainstem gliomas are not usually biopsied. Diagnosis is based on

characteristic imaging findings. Focal lesions, especially if they are exophytic, sometimes can be biopsied.

Differential Diagnosis

Includes ependymoma, medulloblastoma, vascular malformation, cysticercosis, encephalitis, tuberculoma, multiple sclerosis, postinfectious encephalomyelitis, or gliosis.

Treatment

1. Surgery may be indicated for cervicomedullary, focal, cystic, or exophytic tumors.
2. Biopsy (open or CT-guided stereotactic) is indicated when the diagnosis of brainstem glioma is in doubt.
3. Treatment for diffuse brainstem glioma is RT (54 to 56 Gy in daily fractions of 1.8 to 2.0 Gy).
4. VP shunt may be necessary for obstructive hydrocephalus.
5. Chemotherapy with temozolomide, PCV, carboplatin of limited benefit.

Oligodendroglial Tumors

Background

1. Includes oligodendrogliomas and mixed oligoastrocytomas based on histologic morphology.
2. Classified according to grade: Low grade (WHO grade II), anaplastic (WHO grade III). A grade IV oligoastrocytoma is also known as a GBM with oligodendroglial features. For oligodendroglioma, grade III is the highest grade.
3. Comprise up to 20% to 30% of gliomas (increasingly diagnosed as criteria expanded).
4. Most occur at ages 30 to 50 years, men more often than women.
5. Most common primary tumor to hemorrhage.

Pathophysiology

1. Arise from oligodendrocytes or glial precursor cells.
2. Mixed oligoastrocytomas probably develop from a common glial stem cell.

True mixed oligoastrocytomas are very rare; on a molecular level, mixed tumors are either 1p/19q codeleted and IDH mutated (consistent with an oligodendroglial genotype) or *ATRX*/*TP53* mutated (consistent with an astrocytic genotype).

3. Majority of classical oligodendrogliomas and some oligoastrocytomas are associated with 1p/19q codeletion (because of an unbalanced translocation).
4. *IDH1* mutations are found in 60% to 80% of grade 2 and grade 3 oligodendroglial tumors, with or without 1p/19q codeletion.

Prognosis

1. Presence of a major oligodendroglial component is a favorable prognostic factor compared to a pure astrocytic tumor.
2. Deletions in 1p and 19q are favorable prognostic factors as they are sensitive to chemotherapy and radiotherapy.
3. Oligodendroglioma: Median survival is 8 to 15 years.
4. AO: Median survival is 3 to 6 years.
5. Mixed oligoastrocytomas tend to have a prognosis intermediate between oligodendrogliomas and astrocytomas.

Diagnosis

Location

Frontal and temporal lobes most common.

Clinical Presentation

Usually present with seizures; occasionally headaches, focal deficits, or personality changes.

Diagnostic Tests

1. For low-grade oligodendroglial tumors, MRI generally shows a nonenhancing, T2/FLAIR lesion with mass effect. Calcifications can be seen in 50% to 90%. May be well demarcated, located near cortical surface, with little or no edema; cystic (20%); hemorrhage (10%).
2. Anaplastic oligodendroglial tumors usually enhance.
3. Histologic diagnosis ultimately depends on obtaining tissue via biopsy or craniotomy.

Pathology

1. Grossly soft, grayish-pink tumors frequently with calcifications, hemorrhages, cysts, delicate vessels.
2. Microscopically round nuclei with perinuclear halo ("fried-egg" appearance in paraffin), delicate branching vessels ("chicken wire" vasculature), calcification, perineuronal satellitosis (secondary structures of Scherer).
3. Mixed oligoastrocytoma contains both oligodendroglial and astrocytic components.
4. Anaplastic variant has high cellularity, increased mitotic rate, pleomorphism, microvascular proliferation, and occasional necrosis.
5. Low-grade oligodendroglial tumors eventually progress to higher grades.

Differential Diagnosis

1. Oligodendroglioma must be differentiated from astrocytoma, ganglioglioma, and DNT.
2. AO can be confused with AA and GBM.

Treatment

1. Treatment may depend on grade, molecular features, and prognostic factors.
2. Maximal safe resection of tumor improves neurologic deficits and quality of life and results in prolongation of survival.
3. In general, tumors with 1p/19q codeletion are more sensitive to radiation and more sensitive to chemotherapy.
4. Low-grade oligodendroglial tumors (treatment recommendations similar to LGA)
   a. For select patients (such as age <40 years who undergo complete resection and whose tumor has favorable molecular features such as *IDH1/2* mutation and/or 1p/19q codeletion), observation with serial imaging until progression may be a reasonable approach.
   b. For those requiring treatment, options may include radiation alone, radiation combined with chemotherapy, or chemotherapy alone.
   c. For "high-risk" low-grade glioma patients (age ≥40 years and/or incomplete resection), the survival benefit conferred by adding PCV to RT is greatest for oligodendroglial tumors (compared to astrocytomas).

5. Anaplastic oligodendroglial tumors (treatment recommendations distinct from AA)
   a. For patients with 1p/19q codeleted tumors, two large randomized trials demonstrated a survival benefit with RT and PCV compared to RT alone. This study was performed prior to FDA approval of temozolomide so unclear if combining RT with temozolomide (as per GBM standard of care) would have similar results. The international, phase III, randomized CODEL study compares radiation ⩽ PCV versus radiation ⩽ temozolomide in 1p/19q codeleted grade 3 gliomas. Results are pending.
   b. Patients with 1p or 19q nondeleted tumors should receive postoperative radiation with or without chemotherapy. Results from an international, phase III randomized trial (CATNON) of 1p/19q non-deleted grade 3 gliomas comparing at radiation with or without temozolomide are pending, but preliminary results suggest survival benefit with the addition of adjuvant temozolomide to radiation. The benefit of adding concurrent temozolomide to radiation is still unknown as results are not known.
6. Temozolomide is also active in oligodendroglial tumors although randomized studies comparing temozolomide ⩽ RT versus PCV ⩽ RT are ongoing.
7. Treatment recommendations for GBM with oligodendroglial features (GBMO) are the same as GBM, although GBMO may have a more favorable prognosis than GBM.

Ependymal Tumors

Background

1. Ependymomas are tumors derived from ependymal cells that line the ventricular surface.
2. Subependymomas are slow-growing benign lesions that often do not require treatment.
3. Ependymoblastoma is a primitive neuroectodermal tumor (PNET) that occurs in the first 5 years of life.

Epidemiology

1. Comprises 2% to 8% of all PBTs, 6% to 12% of intracranial gliomas in

children (much less common in adults), and 60% of spinal cord gliomas (most common spinal cord glioma).
2. In children, ependymomas are the most common intraventricular tumor and often arise in the fourth ventricle with the propensity to extend into the subarachnoid space. Median age at diagnosis is 6 years.
3. In adults, 75% of ependymomas arise within the spinal cord. The incidence of ependymoma is approximately equal in males and females.
4. Subependymomas and myxopapillary ependymomas are more common in males.
5. Ependymoblastoma are most commonly seen in infants and generally classified with PNETs.

Pathophysiology

1. *NF2* gene inactivation on chromosome 22 and mutations on chromosome 11q13.
2. Amplification of *mdm2* gene in 35% of cases.
3. A 50% incidence of allelic loss of 17p in pediatric cases.

Prognosis

1. Poor prognostic factors: Age younger than 2 years, incomplete resection, supratentorial location, duration of symptoms less than 1 month, and anaplastic histology.
2. The 5-year survival after complete resection and radiotherapy is 70% to 87% compared to 30% to 40% for partial resection; overall 10-year survival of 50%.
3. In children, fourth-ventricle tumors are clinically more aggressive.
4. Anaplastic ependymoma has a 12% 5-year survival.
5. Subependymoma is indolent and often does not require treatment other than surgical resection.
6. The prognosis for ependymoblastoma is poor with death within 1 year of surgery.

Diagnosis

Location

1. Infratentorial in 60% of cases.

2. Most frequently in fourth ventricle (70%), lateral ventricles (20%), and cauda equina (10%).
3. In adults, commonly occurs in lumbosacral spinal cord and filum terminale (myxopapillary ependymoma).
4. May spread via CSF and seed other locations (12%).
5. Ependymoblastoma usually in cerebrum with frequent craniospinal metastasis.

Clinical Presentation

1. Intracranial tumors produce symptoms because of obstruction of CSF flow (headaches, nausea, vomiting, visual disturbance), ataxia, dizziness, hemiparesis, and brainstem symptoms.
2. Spinal cord tumors present as a chronic, progressive myelopathy, or cauda equina syndrome (see section on Spinal Cord Tumors).

Diagnostic Tests

1. MRI shows a well-demarcated, heterogenous, enhancing intraventricular mass, with frequent calcifications. Obstructive hydrocephalus and hemorrhage may be present.
2. Spinal MRI should be done to rule out neuraxis dissemination.

Pathology

1. Subependymoma (WHO grade I) is a benign lesion located within ventricles. Has both ependymal and astrocytic features.
2. In cauda equina, myxopapillary ependymoma (WHO grade I) is common.
3. Ependymoma (WHO grade II) is grossly well-demarcated and is microscopically densely cellular with ependymal rosettes, blepharoplasts, and perivascular pseudorosettes. It arises from the wall of the ventricle or from the spinal canal.
4. Anaplastic ependymomas have malignant features such as mitotic activity, pleomorphism, and necrosis.
5. Ependymoblastoma has ependymoblastic rosettes in fields of undifferentiated cells.

Differential Diagnosis

Subependymoma, anaplastic ependymoma, ependymoblastoma, astrocytoma, and medulloblastoma.

Treatment

1. Surgical resection is treatment of choice, but many tumors recur regardless of completeness of resection.
2. For ependymoma and anaplastic ependymoma, postoperative local RT (4,500 to 6,000 cGy) improves survival.
3. For myxopapillary ependymoma that cannot be completely resected, postoperative local RT improves local control and prevents recurrence but the effect on survival is less clear.
4. Craniospinal radiation reserved for tumors with CSF spread.
5. Chemotherapy is used in children younger than 3 years to delay onset of RT.

Choroid Plexus Tumors

Background

1. Choroid plexus tumors are derived from the choroid plexus epithelium.
2. Peak incidence in the first two decades of life. It is the most common intracranial tumor in the first year of life.
3. Accounts for less than 1% of all intracranial tumors.
4. Choroid plexus papillomas (CPPs) are benign and account for 80% of choroid plexus tumors.

Pathophysiology

1. CPP (WHO grade I) histologically resembles normal choroid plexus and probably represents local hamartomatous overgrowths.
2. Choroid plexus carcinoma (CPC) (WHO grades III to IV) is an aggressive tumor with dense cellularity, mitoses, nuclear pleomorphism, focal necrosis, loss of papillary architecture, and invasion of neural tissue. They frequently seed CSF pathways. Usually occurs in children younger than 8 years. Associated with Li–Fraumeni syndrome (because of mutations in p53).

Prognosis

1. Good with CPP. With complete resection, 80% 5-year survival; 4.3% recurrence rate overall. Malignant transformation to CPC is rare.
2. Poor with CPC, 40% 5-year survival rate.

Diagnosis

Location

1. In adults, common in lateral ventricle (50%), fourth ventricle (40%), and third ventricle (5%).
2. In children, most common in lateral ventricles and cerebellopontine angle (CPA).

Clinical Presentation

Present with symptoms secondary to CSF obstruction or CSF overproduction, headaches, nausea, vomiting, ataxia.

Diagnostic Tests

With CPPs, MRI shows a homogenous, enhancing mass with prominent flow voids caused by rich vascularization, frequent calcification.

Differential Diagnosis

Ependymoma, astrocytoma, and metastases.

Treatment

1. Extent of surgical resection is an important predictor of survival.
2. RT at recurrence for CPP.
3. For CPC, chemotherapy and radiation may be associated with better survival although there is no consensus.

Neuronal and Mixed Neuronal-Glial Tumors

Background

1. Rare tumors characterized by variable amount of neuronal differentiation.
2. Include ganglioglioma, gangliocytoma, DNT, neurocytoma, and dysplastic gangliocytoma of the cerebellum (Lhermitte–Duclos disease).

Epidemiology

1. Occur in children and young adults in the first three decades of life.
2. Account for less than 1% of glial neoplasms.
3. Neurocytomas occur in patients aged 20 to 40 years.

Pathophysiology

1. Gangliogliomas associated with Down syndrome, callosal dysgenesis, and neuronal migration disorders. Up to 60% will harbor a *BRAF V600E* mutation.
2. Lhermitte–Duclos disease may occur as part of Cowden disease (mucosal neuromas and breast cancer), an autosomal dominant disorder caused by germline mutation of *PTEN* gene.
3. Neurocytomas associated with *MYCN* overexpression and reduced expression of *BIN1*.

Prognosis

1. Ganglioglioma: Indolent, cured with surgery. If subtotal resection, 41% progress. Rare malignant transformation from glial component; 89% 5-year and 84% 10-year survival.
2. Neurocytoma: Good with resection, recurrence, and CSF spread are rare.
3. DNTs are indolent.
4. Lhermitte–Duclos disease: Good with resection.

Diagnosis

Location

1. Gangliogliomas have a predilection for temporal lobe but also occur in the basal ganglia, optic pathway, brainstem, pineal gland, cerebellum, and spinal cord.
2. Neurocytomas are intraventricular, usually in body of lateral ventricle, attached to septum pellucidum. Rarely in pons, cerebellum, spinal cord, or brain parenchyma.
3. DNTs involve predominantly the cerebral cortex, especially temporal lobes.
4. Lhermitte–Duclos disease occurs in cerebellum.

Clinical Presentation

1. Gangliogliomas usually present with seizures and, less often, headaches and focal deficits.
2. Neurocytomas present with symptoms of hydrocephalus.
3. DNTs usually have chronic complex partial seizures and a long-standing history of intractable focal epilepsy.

4. Lhermitte–Duclos disease presents with ataxia and hydrocephalus.

Diagnostic Tests

1. Ganglioglioma: MRI is nonspecific and shows a well-demarcated, superficial, nonenhancing mass with increased T2 and FLAIR signal. Can have cysts or calcification.
2. Neurocytoma: MRI shows a heterogenous ventricular mass with multiple cysts, calcification, occasional hemorrhage, variable enhancement; some have a "honeycomb" appearance on T1-weighted images.
3. DNT: MRI shows a T1 hypointense, T2 hyperintense mass with gyrus-like configurations, cortical dysplasia, variable enhancement.
4. Lhermitte–Duclos disease: MRI shows increased T2 and FLAIR abnormality in cerebellum with striped "tigroid" appearance.

Pathology

1. Gangliogliomas (WHO grades I to II) have neuronal and astrocytic neoplastic cells, granular bodies, Rosenthal fibers, large irregular ganglion cells, and perivascular infiltrates.
2. Neurocytomas (WHO grade I) have small, uniform, well-differentiated neuronal cells, frequently misdiagnosed as oligodendrogliomas.
3. DNTs (WHO grade I) have a glioneuronal element, nodular component, and cortical dysplasia.
4. Gangliocytomas (WHO grade I) are well-differentiated neoplastic cells with neuronal characteristics, no malignant transformation.
5. Lhermitte–Duclos (WHO grade I) disease has a dysplastic gangliocytoma confined to cerebellum; Purkinje cell layer is absent.

Treatment

1. Surgical resection; complete resection is curative for all these conditions.
2. RT may have limited role for recurrent gangliogliomas, recurrent neurocytomas.

Pineal Parenchymal Tumor

Background

1. Rare tumors that account for less than 1% of all intracranial tumors; 14% to 30% of pineal region tumors.
2. Pineocytoma most common between 25 and 35 years; pineoblastoma most common in the first two decades.

Pathophysiology

1. Arise from pinocyte in pineal gland.
2. Pineoblastoma associated with germline mutations in *RB1* gene.

Prognosis

1. Pineocytoma is slow growing and has favorable prognosis following resection; 86% 5-year survival.
2. Pineoblastoma has poorer prognosis; less than 50% 5-year survival.
3. Pineal parenchymal tumors of intermediate differentiation (PPTIDs) have an intermediate prognosis.

Diagnosis

Location

Pineal gland; pineoblastoma has relatively frequent leptomeningeal metastases.

Clinical Presentation

1. Most commonly presents with noncommunicating hydrocephalus from obstruction of aqueduct of Sylvius and Parinaud syndrome (paralysis of upgaze, convergence–retraction nystagmus, light-near dissociation) because of compression of midbrain tectum. Ophthalmoplegia, ataxia, weakness, numbness, and memory loss may also occur.
2. Hypothalamic dysfunction (DI, precocious puberty) when tumors encroach anteriorly; sleep disturbance because of abnormal melatonin regulation.

Diagnostic Tests

1. Pineocytomas on MRI are sharply demarcated, T1 hypointense, T2 hyperintense, and enhance homogeneously with contrast. Hydrocephalus seen in one-third cases.
2. Pineoblastomas on MRI are hyperdense with no calcifications, may be lobulated and poorly demarcated, and enhance heterogeneously. Hydrocephalus seen in majority of patients.

3. Serum and CSF α fetoprotein (AFP) (yolk sac tumors) and β-human chorionic gonadotropin (β-hCG) (choriocarcinoma) are negative and help to exclude germ cell tumors.
4. Check CSF cytology and contrast-enhanced MRI of spine to rule out leptomeningeal metastases if not contraindicated.

Pathology

1. Grossly displaces surrounding structures; does not invade; can seed leptomeninges.
2. Pineocytoma: WHO grade I, well-differentiated with small, uniform, mature cells resembling pinocytes. Characteristic pineocytomatous rosettes.
3. PPTID, as name implies, has intermediate histologic appearance and may be WHO grade II or III.
4. Pineoblastoma (WHO grade IV) is aggressive and histologically identical to PNETs. Composed of highly cellular sheets of small cells with round/irregular nuclei and scant cytoplasm. Occasional Homer–Wright or Flexner–Wintersteiner rosettes.

Differential Diagnosis

Germ cell tumors (germinoma, teratoma, dermoid, choriocarcinoma, embryonal carcinoma, endodermal sinus [yolk sac] tumor), astrocytoma, ependymoma, CPP, meningioma, metastases, and nonneoplastic lesions including pineal cyst, arachnoid cyst, arteriovenous malformation, vein of Galen aneurysm, and cavernous malformation.

Treatment

1. Surgical exploration and complete resection.
2. CSF diversion (VP shunt or third ventriculostomy) for hydrocephalus.
3. Local irradiation for incompletely resected or recurrent pineocytoma.
4. Craniospinal RT for pineoblastoma and PPTID.
5. Role of chemotherapy is unclear but usually given for pineoblastoma and often given for PPTID.
6. Chemotherapeutic agents include cisplatin, carboplatin, etoposide, cyclophosphamide, and vincristine, similar to regimens used to treat other PNETs.

Medulloblastoma

Background

1. Medulloblastomas are the most common (20%) malignant tumor of childhood.
2. Comprise more than one-third of all pediatric posterior fossa tumors.
3. Incidence 0.5/100,000 with approximately 500 new pediatric cases in United States each year.
4. Male-to-female ratio is 2:1.
5. Occurs in the first decade of life (ages 5 to 9 years), 70% diagnosed before age 20 years. Second peak in the 20s to 30s (30% of cases).

Pathophysiology

Ninety percent are sporadic but can occur in Gorlin syndrome (basal cell carcinomas, congenital anomalies) caused by germline mutation of gene encoding the SHH receptor PTCH. May also arise in Turcot syndrome caused by germline mutation of the adenomatous polyposis coli (*APC*) gene. Rarely, they occur in patients with ataxia–telangiectasia, xeroderma pigmentosum, or Li–Fraumeni syndrome.

Prognosis

1. Patients generally classified into poor-risk and standard-risk groups.
2. Traditional poor-risk factors include residual disease after surgical resection greater than 1.5 cm, metastases detected by contrast-enhanced MRI, and malignant cells in CSF obtained by LP.
3. The 5-year survival rate for standard-risk patients is approximately 70% to 80%. The 10-year survival rate is above 50%.
4. The 5-year survival rate for poor-risk patients is 40% to 60%.
5. Infants and children under the age of 3 years tend to have worse prognosis than older age groups, with 40% to 50% 5-year survival rate.
6. Adults with medulloblastoma have worse prognosis than children.
7. Desmoplastic variant associated with better prognosis.
8. Tumors with activation of the Wingless (WNT) pathway have better prognosis; tumors with amplification of *MYC* have worse prognosis.

Diagnosis

Location

1. Occurs exclusively in the cerebellum: Midline cerebellum, inferior vermis (85%), and fourth ventricle.
2. Tends to infiltrate the cerebellar hemispheres and frequently (25% to 30% of cases) has leptomeningeal metastases (drop metastases). Systemic metastases are rare (bone and lung).
3. Desmoplastic variant (15%) is more lateral in cerebellar hemisphere.

Clinical Presentation

1. Most tumors present with signs of increased ICP (headache, nausea, and vomiting) because of obstruction of CSF flow. Patients may also have ataxia and diplopia.
2. In older age groups, tumor more often occurs in cerebellar hemispheres, resulting in truncal ataxia and cerebellar dysfunction.

Diagnostic Tests

1. MRI or CT shows a high-density, enhancing tumor, usually midline, often distorting or obliterating the fourth ventricle, and producing hydrocephalus. Calcification may be present.
2. High tendency to metastasize to other parts of the CNS; therefore, entire neuraxis should be imaged. Staging also includes CSF evaluation.
3. May also metastasize outside of CNS to bone; therefore, a bone scan and bone marrow aspirate should often be performed.

Pathology

1. Grossly soft, pinkish-gray mass, granular with necrosis.
2. Microscopically highly cellular tumors with abundant dark staining round or oval nuclei and scant, undifferentiated cytoplasm typical of "small round blue cell tumors." Mitoses and apoptotic cells are abundant. Homer–Wright rosettes (sheets of cells forming rosettes around a central area filled with neuritic processes) in up to 40% of cases.
3. Have both neuronal and glial differentiation and some with mesenchymal differentiation.
4. Desmoplastic variant has abundant reticulin and collagen.

Differential Diagnosis

Astrocytoma, ependymomas, ependymoblastoma, large-cell PNET (aggressive course), medullomyoblastoma (contains immature muscle cells, malignant), melanotic PNET, and embryonal tumors (atypical teratoid or rhabdoid tumors, highly malignant and therapy resistant).

Treatment

1. Surgical resection needed to relieve mass effect and some may require a VP shunt for decompression.
2. Goal is maximal surgical resection because residual tumor greater than 1.5 cm is associated with increased risk of relapse.
3. Surgery occasionally complicated by "cerebellar mutism" (mutism and emotional lability).
4. Craniospinal RT with an additional boost to the tumor site indicated in all patients after surgery.
5. For average risk disease, craniospinal dose is 23.4 Gy, with posterior fossa boost of 30.6 Gy to total dose of 54 Gy. For advanced-stage disease, craniospinal dose is 36 Gy with a posterior fossa boost of 18 Gy to a total dose of 54 Gy.
6. Craniospinal RT frequently produces neurocognitive complications in children, particularly in children younger than 3 years of age.
7. Sensitive to chemotherapy: Adjuvant therapy with agents such as cisplatin and etoposide and cyclophosphamide and vincristine. Other active agents include lomustine, procarbazine, and carboplatin. Adjuvant chemotherapy improves survival in patients with high-risk disease and probably also for patients with standard-risk disease.
8. In infants and young children under the age of 3 years, chemotherapy is sometimes used alone to avoid RT, although the long-term effectiveness of such a strategy is unknown.
9. In adults, there are no randomized studies of chemotherapy. Treatment is often patterned after children.
10. Emerging therapies include smoothened inhibitors for SHH-subgroup medulloblastomas.

CRANIAL AND SPINAL NERVE TUMORS

Schwannoma

Background

1. Schwannomas are benign tumors that originate from the Schwann cell at the glial–Schwann cell junction (Obersteiner–Redlich zone) of the peripheral nerves.
2. Vestibular schwannomas (acoustic neuroma) arise from the vestibular portion of the eighth nerve.
3. In periphery, these arise from paraspinal dorsal nerve roots and cutaneous nerves.

Epidemiology

1. Incidence is 1/100,000; female-to-male ratio is 1.5:1.
2. Occurs in middle adult life and rarely in childhood.
3. Most commonly arises from vestibular nerve (usually solitary; frequently bilateral in neurofibromatosis type 2 [NF2]).
4. Vestibular schwannomas account for 8% of all intracranial tumors and 80% of CPA tumors in adults.

Pathophysiology

1. Increased incidence in NF2. Patients often have bilateral acoustic schwannomas and multiple cranial and spinal schwannomas, meningiomas, and gliomas.
2. Inactivating mutations of *NF2* gene also frequent in spontaneous schwannomas.

Prognosis

1. Slow-growing tumors usually cured by surgery.
2. Malignant degeneration rare in the CNS but more common in the peripheral nervous system (PNS).

Diagnosis

Location

Most common is CN VIII in the CPA but may occur wherever Schwann cells are present (other CNs, spinal nerves, and peripheral nerve trunks).

Clinical Presentation

1. Most common include unilateral hearing loss, tinnitus, and unsteadiness from acoustic nerve dysfunction evolving over months to years.
2. Dysfunction of other CNs and brainstem occurs if it becomes large enough (trigeminal dysfunction [loss of corneal reflex, facial numbness], facial weakness, ataxia, vertigo).
3. Isolated vertigo uncommon as initial symptom.

Diagnostic Tests

1. Audiometry is helpful for detecting unilateral sensorineural hearing loss.
2. Brainstem auditory evoked potentials abnormal in more than 90% of patients (prolongation of waves I to III and I to V latency).
3. MRI with gadolinium is the most sensitive imaging modality and shows intradural, extra-axial, enhancing mass.
4. In the spine, tumor may extend through the intervertebral foramen, resulting in an hourglass appearance.
5. CT scan useful to delineate the anatomy of the bones involved.

Pathology

1. Two types of histology are seen: Antoni A (compact, elongated cells with occasional nuclear palisading) and Antoni B (loose, reticulated tissue).
2. Schwann cells arise at the periphery of nerve; usually encapsulated and compress but do not invade adjacent neural tissue.

Differential Diagnosis

1. Most common CPA tumor. Differential includes meningioma, cholesteatoma, epidermoid, metastatic disease, and glioma.
2. Schwannomas arising from spinal roots may resemble meningiomas and neurofibromas.

Treatment

1. Small asymptomatic lesions can often be observed and treated only if they

increase in size.
2. Surgical resection can be complete for tumors smaller than 2 cm and can preserve hearing in 50% to 75% of patients.
3. Surgical morbidity is related to size of tumor (lower than 5% for tumors smaller than 2 cm, 20% for tumors larger than 4 cm) and includes facial paralysis, hearing loss, CSF leak, imbalance, and headache.
4. If hearing is good, then one should also consider early treatment as delay may result in hearing impairment.
5. SRS probably equally effective, especially in older patients and those at high risk for surgery. Fractionated SRT associated with less morbidity.

Neurofibroma

Background

1. Arise from cells with features of Schwann cells, fibroblasts, and perineural cells and are usually benign.
2. Almost always associated with NF1 and usually multiple.
3. Malignant peripheral nerve tumors (MPNTs) occur in 1/10,000 and arise de novo or from sarcomatous degeneration of a preexisting plexiform neurofibroma.

Pathophysiology

Associated with NF1.

Prognosis

Additional lesions tend to arise, and in NF1, malignant degeneration may occur.

Diagnosis

Location

Most involve dorsal spinal nerve roots, major nerve trunks, or peripheral nerves. CN involvement is very rare.

Clinical Presentation

Cutaneous neurofibromas present as small painless masses. Nerve root

neurofibromas may present with pain and sensorimotor disturbance.

Diagnostic Tests

MRI shows widening of the neural foramina with pedicle erosion in neurofibromas arising from spinal roots.

Pathology

1. Hyperplasia of Schwann cells and fibrous elements of the nerve. Elongated wavy interlacing hyperchromatic cells with spindle-shaped nuclei in a disorderly loose mucoid background with collagen fibrils. Nerve fibers are intertwined in the tumor.
2. Plexiform neurofibroma associated with NF1, which has an increased incidence of malignant transformation.
3. Malignant peripheral nerve sheath tumors (MPNSTs) are highly malignant sarcomas; many occur in NF1 with preexisting plexiform neurofibroma.

Differential Diagnosis

Perineuriomas arise from pericytes.

Treatment

1. Palliative surgical decompression as needed.
2. RT occasionally useful in malignant tumors.

MENINGEAL TUMORS

Meningioma

Background

1. Arise from cells that form the outer layer of the arachnoid granulations of the brain (arachnoid cap cells).
2. Meningioma is the most common PBT in adults.
3. Represents approximately 36.4% of all CNS neoplasms with an incidence rate of 7.86 per 100,000.
4. Rare in the first two decades and increases progressively thereafter.
5. Incidence increases with age. Median age of diagnosis is 65 years old.

6. Strong female predominance (3:2).
7. Possibly higher incidence in patients with breast cancer.
8. Pregnancy may be associated with tumor progression (strong hormonal influence).

Pathophysiology

1. Proven risk factors are female gender, increasing age, NF2, and history of cranial irradiation.
2. Meningiomas have partial or complete deletions of chromosome 22.
3. Patients with NF2 may have multiple meningiomas.
4. Progesterone receptors are present in 70% of tumors and play a role in tumor growth.
5. PDGF, EGFR, VEGF, and their receptors are expressed in meningiomas.

Prognosis

1. Excellent for most patients. Median survival more than 10 years.
2. Most are slow-growing lesions that remain stable for many years.
3. Ninety percent benign (WHO grade I) meningiomas, 4.7% to 7.2% are atypical meningiomas (WHO grade II), and 1% to 2.8% are anaplastic meningiomas (WHO grade III) and have a much worse prognosis. Median survival for anaplastic meningiomas is less than 2 years.
4. Recurrence is related to completeness of the resection, location, and tumor grade.
5. Poor prognostic factors include higher grade, papillary histologic characteristics, large number of mitotic figures, necrosis, and invasion of cortical tissue by tumor cells.

Diagnosis

Location

1. Mostly extra-axial and intracranial.
2. Ninety percent are supratentorial involving the cerebral convexities (50%; parasagittal, falx, or lateral convexity), skull base (40%; sphenoid wing, olfactory groove, or suprasellar), posterior fossa, foramen magnum, periorbital region, temporal fossa, and ventricular system.
3. Intraspinal tumors account for 25% of primary spinal tumors and are usually

in thoracic segment.

Clinical Presentation

1. Present with seizures, headaches, and focal deficits.
2. Over 20% are asymptomatic and are an incidental finding.
3. Spinal meningiomas present with pain, weakness, numbness, and gait unsteadiness.

Diagnostic Tests

1. MRI or CT with contrast shows a well-defined, homogenously enhancing extra-axial mass that may be calcified. If edema is present, it usually indicates a higher grade tumor or a secretory meningioma.
2. On T1- and T2-weighted sequences, meningiomas can be easily missed as they are isointense to slightly hypointense compared with brain or spinal cord.
3. "Dural tail" sign at the margin of tumor is characteristic.
4. MR venography or CT angiography may be useful to determine patency of adjacent venous sinuses.

Pathology

1. Gross examination shows well-circumscribed, rubbery to hard masses that indent brain with no invasion. On sphenoid ridge may be en plaque.
2. Microscopically shows whorls, psammoma bodies, intranuclear pseudoinclusions; epithelial membrane antigen is positive.
3. Benign variants (WHO grade I): Meningothelial, fibrous, transitional, psammomatous, secretory, microcystic, chordoid, lymphoplasmacytic-rich, metaplastic, and clear cell.
4. Atypical meningiomas (WHO grade II): Increased mitotic activity (four mitoses per 10 high-power fields) and increased cellularity, small cells with high nucleus/cytoplasm ratio, prominent nucleoli, patternless growth, and spontaneous necrosis.
5. Anaplastic (malignant) meningioma (WHO grade III) variants: Papillary, rhabdoid, and malignant meningiomas are more aggressive with high rates of metastases.

Differential Diagnosis

Dural metastases, hemangiopericytoma, hemangioblastoma, melanocytoma,

meningioangiomatosis, sarcoma, solitary fibrous tumor, and melanoma.

Treatment

1. Asymptomatic lesions (<2 cm without edema) are frequently seen on routine imaging for unrelated problems and can be followed up clinically and with serial imaging.
2. Asymptomatic lesions near vital structures should be considered for resection because of increased operative morbidity later.
3. Symptomatic or enlarging lesions should be resected.
4. Complete surgical removal of a meningioma confers long-term disease-free survival: 95% at 5 years, 70% to 90% at 10 years, and less than 70% at 15 years. Subtotal resection confers a lower disease-free survival of 63% at 5 years, 45% at 10 years, and 8% at 15 years.
5. RT may be indicated in patients with progressive symptoms caused by recurrent meningioma in whom surgery is subtotal or contraindicated. Disease-free survival at 10 years is approximately 70% and approaches that of patients undergoing a complete surgical resection.
6. Patients with atypical or anaplastic meningiomas should have RT after surgery. Control rates at 10 years after RT for atypical meningioma and malignant meningioma are 13% and 0%, respectively.
7. SRS is an option for tumors smaller than 3 cm and not adjacent to vital structures. Fractionated SRT may be used for larger tumors and those near vital structures.
8. Although meningiomas express estrogen, progesterone, and somatostatin receptors, antiestrogens, antiprogesterone (RU486), and somatostatin inhibitors have not been effective in clinical studies.
9. Anecdotal reports of efficacy with chemotherapy (hydroxyurea, interferon-α, bevacizumab), but efficacy is limited.

Hemangiopericytoma

1. Considered to be a different entity from meningiomas.
2. Densely cellular and vascular tumor arising from dura.
3. Clinical presentation, diagnosis, and treatment (surgery and RT) similar to those for atypical meningioma.
4. Sixty percent survival at 15 years.

Hemangioblastoma

Background

Account for 7% of posterior fossa tumors. Most common cause of intra-axial posterior fossa tumor in adults.

Pathophysiology

Twenty percent of hemangioblastomas are associated with von Hippel–Lindau (VHL) syndrome. Autosomal dominant disorder is caused by germline mutation of *VHL* gene, causing constitutive overexpression of VEGF. Associated with retinal angiomas, renal cell carcinoma, pheochromocytoma, and pancreatic adenomas, pancreatic and liver cysts, and polycythemia.

Prognosis

Good for isolated hemangioblastomas; cured if completely resected. Prognosis of patients with VHL poorer. Dependent on extent and location of hemangioblastomas and other tumors.

Diagnosis

Clinical Presentation

1. Age, 30 to 65 years.
2. Headaches, ataxia, and focal neurologic deficits. Some patients may have symptoms from associated lesions as part of VHL syndrome (visual symptoms from retinal angiomas and symptoms from renal carcinomas and pheochromocytomas).

Diagnostic Test

MRI typically shows enhancing cystic lesion with mural nodule.

Pathology

Hemangioblastomas are grossly well-circumscribed, vascular, often cystic tumors containing yellowish lipid, and nodule on the cyst wall. Microscopically, there are three cell types (stromal, endothelial, and pericyte). Cyst wall may contain Rosenthal fibers (difficult to distinguish from pilocytic astrocytoma). Clusters of foamy cells separated by blood-filled vascular spores.

Differential Diagnosis

Pilocytic astrocytoma, metastases, ependymoma, medulloblastoma, and vascular malformation.

Treatment

1. Small, asymptomatic lesions can be observed.
2. Surgical excision is treatment of choice. Tumors often very vascular.
3. RT and SRS may be of benefit for recurrent or inoperable tumors.
4. Clinical trials using inhibitors of VEGF underway.

Primary Central Nervous System Lymphoma

Background

1. PCNSL is a diffuse non-Hodgkin lymphoma (NHL) that is confined to CNS.
2. Most (90%) are B-cell lymphomas, diffuse and large cell type, and classified as a stage I_E NHL.

Epidemiology

1. Four percent of all CNS tumors; 1% of NHL. Incidence is 0.43/100,000. Slightly greater in males.
2. Main risk factor is immunodeficiency (patients with AIDS, organ transplant recipients).
3. Overall incidence peaked in mid-1990s and has been declining, likely because of changes in HIV/AIDS incidence and management. However, incidence among immunocompetent hosts and elderly males continues to increase for unclear reasons.
4. Frequently disseminates to the leptomeninges (25%) and vitreous humor (20%).
5. In immunocompetent hosts, mean age is 50 to 60 years and in immunocompromised patients, the mean age is 30 years.

Pathophysiology

1. Controversy surrounding its site of origin in immunocompetent patients. No known risk factors.
2. In immunocompromised patients, related to uncontrolled proliferation of B

cells latently infected with Epstein–Barr virus (EBV).

Prognosis

1. Highly malignant, mean survival of 1.5 months with supportive care only.
2. RT alone prolongs median survival to 12 to 18 months.
3. In immunocompetent patients, median survival 19 to 42 months with maximal treatment.
4. In immunocompromised patients, median survival 6 to 16 months with maximal treatment.
5. Neuraxis dissemination (60%) and systemic lymphoma (10%) in patients who survive 1 year after radiation.

Diagnosis

Location

1. Periventricular, subcortical, and usually multifocal in 40% of cases (90% in patients with AIDS).
2. Retinal or vitreous infiltration (20%), sometimes restricted to the eye only.
3. Diffuse meningeal infiltration (40%).
4. Spinal cord involvement occasionally.
5. Lymphomatous invasion of cranial or spinal nerve roots is less common.

Clinical Presentation

1. Frequently present with cognitive and behavioral changes. Some patients may have headache, seizures, and focal deficits.
2. Multifocal symptoms nearly 50% of the time.
3. Symptoms may be present for 1 to 2 months before diagnosis.

Diagnostic Tests

1. MRI hypodense on T2-weighted images, isodense or hypodense on T2-weighted images. Usually homogenously enhancing. In immunocompromised patients, lesions can be ring enhancing. Usually periventricular and may involve deep structures such as basal ganglia.
2. SPECT scanning using gallium^{67} and thallium^{201} and PET show increased uptake in PCNSLs and help differentiate them from infections.
3. Ophthalmologic evaluation is essential to rule out ocular involvement (20% of PCNSL) by slit-lamp exam.

4. Staging to rule out systemic lymphoma with body PET/CT (3% of patients are identified with extraneural disease) and testicular examination/ultrasound in men. Value of bone marrow biopsy is controversial.
5. Biopsy (usually stereotactic) or CSF analysis is needed for diagnosis.
6. LP for CSF analysis shows lymphocytic pleocytosis in over 50% of cases, increased protein 85%, up to 90% positive cytology with three LPs. Polymerase chain reaction (PCR) for *IgH* gene rearrangement is more sensitive.
7. Use of steroids before tissue sampling can decrease the yield. Should hold steroids until after biopsy, if possible.
8. HIV testing should be done on all patients.

Pathology

1. Grossly better demarcated than diffuse gliomas, granular light tan appearance.
2. WHO grade IV microscopically perivascular orientation of cells (angiocentric), often expanding a vessel wall with reticulin deposition. Necrosis common. Noncohesive, large, irregular nuclei, prominent nucleoli, scant cytoplasm, usually large B-cell, but occasionally T-cell.

Differential Diagnoses

1. Infections—especially in HIV-positive patients and includes opportunistic infections such as toxoplasmosis (most common), cryptococcal abscesses, tuberculoma, nocardia abscesses, syphilitic gummas, and Candida abscesses.
2. Metastases from occult non-CNS neoplasms, gliomas, intravascular or systemic lymphoma, and vasculitis.

Treatment

1. Biopsy for histologic diagnosis usually required. No benefit from resection.
2. Chemotherapy is the first treatment of choice and increasingly preferred over radiation.
3. Ninety percent responds to RT (usually 4,000 cGy WBRT ± 1,400 to 2,000 cGy boost to tumor) but recurs in 1 to 2 years and risk of long-term neurotoxicity for long-term survivors.

4. Corticosteroids: 40% have a partial or complete response but tumor rapidly recurs.
5. High-dose IV methotrexate (HDMTX) (3.5 to 8 g/m^2) has a 50% to 80% response rate.
6. Other active agents include procarbazine, high-dose cytarabine, lomustine, vincristine, rituximab, temozolomide, and pemetrexed.
7. No standard regimen, but most patients are treated with a multidrug HDMTX-based regimen with or without RT. Median survival has improved to more than 40 months.
8. CSF penetration of HDMTX good. Probably no need for additional intrathecal chemotherapy to treat leptomeningeal disease.
9. Use of methotrexate before RT reduces risk of leukoencephalopathy. However, RT in patients above 60 years is still associated with significant leukoencephalopathy. Trend is toward deferring RT in these patients and treating them only with chemotherapy.
10. Clinical trials are underway examining the role of high-dose chemotherapy and autologous stem cell transplantation for immunocompetent patients with PCNSL. Early small studies suggest increased survival times with this approach.

Germ Cell Tumors

Background

1. Most common tumor of pineal gland (60%) and most are malignant.
2. Peak incidence is in the second decade, predominantly in males (3:1); 95% occur before age 33 years.
3. Germinomas account for 60% of germ cell tumors and teratoma and mixed germ cell tumors 20% to 30%. Embryonal carcinoma, endodermal sinus (yolk sac) tumor, and choriocarcinoma are rare.

Pathophysiology

Arise from primitive midline germ cells in the pineal or hypothalamic regions. Indistinguishable histologically from those tumors that occur in the gonads of young adults.

Prognosis

1. Benign teratomas have a 100% 5-year survival.
2. Germinomas have an 80% to 90% 5-year survival following surgery and RT. Some patients were cured.
3. Malignant nongerminomatous germ cell tumors have a poor prognosis. Survival is rarely more than 2 years.

Diagnosis

Location

Midline in pineal, sellar and suprasellar regions, posterior fossa, and sacrococcygeal area.

Clinical Presentation

1. Parinaud syndrome (paralysis of upgaze, convergence–retraction nystagmus, light-near dissociation) secondary to compression of the tectum of the midbrain.
2. Obstructive hydrocephalus.
3. Suprasellar tumors may present with visual symptoms and hypothalamic and endocrine dysfunction.
4. Teratoma is associated with spina bifida if located in sacrococcygeal area.

Diagnostic Tests

1. MRI or CT scan of brain: Most tumors show calcification. Usually enhances significantly with contrast. Teratomas have heterogenous appearance with solid and cystic areas and frequently areas of fat and calcification.
2. Spine MRI and CSF examination are necessary to determine the extent of CSF seeding.
3. Serum and CSF tumor markers can be helpful. These include AFP (endodermal sinus tumor, embryonal carcinoma, and malignant teratoma) and β-hCG (germinoma, teratoma, choriocarcinoma, embryonal carcinoma, malignant teratoma, and undifferentiated germ cell tumor). Germinomas rarely secrete markers (fewer than 10% secrete β-hCG).
4. Endocrine evaluation and visual field examination (suprasellar lesions).

Pathology

1. Germinoma is composed of large malignant germ cells and small reactive

lymphocytes.
2. Teratoma has all three germ cell layers present (epidermal, dermal, vascular, glandular, muscular, neural, cartilaginous).
3. Yolk sac tumor is composed of primitive-appearing epithelial cells.
4. Embryonal carcinoma is composed of large cells that proliferate in sheets that form papillae.
5. Choriocarcinoma contains cytotrophoblasts and syncytiotrophoblastic giant cells.

Differential Diagnosis

Same as that for pineal parenchymal tumors and pituitary adenomas, depending on location.

Treatment

1. Stereotactic biopsy for tumors with evidence of CSF dissemination and elevated AFP.
2. Open biopsy allows for more accurate tissue sampling.
3. Resection appropriate for more benign pathologies such as teratoma.
4. Ventricular shunting for hydrocephalus.
5. Germinomas highly radiosensitive (focal irradiation of 4,500 to 5,000 cGy).
6. Cranial irradiation for all other germ cell tumors.
7. Craniospinal RT reserved for patients with evidence of CSF seeding.
8. SRS used to treat residual areas of tumor after conventional RT.
9. Chemotherapy used for nongerminomatous malignant germ cells tumors. A wide variety of regimens have been tried including those derived from treatments for testicular cancer such as cisplatin, vinblastine, and bleomycin or cisplatin, etoposide, and ifosfamide.

Cysts and Tumorlike Lesions

Background

1. There are several nonneoplastic lesions that can be found incidentally and include epidermoid and dermoid cysts, lipoma, and hamartomas.
2. Epidermoids and dermoids represent approximately 2% of intracranial tumors.

3. Colloid cyst affects young-to-middle-aged adult.
4. Hypothalamic hamartoma is a dysplastic lesion usually occurring in the first decade of life.

Pathophysiology

Usually incidental lesions because of rests of embryonal tissue remaining in the nervous system.

Prognosis

These are benign lesions that can usually be resected. Epidermoid and dermoid cysts may recur.

Diagnosis

Location

1. Epidermoid cyst is usually found in CPA, intrasellar and suprasellar regions, and intraspinal.
2. Dermoid cyst is usually midline, related to fontanel, fourth ventricle, or spinal cord.
3. Colloid cyst is usually in the third ventricle at foramen of Monro.
4. Lipomas are found in corpus callosum, hypothalamus, sella, and spinal cord.
5. Hypothalamic hamartoma is in the hypothalamus.

Clinical Presentation

1. Epidermoid cyst presents with cranial abnormalities, seizures, hydrocephalus, and aseptic meningitis.
2. Dermoid cyst presents with symptoms of hydrocephalus, focal deficits, and occasionally repeated bacterial meningitis because of association with dermal sinus tract.
3. Colloid cyst presents with headaches, drop attacks, and rarely sudden death because of obstruction of foramen of Monro. However, most are asymptomatic.
4. Lipomas are usually incidental and frequently associated with other congenital anomalies, such as agenesis of corpus callosum. Occasionally they cause symptoms from mass effect.
5. Hypothalamic hamartoma presents with gelastic seizures and endocrine

abnormalities (precocious puberty).

Diagnostic Tests

1. Epidermoid cyst on CT is a low-density cyst with irregular enhancing rim; on MRI, it has variable signal depending on lipid content and increased signal on diffusion-weighted images.
2. Dermoid cyst on MRI has heterogenous signal because of hair and sebaceous content.
3. Colloid cyst on MRI is a spheric, thin-walled lesion, and hyperintense on T1-weighted lesion.
4. Lipoma is low density on all imaging modalities.
5. Hypothalamic hamartoma on MRI usually is a small discrete mass near the floor of third ventricle, which does not enhance. Hypothalamic–pituitary hormones may be abnormal.

Pathology

1. Epidermoid cyst contains squamous epithelium surrounding a keratin-filled cyst.
2. Dermoid cyst contains both epidermal and dermal structures (hair follicles, sweat glands, sebaceous glands).
3. Colloid cyst contains goblet and ciliated columnar epithelial cells surrounding a cystic cavity.
4. Lipoma contains mature adipose tissue.
5. Hypothalamic hamartoma consists of a well-differentiated but disorganized neuroglial tissue.

Differential Diagnosis

Pilocytic astrocytoma, glioma, metastases. CPA epidermoids should be differentiated from vestibular schwannomas, meningiomas, and arachnoid cysts.

Treatment

1. Epidermoid, dermoid, and colloid cysts can be surgically resected.
2. Lipomas should be followed clinically and excision is usually not necessary.
3. Hypothalamic hamartoma should undergo resection if possible. Long-acting gonadotropin-releasing hormone analogs may also be helpful. Some patients

need endocrine replacement.

TUMORS OF THE SELLAR REGION

Pituitary Adenoma

Background

1. Pituitary adenoma is the most common sellar tumor and may grow up into suprasellar space and laterally to invade cavernous sinus (primary suprasellar masses usually do not grow down through the diaphragm).
2. Arise from cells of the adenohypophysis, predominantly corticotrophs, somatotrophs, lactotrophs, gonadotrophs, and rarely, thyrotrophs.
3. Classified anatomically as microadenomas (<10-mm diameter) and macroadenomas (>10-mm diameter).
4. Classified functionally according to secreted products.
5. Prolactinoma is the most common (27%), usually a microadenoma. Symptoms are from primary hypersecretion or stalk effect (flow of dopamine impeded). Presents with amenorrhea and galactorrhea in females, and decreased libido and impotence in males.
6. Growth hormone (GH) (21%) secretion causes gigantism and acromegaly.
7. Corticotropin-secreting adenomas (8%) produce Cushing disease.
8. Follicle-stimulating hormone (FSH)/luteinizing hormone (LH) (6%) secreting adenomas.
9. Thyrotropin-secreting adenomas (1%) are rare and are usually secondary to primary thyroid myxedema.
10. Nonsecreting adenomas (35%) usually present with compressive symptoms.

Epidemiology

1. Ten percent to 15% of all intracranial neoplasms, male-to-female ratio 1:2, and third most common primary intracranial neoplasm.
2. Incidence 1 to 14/100,000 and found in 6% to 22% of unselected autopsies.
3. Present from late adolescence through adulthood.
4. Frequency in decreasing order is prolactinoma, nonsecreting adenoma, GH-secreting adenoma, corticotropin-secreting adenoma, and glycoprotein-

secreting adenoma.

Pathophysiology

1. Symptoms are caused by disrupting hypothalamic–pituitary–adrenal axis or by direct compression of adjacent structures.
2. Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant syndrome caused by allelic loss of tumor suppressor gene menin on chromosome 11q13. Patients develop tumors of the pituitary gland, pancreatic islets, and parathyroid glands.
3. Expression on *c-myc* correlates with clinical aggressiveness and *ras* mutations mark an invasive tumor.

Prognosis

1. Related to size and cell type of tumor.
2. Seventy percent to 90% remission rate 1 year after resection.
3. Visual recovery best when impairment has been brief.
4. Endocrine status improves after surgery (fertility may return in 70% of patients).
5. Pregnancy can precipitate symptomatic tumor growth of prolactinomas in 25% of macroadenomas, but only 1% of microadenomas.
6. Prolactinomas can be controlled in 95% patients with dopamine agonists, surgery, and RT.
7. Cushing disease can be controlled with surgery in 93% of microadenomas and 50% of macroadenomas.
8. Acromegaly can be controlled with surgery in 85% of microadenomas and 40% of macroadenomas.

Diagnosis

Location

1. Sella and parasellar. Compresses optic chiasm.
2. Can invade the cavernous sinus, third ventricle, hypothalamus, or temporal lobe.

Clinical Presentation

1. Present with insidious neurologic symptoms late including headaches and

visual disturbance because of compression of optic chiasm located above the sella.

a. Usually bitemporal superior quadrantanopia and then bitemporal hemianopia.

2. Present with insidious endocrine manifestations early if hormonally active and include hypofunction or hyperfunction.

a. Hypopituitarism especially of gonadotropin and GH systems.

b. Prolactin excess causes galactorrhea or amenorrhea in women (one-fourth of all women with secondary amenorrhea and galactorrhea have prolactin-secreting tumors). Men present with impotence and loss of libido.

c. GH excess causes acromegaly or gigantism (rarely caused by ectopic tumor).

d. Corticotropin excess causes Cushing disease.

3. Hemorrhage or infarct of tumor may produce pituitary apoplexy (abrupt headache, visual loss, diplopia, drowsiness, confusion, coma).

4. Pregnancy, head trauma, acute hypertension, and anticoagulation predispose to apoplexy.

Diagnostic Tests

1. MRI with sagittal and coronal views with contrast may reveal microadenoma or larger compressive lesions and demonstrate the relationship between tumor and surrounding vital structures (optic chiasm, cavernous and sphenoid sinuses, hypothalamus). Visual field testing.

2. Serum studies

a. Prolactin (normal <15 ng/mL, >200 ng/mL usually caused by tumor, level of 15 to 200 ng/mL can be because of adenoma or caused by medications [phenothiazines, antidepressants, estrogens, metoclopramide] or by disorders that interfere with normal hypothalamic inhibition of prolactin secretion [hypothyroidism, renal and hepatic disease, hypothalamic disease]).

b. Insulin-like growth factor 1 (IGF1), GH, thyroid function tests (TFTs), FSH, LH, testosterone (male), estrogen (female), cortisol, corticotropin, electrolytes, and glucose.

c. Urine electrolytes, 24-hour urine-free cortisol, and dexamethasone suppression test for Cushing disease.

d. With pituitary source, cortisol does not suppress with low-dose dexamethasone (0.5 mg q6h for eight doses) but does suppress with higher dose (2 mg q6h for eight doses).
e. Adrenal or ectopic sources do not suppress with either dose.
f. Elevated IGF and decreased GH response to oral glucose load for GH excess.

3. If MRI does not show a tumor, petrosal sinus sampling can provide evidence for a pituitary origin of corticotropin. Body CT also needed to search for lung or adrenal tumors.

Pathology

Classified according to hormonal products.

Differential Diagnosis

Craniopharyngioma, germinomas, teratomas, meningiomas, pituitary carcinoma, dermoids, epidermoids, metastatic tumors, hypothalamic/optic nerve glioma, hypothalamic hamartoma, nasopharyngeal tumors, posterior pituitary tumors (granular cell tumor and astrocytoma), metastases, chordoma, and nonneoplastic lesions such as Rathke cleft cyst, lymphocytic hypophysitis, abscess, histiocytosis X, sarcoidosis, and aneurysms.

Treatment

1. Surgery is treatment of choice for most pituitary tumors (except prolactinomas), especially if there is visual compromise. Tumors within the pituitary sella and those with limited extrasellar extension can usually be approached via the transsphenoidal route with substantially reduced operative morbidity. Extension beyond the sella laterally or superior extension with invasion or entrapment of the optic chiasm typically necessitates a superior surgical approach through a transfrontal craniotomy.
2. Patients undergoing surgery are usually treated with corticosteroids as prophylaxis against adrenal insufficiency.
3. DI can occur after surgery but is usually transient.
4. Adjuvant postoperative RT (including SRT) reduces the rate of recurrence for functioning adenomas (one series reports from 42% to 13%). Usually 5,000 cGy given over 5 to 6 weeks.
5. Subtotally resected nonfunctioning tumors and functioning tumors with

normal hormone levels often watched with serial MRI and hormone levels. RT used only if there is evidence of tumor growth.

6. Prolactinoma responds well to medical therapy (bromocriptine: a dopamine agonist that shrinks tumor by reducing prolactin) and seldom requires surgery. In symptomatic women, 80% success with medical therapy. Bromocriptine is safer in pregnancy. Initial dosage of bromocriptine is 1.25 to 2.5 mg/d, increasing by 2.5 mg/d every 3 to 7 days, up to l5 mg/d.
7. Cabergoline (0.25 mg p.o. twice weekly; maximum, 1 mg twice weekly) and quinagolide (0.03 to 0.5 mg daily) are dopamine agonists that have longer half-lives, greater potency, and fewer side effects than bromocriptine.
8. GH-secreting adenoma: Transsphenoidal resection with or without the somatostatin analogs octreotide (50 μg subcutaneously [s.c.] three times daily [t.i.d.]) and lanreotide (30 to 60 mg intramuscularly [IM] every 10 to 14 days). Bromocriptine, cabergoline, and quinagolide have also been used.
9. Others symptomatic tumors need transsphenoidal resection.

Craniopharyngioma

Background

1. Slow-growing tumor that originates from remnants of embryonic squamous cell rests (Rathke pouch) in the region of the pituitary stalk.
2. Incidence 0.5 to 2 cases per million per year.
3. Account for less than 1% of adult intracranial tumors and 6% to 10% of childhood intracranial neoplasms.
4. Bimodal age distribution (first peak, 5 to 10 years; second peak, 50 to 60 years).
5. Most common supratentorial tumor in childhood and second most common parasellar tumor.

Pathophysiology

Sporadic, no genetic association known.

Prognosis

1. Usually benign.
2. Sixty percent to 93% 10-year recurrence-free survival; 64% to 96% 10-year

overall survival.
3. Recurrence rate worse for tumors larger than 5 cm and incompletely resected tumors.

Diagnosis

Location

Above sella, but some in sella.

Clinical Presentation

1. Because of slow growth, diagnosed 1 to 2 years after onset of symptoms.
2. Hypopituitarism and DI secondary to compression of pituitary gland and hypothalamus.
3. Visual abnormalities (bitemporal hemianopsia) secondary to compression of optic chiasm/tracts.
4. Headache and vomiting because of elevated ICP.

Diagnostic Tests

Strongly enhancing, cystic, and calcified mass (80% in children and 40% in adults) in the suprasellar region with frequent intrasellar component.

Pathology

1. Grossly multicystic, well-delineated lesions that contain dark, viscous liquid within cystic spaces.
2. Microscopically variable types of epithelium, some resembling "adamantinomatous" (more common) and others papillary and squamous. May have calcification, keratin debris, cholesterol clefts, macrophages, and hemosiderin. Rosenthal fibers in adjacent brain.

Differential Diagnosis

Pituitary adenoma, hypothalamic/optic system glioma, Rathke cleft cyst, dermoid, epidermoid, hypothalamic hamartoma, germinoma, giant aneurysm, sarcoidosis, histiocytosis X, and lymphocytic hypophysitis.

Treatment

1. Surgical resection treatment of choice. Complete resection is possible in 50% to 90% of cases, but often, it is associated with significant morbidity

because of relation to vital neural and neuroendocrine structures. Even with complete resection, only 65% of patients are free of recurrence at 10 years.
2. RT, especially SRT, is assuming an increasing role, particularly for patients with incomplete resection and recurrent disease. Ninety percent 10-year survival when surgery is combined with RT.
3. Radioisotopes such as phosphorus 32 (^{32}P) are occasionally administered into cysts to prevent recurrence.
4. Ventriculostomy is needed for hydrocephalus.
5. Cyst material can cause chemical meningitis.
6. Endocrine dysfunction and learning disabilities are common and require therapy.

SPINAL CORD TUMORS

Background

1. Spinal cord tumors account for 10% of all primary CNS tumors.
2. Spinal cord tumors can be divided into three groups on the basis of their location: Intradural/intramedullary, intradural/extramedullary, and extradural.
3. Intradural/intramedullary account for 4% to 10% of spinal cord tumors, 80% of which are gliomas and ependymoma. Myxopapillary ependymomas predominate in the cauda equina and lumbar region, astrocytomas predominate in the cervical region. They are slow growing and usually cause symptoms for many years. Other tumors include hemangioblastoma, paraganglioma, dermoid, epidermoid, and lipoma.
4. Intradural/extramedullary tumors are mostly benign. In adults, schwannomas are the most common intraspinal tumor. They are slow-growing tumors that usually arise from posterior nerve roots. Meningiomas are the second most common primary intraspinal tumor. Most (80%) occur at the level of the thoracic spinal cord. Together, schwannomas and meningiomas account for 80% of intradural/extramedullary tumors. Other tumors include neurofibroma, ependymoma, lipoma, epidermoid, and dermoid.
5. Extradural benign tumors include osteoid osteoma, osteoblastoma, osteochondroma, giant cell tumor, aneurysmal bone cyst, hemangioma, and

eosinophilic granuloma.

5. Extradural malignant tumors include metastatic disease, plasmacytoma, myeloma, chordoma, osteosarcoma, Ewing sarcoma, chondrosarcoma, lymphoma, and malignant fibrous histiocytoma.

Pathophysiology

Cause dysfunction by compression and edema.

Prognosis

1. Complete resection of nerve sheath tumors and meningiomas is curative.
2. Intramedullary tumors such as ependymomas can often be resected. Recurrence-free survival is greater than 75% at 10 years. Myxopapillary ependymomas of the cauda equina have a particularly good prognosis. Astrocytomas are more difficult to resect, and a minority have high-grade histology and a poor prognosis.
3. Patients with NF1 or NF2 have an increased risk of developing secondary tumors and patients with NF1 with spinal neurofibromas have an increased risk of long-term mortality (60% 10-year survival).

Diagnosis

Clinical Presentation

1. Pain is the most common symptom.
2. Extramedullary tumors produce symptoms by compression of nerve roots before cord.
3. Intramedullary tumors present with symptoms for 6 months to 3 years, commonly with axial spinal pain, radicular pain, and sensorimotor deficits.
4. For schwannomas, the most common symptom initially is pain in a radicular distribution. They grow slowly so patients may have symptoms for months to years before diagnosis.
5. Extradural tumors produce unremitting back pain that may be radicular in nature. Initially there are no neurologic deficits, but advanced tumors produce myelopathy.

Diagnostic Tests

1. Imaging may show bone erosion of the pedicles and intervertebral foramina (e.g., schwannoma) or bony destruction (metastases, lymphoma).
2. Contrast-enhanced MRI shows much better anatomic soft-tissue detail than CT.
3. MRI shows expansive lesion; gliomas frequently associated with syringomyelia.
4. CT myelography may be useful if MRI cannot be done.

Pathology

Depends on the tumor type.

Differential Diagnoses

1. Intramedullary: Demyelination, amyotrophic lateral sclerosis (ALS), dural arteriovenous fistula, atriovenous malformation (AVM), hemangioblastoma, lipoma, and epidermoid.
2. Extramedullary: Cervical spondylosis, epidermoid, dermoid, sarcoma, metastasis, myeloma, and extramedullary hematopoiesis.

Treatment

1. Surgical resection is usually the treatment of choice for most spinal cord tumors. Preoperative embolization may be helpful for vascular tumors such as hemangioblastoma. Complete resection often feasible for schwannomas, meningiomas, and ependymomas.
2. Intraoperative neurophysiologic monitoring helpful in decreasing morbidity.
3. Astrocytomas are more infiltrating and complete resection possible only in 20% of cases but can be decompressed by laminectomy, partial resection, and repair of syringomyelia.
4. Postoperative results are generally related to preoperative neurologic condition. Where there are maximal deficits before surgery, significant recovery is unlikely. Where there are mild or modest deficits, excellent functional recovery may be expected.
5. Patients with subtotal resection may be treated with RT or observed closely and treated with further surgery or RT when recurrent disease is

documented.

6. Postoperative radiation can delay recurrence or progression of symptoms. Patients usually receive 3,500 to 4,500 cGy.
7. Chemotherapy has a limited role for high-grade gliomas and recurrent tumors.

NEUROLOGIC COMPLICATIONS OF SYSTEMIC CANCER

Brain Metastases

Background

1. BMs are the most common intracranial tumors in adults, occurring in 10% to 30% of patients with cancer.
2. Incidence may be increasing because of better detection by MRI and as cancer patients live longer.
3. Frequency in decreasing order is lung, breast, melanoma, unknown primary, colon/rectum, renal cell, testicular, and thyroid.
4. Seventy percent to 80% have multiple metastases in CNS (especially melanoma and lung cancer).
5. Most common primary in men is lung, and in women, breast.
6. Melanoma has a strong propensity for the CNS.
7. Prostate cancer commonly metastasizes to skull but rarely to brain parenchyma.
8. Hematologic cancers such as Hodgkin disease (HD) and chronic lymphocytic leukemia (CLL) rarely cause parenchymal metastases.
9. Hemorrhagic metastases include melanoma, choriocarcinoma, renal, thyroid, and lung.

Pathophysiology

1. Metastases reach the brain by hematogenous or directly spread from adjacent structures such as leptomeninges and dura.
2. Eighty percent of metastases are supratentorial at gray-white junction

because of tumor emboli lodging at small vessels.

3. Frequency of structures is proportional to blood flow (cerebral hemisphere [80% to 85%], cerebellum [10% to 15%], brainstem [5%]).
4. Exceptions to this are tumors arising from the pelvis (prostate, uterine, gastrointestinal [GI] tract), which have a predilection for the posterior fossa for unclear reasons.
5. Symptoms are caused by mass effect, edema, destruction of brain structures, increased ICP, cerebral irritation resulting in seizures, and intratumoral hemorrhage.
6. Patients with BM may also have leptomeningeal metastasis (LM) (especially posterior fossa metastases).

Prognosis

1. Generally poor because most patients have active systemic disease.
2. If treated with steroids alone, the median survival is 1 month; RT extends mean survival to 3 to 6 months.
3. Single metastasis treated with surgery or SRS and WBRT have a median survival of 8 to 16 months.
4. Traditionally, prognosis classified according to one of three classes based on recursive partitioning analysis:
   Class I: KPS above 70%; age, younger than 65 years; controlled primary disease, metastases only to brain; median survival, 7.1 months.
   Class II: Patients who do not fall into class I or III; median survival, 4.2 months.
   Class III: KPS lower than 70%; median survival, 2.3 months.
5. Newer diagnosis-specific graded prognostic assessments provides prognostic assessment based upon the primary tumor.

Diagnosis

Clinical Presentation

Most patients present with headaches, behavioral change, and focal neurologic deficits such as weakness, numbness, gait unsteadiness, and visual symptoms; 10% to 20% present with seizures; 5% present with intracranial hemorrhage.

Diagnostic Tests

1. On CT scan, 40% of patients have solitary lesions, 60% have multiple

lesions.

2. Contrast-enhanced MRI is more sensitive and shows a higher percentage with multiple lesions (70% to 80%). Triple-dose-contrast MRI and magnetization-transfer MRI may increase the sensitivity of the test but are not performed routinely.
3. For patients with known primary tumor, restaging studies to determine the extent of systemic disease should be performed (chest, abdomen, pelvic CT, PET scan, bone scan, serum tumor markers, possible spine MRI).
4. For patients without a known primary tumor, a systemic evaluation to find the primary tumor is required as it is generally easier to biopsy a non-CNS site. The focus of the search should be the lung.
   a. Evaluation may include chest, abdomen, and pelvic CT; peripheral blood smear; breast examination; stool guaiac; liver function tests; and urinalysis.
   b. Blood tumor markers and PET scan may also be helpful.

Pathology

1. Depends on primary and generally has the same features as the primary neoplasm.
2. Grossly most are spheroid and well-demarcated but on microscopic examination have a somewhat infiltrative appearance.

Differential Diagnosis

PBTs, especially gliomas and lymphomas, demyelination, abscess, emboli.

Treatment

Supportive Care

1. Patients with symptomatic edema should receive treatment with corticosteroids (10-mg dexamethasone loading dose and then 8 mg twice a day [b.i.d.] or 4 mg four times a day [q.i.d.]).
   a. Oral absorption of dexamethasone is excellent; IV administration is necessary only if the patient cannot take oral medications.
   b. There is some evidence that 4 mg b.i.d. may be as useful as 8 mg b.i.d. The minimum dose of steroids necessary to prevent symptoms from peritumoral edema should be used.
   c. Patients who are likely to require prolonged treatment with

corticosteroids should also receive PCP prophylaxis (e.g., sulfamethoxazole 800 mg/trimethoprim 160 mg [Bactrim DS] daily or three times weekly).

2. Patients with seizures should be treated with standard AEDs. Patients who have never had seizures usually do not require AEDs (possible exceptions are patients with melanoma metastases, which have a predilection for the cortex, and patients with both metastases and LMs).

Surgery

1. High-dose steroids (4 to 6 mg q6 to q12h) are useful in decreasing cerebral edema and should be started when diagnosis is made before surgery. If lymphoma is in the differential, steroids should be avoided.
2. Surgery is recommended with a single metastasis in an accessible location and controlled systemic disease. It provides symptomatic relief and improves survival, local tumor control, and quality of life.
3. Surgery may also be considered in some patients with
   a. Multiple metastases in which there is a large symptomatic lesion
   b. Symptomatic recurrent tumors in patients with controlled systemic disease
   c. Symptomatic radiation necrosis from SRS

Whole-Brain Radiation

1. WBRT (3,000 cGy given in 10 to 20 fractions) is generally considered treatment of choice for patients with multiple metastases (>3 BM) or poor prognosis patients, particularly those with progressive systemic disease.
2. WBRT following surgery or focal RT decreases local recurrence and risk of neurologic death but does not improve overall survival.
3. WBRT may occasionally be useful in patients who have received prior WBRT and developed recurrent metastases. Reirradiation in selected patients may prolong survival by 3 to 4 months.
4. Clinical trials of several radiosensitizers such as RSR13, motexafin gadolinium, chemotherapeutic agents such as temozolomide, and targeted agents such as erlotinib (EGFR inhibitor) have not demonstrated a survival benefit over WBRT alone.

Stereotactic Radiosurgery

1. SRS is used to treat tumors 3 cm in diameter or less. Larger lesions can be

treated with SRT in which the focused radiation is given in several fractions to reduce the incidence of neurotoxicity and radiation necrosis.

2. Advantages of SRS
   - **a.** Noninvasive
   - **b.** Outpatient procedure
   - **c.** Cost-effective compared with surgery
3. Produces good local tumor control (range, 65% to 95%; median, 81%) in radiosensitive tumors such as breast cancer and radioresistant tumors such as melanoma, renal cancer, and sarcoma.
4. Overall median survival of approximately 11 months, but this is dependent on patient selection.
5. Indications
   - **a.** As an alternative to surgery in patients with one to three small (<3 cm in diameter) lesions, which are not amenable to surgery, or in patients who are not surgical candidates
   - **b.** Recurrent metastases in patients with prior RT.
   - **c.** SRS can be considered in selected patients with four or more newly diagnosed BM, especially those with radioresistant pathologies such as sarcoma and renal cell cancer.
6. Complications of SRS
   - **a.** Acute (fewer than 10%): Seizures, headache, edema, nausea, and rarely, hemorrhage.
   - **b.** Subacute: Alopecia, edema, and necrosis.
   - **c.** Chronic (8% to 16%): Seizures, headache, neurologic deterioration (edema/necrosis). Surgery to remove necrosis required in 5% to 20% of patients.

Chemotherapy

1. Systemic chemotherapy is generally not thought to be useful because of
   - **a.** Inability of many drugs to cross BBB.
   - **b.** Tumors causing BM are relatively insensitive to chemotherapy.
   - **c.** Patients with metastases have been treated with chemotherapy for their systemic disease and the brain lesions represents chemoresistant clones.
   - **d.** Tendency in prior studies to use drugs that cross the BBB rather than drugs that are most effective for the particular histology being evaluated.

2. Metastases from chemosensitive tumors often respond to chemotherapy (choriocarcinoma, germ cell tumors, ovarian cancer, and small cell lung carcinoma [SCLC]). Some patients with breast cancer and non–small cell lung carcinoma (NSCLC) may also respond to chemotherapy.
3. Increasing evidence that targeted agents such as erlotinib (EGFR inhibitor) in NSCLC, lapatinib (HER2 inhibitor) in breast cancer, and vemurafenib or dabrafenib (*BRAF* inhibitor) in melanoma have activity in subgroup of patients whose tumor expresses the appropriate molecular targets.
4. Increasing evidence that immunotherapy (ipilimumab) has activity in BMs for melanoma.

Calvarial and Skull Base Metastases

Background

1. Fifteen percent to 25% of all patients with cancer, usually in the setting of bony metastases elsewhere in the body.
2. More than 50% are asymptomatic.
3. Most common tumors are from the breast, lung and prostate, renal, thyroid, and melanoma.

Pathophysiology

1. Hematogenous spread or invasion from skull base tumor.
2. May cause venous sinus thrombosis.

Prognosis

Prognosis is generally good. Most dural metastases can be effectively treated with RT and surgery.

Diagnosis

Clinical Presentation

Local mass, pain, headache, seizures, focal deficits.

Diagnostic Tests

Contrast-enhanced MRI.

Differential Diagnosis

Meningioma.

Treatment

1. RT.
2. Large symptomatic lesions may require surgical resection.
3. Dural metastases are outside the BBB and may respond to systemic agents as well.

Spinal/Vertebral Metastases

Background

1. Epidural spinal cord compression (SCC) is a neurologic emergency.
2. Should be suspected in any patient with cancer with back pain, leg weakness, or numbness.

Epidemiology

1. Epidural SCC occurs in 5% of all patients with cancer (more than 25,000 cases each year in the United States).
2. In 10% to 20% of cases, SCC is the initial manifestation of cancer (especially lung cancer).
3. Most common tumors in adults associated with SCC include lung (15% to 20%), breast (15% to 20%), prostate (15% to 20%), multiple myeloma (5% to 10%), NHL (5% to 10%), renal cell carcinoma (5% to 10%), colorectal carcinoma, and sarcoma.
4. In children, the most common associated tumors are sarcomas (especially Ewing), germ cell tumors, and HD.
5. Sixty percent of symptomatic metastases occur in thoracic spine, 30% in lumbosacral spine, and 10% in cervical spine.
6. Ten percent to 30% of patients will have multiple SCC sites; therefore, imaging of the entire spine is crucial.

Pathophysiology

1. Epidural location account for only 5% to 10%; most occur in vertebral body (60%) or posterior elements (30%).

2. Tumor usually reaches the vertebral column by hematogenous spread. Less commonly, tumor may reach the spinal cord through an intervertebral foramen from a paraspinal mass (especially lymphoma), by direct hematogenous spread to the extradural fat or bone marrow, or by retrograde spread via communication with Batson venous plexus.
3. Compression of spinal cord from tumor and peritumoral edema.

Prognosis

1. Depends on the primary tumor, extent of systemic disease, and severity of symptoms at presentation.
2. Ninety percent to 100% of patients who are ambulatory at onset of treatment remain so at the end of treatment.
3. Only 13% to 30% of patients who are nonambulatory at presentation regain the ability to ambulate following treatment.
4. Early diagnosis and treatment of SCC is therefore crucial for good outcome.
5. Seventy percent to 90% of patients have significant pain relief with treatment.
6. Median survival of patients presenting with SCC is 6 to 10 months and depends on degree of disability, extent of extraspinal metastases, clinical status, and sensitivity of underlying malignancy to RT and chemotherapy.

Diagnosis

Clinical Presentation

1. At presentation, 95% of patients with SCC have back pain.
2. Pain precedes SCC by weeks to months.
3. Unlike pain from osteoarthritis, pain from SCC tends to be worse with recumbency and awaken the patient at night, possibly as a result of distention of the epidural venous plexus.
4. Seventy-five percent have neurogenic weakness, sensory level may be present. In general, sensory complaints and findings are less prominent than motor complaints and findings.
5. SCC involving the spinal cord (which usually ends at the level of L1) produces upper motor neuron weakness, hyperreflexia, extensor plantar responses, and sensory loss. The sensory level is usually several spinal segments lower than the true level of SCC. Radicular sensory loss or loss of

reflexes tends to be a more reliable indicator of the level of SCC.

6. Tumors that compress the cauda equina (below L1) causes pain, weakness, and sensory loss in a radicular distribution; decreased reflexes; and flexor plantar responses.
7. Patients with advanced SCC develop urinary retention with overflow and progress to paraplegia.
8. Patients with cervical cord lesions may have Lhermitte sign, which is an electric sensation in the back and extremities produced by flexion of the neck.

Diagnostic Tests

1. Spinal radiographs show evidence of metastasis in 80% to 90% of patients. Plain films have been falsely negative in 10% to 17% of patients.
2. Bone scan is more sensitive than plain radiographs and is occasionally used.
3. MRI with gadolinium is the imaging modality of choice to diagnose epidural SCC. Because 10% to 30% of patients have more than one SCC site, the entire spine must be imaged.
4. CT myelography may be helpful in patients who cannot have MRI. Myelography carries a small risk of exacerbating a neurologic deficit caused by pressure shifts in the event of complete spinal subarachnoid block (spinal coning).

Differential Diagnosis

1. Benign disorders: Degenerative spine disorders, osteomyelitis, epidural abscess, hematomas, transverse myelitis, granulomatous disorders, vascular malformation, epidural lipomatosis, and extramedullary hematopoiesis.
2. Cancer-related disorders: LMs, spinal cord metastases (often cause hemicord syndrome [Brown–Sequard syndrome]), radiation myelopathy, chemotherapy-related myelopathy, paraneoplastic myelopathy, and neoplastic or radiation plexopathy.

Treatment

Supportive Care

1. Corticosteroids: Controversy regarding the dose of corticosteroids. No definite evidence that an initial bolus of 100 mg of dexamethasone is more effective than 10 mg. Higher doses are associated with greater frequency of

side effects. For most patients, 10-mg bolus of dexamethasone and then 16-mg/d maintenance in divided doses is adequate. A 100-mg bolus and 96-mg/d maintenance may be reasonable for patients who are paraplegic. Patients receiving high doses of dexamethasone should receive H_2-blockers or proton pump inhibitors.

2. Nonsteroidal anti-inflammatory medications and opiates for pain control.
3. Stool softeners and laxatives to prevent constipation.
4. DVT prophylaxis in patients who are not ambulatory.

Radiation Therapy

1. RT is the preferred treatment and should be started as soon as possible after SCC is diagnosed. No evidence that laminectomy is more effective than RT.
2. Usually give 10 fractions of 300 cGy to involved area with a margin of one to two vertebral bodies.
3. For patients who have received prior irradiation for SCC with good results, reirradiation for recurrent SCC may provide useful palliation.

Surgery

1. Surgery is indicated if there is spinal instability, tissue diagnosis is needed, tumor is radioresistant, or for patients who have received prior RT.
2. Anterior decompression is used to resect tumor and stabilize the spine but is associated with greater morbidity. Randomized study suggests that surgical resection via anterior decompression and RT may be more effective than RT alone in selected patients.

Chemotherapy

Can be given for chemosensitive tumors such as lymphoma and SCLC.

Hormonal Therapy

May occasionally be useful in hormone-responsive tumors such as prostate and breast cancer, although RT remains the treatment of choice for these tumors.

Leptomeningeal Metastases

Background

1. LM is defined as infiltration of the leptomeninges by systemic cancer. It is

also referred to as carcinomatous/neoplastic meningitis or leptomeningeal carcinomatosis.
2. Should be considered in any patient with multifocal symptoms and signs in the neuraxis.

Epidemiology

1. LM is an increasingly common complication of cancer and occurs in 5% of patients with solid tumors and more than 10% of patients with leukemias and lymphomas.
2. One-third have concomitant parenchymal BMs.
3. Most common causes are breast cancer, lung cancer, NHL, malignant melanoma, GI neoplasms, and acute leukemias.
4. LM is very common in acute lymphoblastic leukemia (ALL) and some types of lymphomas (e.g., Burkitt lymphoma). Prophylactic CNS treatment is generally given in these conditions.

Pathophysiology

1. Tumor cells travel to CSF space via hematogenous route, direct extension from BMs, venous route (from bone marrow), and perineural spread.
2. Once these cells reach the CSF, they are disseminated throughout the neuraxis by the constant flow of CSF.
3. Cause symptoms by direct invasion of neural structures, alternation of metabolism in CSF, and obstruction of CSF flow.

Prognosis

1. Generally poor response to treatment. Many patients also have uncontrolled systemic disease.
2. In untreated patients, disease is progressive and leads to death within 6 to 8 weeks because of progressive neurologic dysfunction.
3. Early, aggressive treatment can occasionally improve neurologic symptoms and quality of life, especially in patients with lymphoma/leukemia (80%) and breast cancer (50%).
4. Melanoma and lung cancer tend to have a poor response.
5. Even with optimal treatment, median survival is 2 to 4 months and patients often die of systemic disease.

Diagnosis

Clinical Presentation

1. Usually multifocal symptoms and signs in the neuraxis, including subacute altered mental status, headaches, seizures, papilledema, cranial neuropathies (especially CNs III, VI, and VII), polyradiculopathies and occasionally, bladder and bowel dysfunction.
2. Can be fulminant in ALL.

Diagnostic Tests

1. MRI of the brain and spine with gadolinium may show nodular or diffuse enhancement of the leptomeninges, dura or nerve roots, and hydrocephalus.
2. LP for CSF cytology can confirm the diagnosis; however, several LPs may be needed (85% sensitive after three LPs).
3. An abnormal CSF profile (elevated CSF protein, decreased glucose, and lymphocytic pleocytosis) is present in 95% of patients and may be sufficient in the appropriate clinical context in the absence of positive CSF cytology.
4. Reactive processes can sometimes be mistaken for malignant lymphocytes.
5. PCR for immunoglobulin gene rearrangement studies for lymphoma may be helpful.
6. Leptomeningeal biopsy may be needed if CSF is nondiagnostic and no primary tumor is identified.
7. CSF tumor markers are usually not very sensitive or specific. Carcinoembryonic antigen (CEA) may be useful for carcinomas, cancer antigen 125 (CA-125) for ovarian cancer, cancer antigen 15-3 (CA 15-3) for breast cancer, melanin for melanoma, β-hCG for choriocarcinoma and germ cell tumors, AFP for teratoma and yolk sac tumors.

Differential Diagnosis

Inflammatory (vasculitis, paraneoplastic), demyelinating (multiple sclerosis), granulomatous (Wegener, sarcoidosis), infectious (bacterial, viral, Lyme disease, tuberculosis, cryptococcus, cysticercosis), primary leptomeningeal neoplasms, and intracranial hypotension following LP.

Treatment

1. Goals of treatment in patients with LMs are to improve or stabilize the

neurologic status of the patient and to prolong survival.

2. Corticosteroids occasionally relieve symptoms transiently until definitive treatment.
3. Standard therapy involves RT to symptomatic sites of the neuraxis and to disease visible on neuroimaging studies. Intrathecal chemotherapy may have a role in some patients.
4. Treatment should be determined on the basis of the patient's functional status (KPS) and patients stratified into "poor-risk" and "good-risk" groups.
   a. The poor-risk group includes patients with a low KPS; multiple, serious, fixed neurologic deficits; and extensive systemic disease with few treatment options.
   b. The good-risk group includes patients with a high KPS, no fixed neurologic deficits, minimal systemic disease, and reasonable systemic treatment options.
5. Patients in the poor-risk group are usually offered supportive care measures including analgesics for pain, increased ICP, or leptomeningeal irritation. RT may occasionally be administered to symptomatic sites.
6. Good-risk patients should also receive appropriate supportive care measures as described earlier, along with radiation to symptomatic sites and to areas of bulk disease identified on neuroimaging studies. In addition, intrathecal or intraventricular (using a surgically implanted subcutaneous reservoir and ventricular catheter [SRVC]) chemotherapy is administered. Initially, intrathecal chemotherapy is usually given by LP, and the SRVC is placed later to administer the drugs more conveniently.
7. Because of CSF flow abnormalities in these patients, a CSF flow study (e.g., ^{111}I-DTPA) allows detection of flow abnormalities, which may predict impaired targeting of areas and increased toxicity (leukoencephalopathy).
8. Intrathecal methotrexate is administered twice weekly at a dose of 10 to 12 mg. Oral leucovorin (10 mg every 12 hours for six doses) is sometimes administered to prevent myelosuppression and mucositis. Once the CSF clears, the drug is administered less frequently.
9. Intrathecal thiotepa (10 mg twice a week) can be effective in solid tumors.
10. Cytarabine (AraC, 50 mg twice a week) is effective for lymphomatous and leukemic meningitis and can be effective in some solid tumors.
    a. A liposomal encapsulated formulation of cytarabine (DepoCyt) (50 mg

every 2 weeks) allows patients with lymphomatous meningitis to be treated every 2 weeks rather than twice weekly and appears to be more effective than AraC.

b. High-dose systemic cytarabine (3 g/m^2 q12h) penetrates well into the CNS and is sometimes used in patients with leukemia or lymphoma who have both systemic and CNS disease.

1. Systemic high-dose methotrexate may be considered in patients with LM from solid tumors.
2. For patients with EGFR mutant NSCLC, pulsatile erlotinib can help treat LM even in patients who have previously received standard dose erlotinib.
3. Treatment duration is dependent on response. Should follow clinically and with CSF cytology.
4. Steroids are recommended during treatment to reduce headaches caused by the chemical meningitis.

PARANEOPLASTIC SYNDROMES

Background

1. In patients with cancer, paraneoplastic syndromes of the nervous system are disorders that are not caused by the direct effects of the cancer itself or its metastases or by indirect effects such as infections, metabolic disturbances, nutritional deficiencies, or cerebrovascular disorders, or by the effects of antineoplastic therapies.
2. Although neurologic complications are common in patients with cancer, most are caused by metabolic disarray, nutritional deficiencies, and complications related to cancer treatment. True paraneoplastic syndromes are rare, occurring in fewer than 1% of patients with cancer.
3. Paraneoplastic disorders may fall into one of four categories:
   a. Neuromuscular paraneoplastic disorders such as myasthenia gravis (MG) with pathogenic antibodies that direct attack the neuromuscular junction or peripheral nerve membrane proteins. These disorders respond to immunotherapy.
   b. Classic paraneoplastic syndromes such as anti-Hu involving T-cell

processes and strongly associated with cancer. These disorders may not respond to immunotherapy.

c. Antibodies against intracellular synaptic proteins such as GAD65 and amphiphysin, unclear whether the antibodies are directly pathogenic and/or represent at T-cell response

d. Antibodies against cell surface proteins such as *N*-methyl-D-aspartate (NMDA) where antibodies are pathogenic and where the disorder can improve with immunotherapy.

Pathophysiology

1. Autoimmune-mediated injury to the nervous system accounts for most cases.
2. Antibodies and cellular immunity directed against tumor antigens also react with similar antigens in neuronal tissues in the CNS and PNS, resulting in neurologic injury.
3. Autoimmune pathophysiology is well documented only for a few paraneoplastic syndromes: Lambert–Eaton myasthenic syndrome (LEMS), MG, neuromyotonia.
4. Autoantibodies can be detected in serum and CSF. Most react with both tumor and neurons.
5. Affected tissues usually have inflammatory infiltrate, cell loss, microglial proliferation, and gliosis present.

Significance

1. Paraneoplastic neurologic syndromes account for a high percentage of certain disorders (70% of LEMS, 50% of subacute cerebellar degeneration, 50% of opsoclonus–myoclonus in children, 20% of opsoclonus–myoclonus in adults, 20% of subacute sensory neuronopathy).
2. Frequently occur before diagnosis of the underlying cancer. Recognition of these syndromes may lead to the diagnosis of the underlying tumor at an early stage.
3. Usually produce significant neurologic disability.
4. Often mistaken for metastatic disease.
5. Provide information concerning autoimmune disorders and tumor immunology.
6. In some patients with cancer, paraneoplastic antibodies such as anti-Hu can be found in asymptomatic patients suggesting that these antibodies are

markers but not pathogenic.

Prognosis

1. Patients can develop profound neurologic disability. Response of neurologic deficits to treatment is often poor in patients with autoantibodies to intracellular antigens (anti-Hu, anti-Yo, etc.). Prognosis is better and treatment may be effective in patients with autoantibodies to extracellular antigens (LEMS, MG, anti-NMDA).
2. Course of underlying neoplasm often indolent, possibly because of antitumor immunologic response.

Diagnosis

Clinical Presentation

Presents as subacute disorder (over several weeks) affecting nervous system. Can occur from months to years before discovery of the malignancy. See the following section for specific features of individual paraneoplastic disorders.

Diagnostic Tests

1. Appropriate antibody testing should be performed depending on the clinical presentation. Antibodies are present in both serum and CSF, but titers are higher in the CSF.
2. CSF can show lymphocytic pleocytosis, elevated protein level, elevated IgG level, and oligoclonal bands or may be normal.
3. MRI is usually normal but may show abnormal T2 signal in the affected areas and allows metastatic disease to be excluded.
4. Body CT scans and occasionally PET scans may help locate primary tumor.

Differential Diagnosis

Direct infiltration by primary tumor, metastatic disease, reversible nutritional deficiencies, drug toxicity, cerebrovascular disease, and infections.

Treatment

Some respond to treating the underlying cancer. Most paraneoplastic syndromes with autoantibodies directed to intracellular antigens do not respond to treatment. Paraneoplastic syndromes with autoantibodies to extracellular antigens such as anti-NDMA do respond to steroids, IV

immunoglobulins (IVIGs), or plasmapheresis, or other forms of immunosuppression.

Paraneoplastic Syndromes of the Brain and Cerebellum

Cerebellar Degeneration

1. Subacute cerebellar syndrome with truncal and appendicular ataxia progressing over weeks or months. Dysarthria, diplopia, vertigo, nystagmus (Tables 6-2 and 6-3).
2. Usually associated with SCLC, HD, breast cancer, and gynecologic malignancies.
3. Autoantibodies: Anti-Yo (breast and gynecologic malignancies), anti-Tr (HD), anti-Hu (SCLC), anti-Ri (breast cancer), anti-voltage-gated calcium channel (anti-VGCC—often with concurrent Lambert–Eaton syndrome).
4. Poor response to antitumor therapy, immunosuppression with IVIG, or plasmapheresis.

Table 6-2 Paraneoplastic Syndromes Affecting the Nervous System

Paraneoplastic syndromes of the brain and cerebellum
Cerebellar degeneration
Encephalomyelitis (limbic encephalitis, brainstem encephalitis, myelitis)
Opsoclonus–myoclonus
Visual paraneoplastic syndromes
Cancer-associated retinopathy
Melanoma-associated retinopathy
Optic neuritis
Paraneoplastic syndromes of the spinal cord
Stiff man syndrome
Necrotizing myelopathy
Motor neuron syndromes (amyotrophic lateral sclerosis, subacute motor neuronopathy)
Paraneoplastic syndromes of the peripheral nervous system

- Paraneoplastic sensory neuronopathy
- Acute polyradiculoneuropathy (Guillain–Barré syndrome)
- Brachial neuritis
- Vasculitis of the nerve and muscle
- Subacute or chronic sensorimotor peripheral neuropathy
- Sensorimotor neuropathies associated with plasma cell dyscrasias
- Autonomic neuropathy
- Neuromyotonia (Issacs syndrome)

Paraneoplastic syndromes of the neuromuscular junction

- Lambert–Eaton myasthenic syndrome
- Myasthenia gravis
- Paraneoplastic syndromes of muscle
- Polymyositis/dermatomyositis
- Acute necrotizing myopathy
- Carcinoid myopathy
- Cachectic myopathy

Table 6-3 Antibodies Associated with Paraneoplastic Neurologic Syndromes

Antibody	Antigen(s)	Associated Cancer	Syndrome
Anti-Hu (ANNA-1)	Intracellular (HuD and related nuclear proteins)	SCLC, other	Focal encephalitis, myelitis, encephalomyelitis, sensory neuronopathy, peripheral neuropathy
Anti-Yo (PCA-1)	Intracellular cdr2	Gynecologic, breast	Cerebellar degeneration
Anti-Ri (ANNA-2)	Intracellular NOVA proteins	Breast, gynecologic, SCLC	Cerebellar ataxia, opsoclonus, brainstem encephalitis
Anti-Tr (DNER)		Hodgkin lymphoma	Cerebellar degeneration
Anti-CV2 or anti-	Intracellular neuronal	SCLC, other	Focal encephalitis,

CRMP1 to CRMP5	protein critical for growth cone function		myelitis, encephalomyelitis, cerebellar degeneration, peripheral neuropathy
Anti-Ma proteins[a]	Intracellular PNMA1 and PNMA2	Testicular germ cell tumors and other cancers	Limbic, brainstem encephalitis, cerebellar degeneration
Anti-NMDA	Ionotropic glutamate receptor	Ovarian teratoma	Limbic encephalitis
Anti-AMPA	Ionotropic glutamate receptor	Lung, breast, thymus	Limbic encephalitis, psychiatric manifestations
Anti-GABA-B	Metabotropic inhibitory receptor	SCLC	Limbic encephalitis with seizures, opsoclonus, ataxia
Anti-GABA-A	Ionotropic inhibitory receptor	Hodgkin lymphoma	Refractor status epilepticus or epilepsia partialis continua
Anti-GAD65	Intracellular synaptic enzyme that synthesizes GABA	Usually none	Cerebellar degeneration, stiff person syndrome
Antiamphiphysin	Intracellular synaptic antigen amphiphysin	Breast, SCLC	Stiff person syndrome, encephalomyelitis
Anti-Caspr2	Cell adhesion molecular that organizes potassium channels on axons	Thymoma	Neuromyotonia, encephalitis, Morvan syndrome
Anti-LGI1	Secreted synaptic protein that organizes AMPA and potassium channels at CNS synapses	Usually none	Encephalitis, faciobrachial dystonic seizures, myoclonus
Anti-mGluR1	Metabotropic glutamate receptor in the cerebellum	Hodgkin lymphoma, prostate	Cerebellar degeneration
Anti-VGCC[b]	Neuromuscular junction	SCLC	LEMS, cerebellar degeneration
Antiacetylcholine	Neuromuscular	Thymoma	Myasthenia gravis

	receptor[b]	junction

[a]Antibodies Ma2 (also called anti-Ta antibodies) usually associated with limbic and brainstem encephalitis and germ cell tumors. Antibodies directed at Ma1 usually associated with brainstem encephalitis, cerebellar degeneration, and several types of cancer (lung, breast, ovary, etc.).

[b]These antibodies are also identified in the nonparaneoplastic form of the syndrome.

SCLC, small cell lung cancer; NMDA, *N*-methyl-D-aspartate; GABA, γ-aminobutyric acid; CNS, central nervous system; LEMS, Lambert–Eaton myasthenic syndrome.

Paraneoplastic Encephalomyelitis

1. Paraneoplastic encephalomyelitis (PEM) is a specific neurologic syndrome dependent on predominant site of inflammation (cortical encephalitis, limbic encephalitis, brainstem encephalitis, cerebellitis) but can involve multiple sites within the nervous system.
2. Frequently associated with subacute sensory neuronopathy, myelitis, and autonomic dysfunction.
3. Limbic encephalitis characterized by subacute confusion, memory loss, psychiatric symptoms, and seizures.
4. Pathology characterized by perivascular inflammatory infiltrate and neuronal loss.
5. MRI may occasionally show increased T2 signal in affected area.
6. Usually associated with SCLC (anti-Hu, anti-CV2, anti-CRMP 5), testicular cancer (anti-Ma2), and a variety of tumors (anti-Ma1).
7. Some patients respond to treatment of cancer. Rare responses to immunosuppression.
8. Antibodies to NMDA receptors associated with severe limbic encephalitis with encephalopathy and psychiatric symptoms. Several underlying neoplasms have been linked to this condition, especially ovarian teratomas. Removal of the under tumor can lead to significant improvement.

Opsoclonus–Myoclonus

1. Subacute opsoclonus, myoclonus, ataxia.
2. Usually associated with neuroblastoma in children; breast cancer, SCLC in adults.
3. Anti-Ri (breast and gynecologic cancer), anti-Hu, anti-Yo, anti-Ma2.
4. May respond to treatment of tumor, steroids, and IVIG. Prognosis better in children.

Paraneoplastic Syndromes of the Eye

Carcinoma-Associated Retinopathy

1. Carcinoma-associated retinopathy (CAR) is subacute onset of episodic visual obscuration, photosensitivity, night blindness, impaired color vision, and light-induced glare.
2. Examination shows decreased visual acuity, impaired color vision, scotomas, attenuated retinal arterioles.
3. Electroretinogram (ERG) demonstrates reduced or flat photopic and scotopic responses, consistent with dysfunction of the cone and rod photoreceptors.
4. Usually precedes diagnosis of underlying cancer (SCLC).
5. Serum may have antibodies against retinal photoreceptor antigens such as recoverin.
6. Prognosis poor. Anecdotal reports of improvement with steroids, plasmapheresis, and IVIG.

Melanoma-Associated Retinopathy

1. Melanoma-associated retinopathy (MAR) affects patients with melanoma.
2. Patients present with photopsias and progressive visual loss.
3. ERG reveals a markedly reduced B wave in the presence of a normal dark-adapted A wave.
4. Serum contains antibody against bipolar cells of retina.
5. Response to treatment is usually poor.

Optic Neuritis

Usually associated with PEM but occasionally may be only finding.

Paraneoplastic Syndromes of the Spinal Cord

Stiff Person Syndrome

1. Characterized by rigidity and stiffness of axial musculature and painful spasms.
2. Electromyography (EMG) shows continuous motor unit activity, improved

with diazepam.

3. Associated with antibodies to γ-aminobutyric acid (GABA)-glycine synapses; presynaptic (anti-GABA, antiamphiphysin); postsynaptic (antigephyrin).
4. Most commonly associated with breast, lung, and colon cancer and HD.
5. May respond to treatment of the underlying tumor, steroids, diazepam, and other drugs that enhance GABA-ergic transmission (baclofen, sodium valproate, and vigabatrin). Role of IVIG and plasmapheresis is unclear.

Myelitis (Usually Part of Paraneoplastic Encephalomyelitis)

1. Acute necrotizing myelopathy.
   - **a.** Acute or subacute myelopathy resulting in death.
   - **b.** Associated with lymphoma and lung cancer.
   - **c.** No known therapy.
2. ALS.
   - **a.** Association with cancer controversial.
   - **b.** Possibly associated with lymphoma, breast cancer, SCLC.
3. Subacute motor neuronopathy.
   - **a.** Subacute lower motor neuron weakness, usually affecting lower extremities.
   - **b.** Associated with HD and NHL.
   - **c.** Improves spontaneously.
   - **d.** No specific treatment except for physical therapy.

Paraneoplastic Syndromes of the Dorsal Root Ganglia and Nerve

Subacute Sensory Neuronopathy

1. Subacute sensory loss, often associated with painful paresthesias and dysesthesias.
2. All sensory modalities affected. May be asymmetric.
3. Patients frequently have sensory ataxia and pseudoathetosis.
4. Nerve conduction studies (NCS) show small amplitude or absent sensory nerve action potentials with normal motor potentials and F waves.

5. Often associated with encephalomyelitis and autonomic dysfunction.
6. Associated with SCLC and anti-Hu antibody.
7. Pathologically there is inflammation of dorsal root ganglion and neuronal loss.
8. Occasional response to steroids and treatment of underlying tumor. Response to other forms of immunosuppression is poor.

Peripheral Neuropathies

Subacute Axonal or Demyelinating Neuropathies

1. Difficult to differentiate from neuropathies caused by nutritional and metabolic causes and by chemotherapy.
2. Some neuropathies develop before or at the time of diagnosis of the cancer.
3. May respond to steroids or IVIG.

Vasculitis of the Nerve and Muscle

1. Painful, asymmetric, or symmetric sensorimotor polyneuropathy or mononeuritis multiplex.
2. Associated with SCLC and NHL.
3. Erythrocyte sedimentation rate (ESR) and CSF protein levels are usually elevated.
4. Nerve biopsy shows intramural and perivascular inflammatory infiltrate, usually without necrotizing vasculitis. Muscle biopsy may also show vasculitis.
5. May respond to treatment of tumor and immunosuppression (steroids, cyclophosphamide).

Peripheral Neuropathies of Monoclonal Gammopathies

Associated with multiple myeloma, osteosclerotic myeloma, Waldenström macroglobulinemia, B-cell NHL, and CLL (see Chapter 9).

Multiple Myeloma

1. Five percent to 10% of patients with multiple myeloma have symptomatic neuropathy; one-third have electrophysiologic evidence of neuropathy.
2. Patients may develop mild sensorimotor axonal neuropathy, pure sensory neuropathy, subacute or chronic demyelinating neuropathy, or amyloid neuropathy.

3. Treatment of myeloma often does not improve neuropathy.

Osteosclerotic Myeloma

1. More than 50% of patients have chronic demyelinating polyneuropathy with motor predominance.
2. May be part of POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *M* component, and *s*kin changes).
3. Treatment of sclerotic lesions often leads to improvement in neuropathy.

Waldenström Macroglobulinemia

1. Five percent to 10% of patients have neuropathy resulting from IgM M-protein against myelin-associated glycoprotein (MAG) or various gangliosides.
2. Symmetric sensorimotor polyneuropathy; predominant involvement of large sensory fibers.
3. NCS show slow conduction velocities and prolonged distal motor and sensory latencies consistent with demyelinating neuropathy.
4. Treatment can improve neuropathy and includes therapy for underlying Waldenström macroglobulinemia (chlorambucil, cyclophosphamide, fludarabine) and IVIG or plasmapheresis.

Guillain–Barré Syndrome and Brachial Plexopathy

1. Associated with HD and NHL.
2. Identical clinically to Guillain–Barré syndrome (GBS) and brachial plexopathy from nonneoplastic causes.
3. Responds to standard treatments for GBS (IVIG, plasmapheresis) and brachial plexopathy (steroids).

Neuromyotonia (Isaacs Syndrome)

1. Autoimmune basis not well understood but can be associated with autoantibodies against the voltage-gated potassium channel complex, particularly contactin-associated protein-like 2 (Caspr2).
2. Patients experience cramps, muscle weakness, hypertrophic muscles, excessive sweating.

3. EMG shows fibrillations, fasciculation, continuous discharges.
4. Associated with thymoma, HD, SCLC, plasmacytoma.
5. Phenytoin, carbamazepine, and plasmapheresis produce symptomatic relief.

Autonomic Neuropathy

1. Usually associated with PEM.
2. Associated with SCLC (anti-Hu antibodies), HD, NHL, carcinoid tumor of the lung, pancreatic, and testicular cancer.
3. Orthostatic hypotension, dry mouth, erectile dysfunction, sphincter dysfunction, esophageal and GI dysmotility, and cardiac dysrhythmia.
4. Can also be seen in patients with thymoma who have antibodies to the acetylcholine receptors (AChRs) found in autonomic ganglia.

Paraneoplastic Syndromes of the Neuromuscular Junction

Lambert–Eaton Myasthenic Syndrome

1. Caused by antibodies to presynaptic VGCCs impairing acetylcholine release from presynaptic motor terminal.
2. Fifty percent to 70% of patients have underlying cancer, usually SCLC.
3. Neurologic symptoms usually precede or coincide with diagnosis of cancer.
4. Symptoms include fatigue, leg weakness, muscle aches, vague paresthesias.
5. Dry mouth and other autonomic symptoms are common.
6. CNS symptoms are usually mild and transient (usually diplopia).
7. Examination shows proximal muscle weakness, absent reflexes, sluggishly reactive pupils, and occasionally, ptosis.
8. Brief exercise may potentiate reflexes and improve strength transiently.
9. NCS show small-amplitude compound muscle action potential (CMAP).
   a. At slow rates of repetitive nerve stimulation (2 to 5 Hz), decremental response more than 10% is seen.
   b. At fast rates (20 Hz or greater), facilitation occurs (more than 100%).
   c. Maximal muscle contraction results in increased amplitude of CMAP.
   d. Facilitation of more than 100% in multiple muscles or more than 400% in a single muscle diagnostic of LEMS.

e. Presence of antibodies to P/Q-type VGCC in serum is also diagnostic of LEMS.
f. Treatment involves therapy for underlying cancer; 3,4-diaminopyridine, pyridostigmine, and immunosuppression with IVIG, plasmapheresis, prednisone, or azathioprine may also be helpful.

d. May have associated cerebellar degeneration with ataxia.

Myasthenia Gravis

1. Ten percent of patients with MG have thymoma; one-third of patients with thymoma develop myasthenia.
2. Patients have antitintin and AChR antibodies.
3. Treatment consists of removal of thymoma, anticholinesterases, and immunosuppression.

Paraneoplastic Syndromes of the Muscle

Polymyositis/Dermatomyositis

1. Polymyositis is caused by cell-mediated cytotoxic mechanisms; dermatomyositis is caused by humoral-mediated vasculopathy.
2. Polymyositis may be associated with graft versus host disease (GVHD).
3. Association of cancer with polymyositis is controversial.
4. Approximately 29% of patients with dermatomyositis have an underlying cancer, mostly commonly breast, ovary, or bladder.
5. Ovarian and breast cancer in women; lung and GI cancer in men.
6. Patients present with subacute proximal muscle weakness (especially neck flexors, pharyngeal, and respiratory muscles). In dermatomyositis, there may be purplish discoloration of eyelids (heliotrope rash) with edema, and erythematous, scaly lesions over knuckles.
7. Serum creatine kinase level is elevated. EMG shows myopathic changes.
8. Course of myositis is independent of underlying cancer.
9. Treatment of tumor may or may not improve neurologic syndrome. Steroids, immunosuppressants, and IVIG may be helpful.

Acute Necrotizing Myopathy

1. Rapidly progressive myopathy leading to death in weeks. Rare.
2. Associated with many cancers, especially SCLC.

NEUROLOGIC COMPLICATIONS OF CANCER TREATMENT

Chemotherapy

Background

1. Neurologic complications of chemotherapy can affect the CNS and PNS.
2. Can be the dose-limiting factor in many cases.
3. Neurotoxicity often is increased when combined with RT.
4. Very common in patients undergoing treatment.

Pathophysiology

Cause symptoms by a variety of mechanisms but mostly caused by direct toxic nervous system damage.

Prognosis

Usually good, most symptoms stabilize or improve after stopping drug.

Diagnosis

Location

Injury anywhere along neuraxis depending on drug.

Clinical Presentation

1. Neurologic symptoms depend on agent and route of administration.
2. Acute encephalopathy: Ifosfamide, procarbazine, 5-fluorouracil (5-FU), methotrexate (high dose), cisplatin, cytarabine, interferons, interleukin-2, corticosteroids.
3. Seizures: Busulfan (high dose), ifosfamide, interferon.
4. Vasculopathy and strokes: High-dose methotrexate, asparaginase, bevacizumab.

5. Chronic encephalopathy: Methotrexate, cytarabine, interferon.
6. Reversible posterior encephalopathy syndrome associated with a variety of targeted agents, especially those targeting VEGF such as bevacizumab.
7. Methotrexate and cytarabine increase risk of leukoencephalopathy when given with RT.
8. Cerebellar dysfunction: Cytarabine (high dose), 5-FU, ifosfamide.
9. Cranial neuropathies: Cisplatin, vincristine.
10. Myelopathy/meningitis: Intrathecal methotrexate, cytarabine, and thiotepa.
11. Peripheral neuropathy: Cisplatin, oxaliplatin, vinca alkaloids, paclitaxel, docetaxel, thalidomide, bortezomib.
12. Myopathy: Corticosteroids.

Diagnostic Tests

MRI, EMG/NCS, electroencephalogram (EEG), and routine blood work may be needed depending on symptomatology.

Pathology

Depends on agent and symptoms but usually diagnosed on clinical grounds.

Differential Diagnosis

Paraneoplastic disorders, metastases, metabolic encephalopathy, and radiation toxicity.

Treatment

1. Usually need to discontinue chemotherapy.
2. Supportive care.
3. Randomized data supports the use of duloxetine for neuropathic pain from chemotherapy-induced peripheral neuropathy.

Radiation Therapy

Background

1. RT may affect the nervous system by (a) direct injury to neural structures included in the radiation portal or (b) indirectly by damaging blood vessels or endocrine organs necessary for functioning of the nervous system or by producing tumors.

2. RT complications typically divided into acute (hours or days), early delayed (2 weeks to 4 months), and late delayed (4 months to several years) reactions.
3. Very common in treated patients and increases with increasing duration of survival.

Pathophysiology

1. Injury to glia, neurons, blood vessels, and stem cells.
2. Neurotoxicity is dependent on the total dose, fraction size, length of treatment, and the total volume of the involved nervous system in addition to length of survival, comorbid factors (diabetes, hypertension, older age), and concomitant chemotherapy.

Prognosis

Generally poor as these are irreversible processes.

Diagnosis

Usually clear from history but must repeat imaging studies to rule out recurrent tumor and in the case of radiation necrosis, a biopsy or resection may be needed.

Treatment

1. Supportive care with steroids.
2. May require surgery in case of radiation necrosis and tumors.
3. Bevacizumab may be helpful for brain radiation necrosis.
4. Anecdotal reports of benefit with anticoagulation and hyperbaric oxygen but efficacy unproven.

Sequelae of Radiation Therapy to the Brain

1. Acute reactions
   a. May occur when large fractions of radiation (usually >300 cGy) are given to patients with cerebral edema and increased ICP.
   b. Within hours of RT, the patients develop evidence of increased ICP with headache, nausea, vomiting, somnolence, and exacerbation of signs and symptoms caused by the lesion. Rarely, cerebral herniation and death may

occur.

c. Usually respond to corticosteroids, and if necessary, mannitol and diuretics.

d. Can often be avoided by starting patients on steroids before beginning RT and initiating RT with fractions of 200 cGy or less if patients have large amounts of edema.

2. Early delayed reactions

a. Several weeks to several months following radiation.

b. Possibly related to transient demyelination resulting from injury to oligodendrocytes.

c. Characterized by somnolence, headache, nausea, vomiting, fever, exacerbation of neurologic deficits, and transient deterioration in cognitive function.

d. When the posterior fossa is irradiated, ataxia, dysarthria, diplopia, and nystagmus may occur.

e. MRI and CT scan findings are usually normal.

f. Corticosteroids can be helpful, but most patients recover spontaneously within 6 to 8 weeks. Very rarely, the condition can be progressive and result in death.

g. Recognition of the early delayed reaction is important because it is usually transient and the appearance of new symptoms at this time does not necessarily indicate treatment failure or the need for a change in therapy.

3. Late delayed reaction

a. Develops months to years after radiation and affects white matter more than gray matter.

b. Etiology is unknown but hypothesis include

1) Injury to small and medium vessels and tissue necrosis from ischemia

2) Radiation injury to glial cells, especially oligodendrocytes, leading to demyelination

3) Injury to neural stem cells

4) Autoimmune damage

c. Several syndromes are recognized.

4. Leukoencephalopathy

a. Delayed encephalopathy (leukoencephalopathy) presents with progressive dementia, apathy, gait disturbance, and incontinence of urine. MRI shows

cerebral atrophy and white matter changes without recurrent tumor or radiation necrosis.

b. Symptoms occur 6 to 36 months or more after treatment. Large daily fractions increase risk.

c. Communicating hydrocephalus may be caused by radiation-induced obliteration of the arachnoid granulations. Some patients improve after ventricular shunting.

5. Radiation necrosis

a. Related to radiation dose, fraction size, and duration of therapy; usually occurs in radiation field.

b. Delayed by 6 months to several years (peak, 18 months) after RT.

c. Interstitial brachytherapy and radiosurgery associated with high risk for radiation necrosis.

d. May also occur if brain is included in the radiation field of head and neck neoplasm.

e. Symptoms are similar to those of an expanding recurrent tumor.

f. MRI/CT usually not able to distinguish recurrent tumor from radiation necrosis.

g. PET, thallium/technetium SPECT, and MRS may help distinguish recurrent tumor from radiation necrosis.

h. High-dose steroids can temporarily palliate the symptoms.

i. Surgical resection of necrotic mass may be needed.

j. A small randomized study suggests benefit from bevacizumab.

Secondary Involvement of the Brain by Irradiation

1. Vascular effects

a. Stenosis of both intra- and extracranial vessels may occur months or years after RT, resulting in transient ischemic attacks and strokes. Pathology is similar to that of atherosclerosis. In general, the larger the diameter of the vessel involved, the longer the latency between the RT and the vasculopathy. Treatment is identical to that for cerebrovascular disease from typical atherosclerosis. When extracranial vessels are involved, endarterectomy may occasionally be of benefit, but the surgery may be technically difficult.

b. Small-vessel disease may also complicate RT.

c. Vascular abnormalities are especially common in children and have a predilection for the supraclinoid portion of the internal carotid artery. Occlusion of the vessel is sometimes associated with Moyamoya changes.

d. Radiation-induced telangiectasia, Moyamoya, cavernomas, angiomatous malformations, and aneurysms occur rarely and may lead to delayed hemorrhage in the brain.

e. Cervical RT may rarely lead to carotid rupture.

2. Radiation-induced tumors

a. Uncommon. More frequent in patients who have been exposed to radiation in childhood.

b. Usually appear years or decades after RT. Mean latent interval is 17.6 years.

c. Meningiomas and sarcomas are the most common tumors occurring in the nervous system, but gliomas and malignant schwannomas may also develop.

d. Relative risk for developing brain tumors was 9.5 for meningiomas, 2.6 for gliomas, 18.8 for nerve sheath tumors, and 3.4 for other tumors.

e. Clinical features and treatment of these tumors are similar to those of tumors that arise without prior RT, but the tumors are often more aggressive.

3. Endocrinopathies

a. Endocrine disorders can be the consequence of direct irradiation of an endocrine gland (e.g., thyroid irradiation in patients with HD) or as a result of hypothalamic–pituitary dysfunction secondary to cranial irradiation.

b. In children, the most common endocrinopathy is GH deficiency. Gonadotropin deficiency and secondary and tertiary hypothyroidism occur less frequently.

c. In adults, GH deficiency is common but rarely symptomatic. Sixty-seven percent of adult males experience sexual difficulties, usually decreased libido and impotence, within 2 years of RT. These problems are thought to result from gonadotropin deficiency from hypothalamic damage. Hypothyroidism and hypoadrenalism occur less commonly and may require hormonal replacement. Hyperprolactinemia may also occur.

Myelopathy

1. Spinal cord more sensitive than brain to radiation.
2. Early delayed radiation myelopathy results in Lhermitte sign, a sudden "electric shock" sensation with neck flexion; begins several weeks to 6 months after treatment to neck or upper respiratory tract tumors and slowly improve within several months.
3. Late delayed radiation myelopathy occurs in two forms:
   - **a.** Most common form. Occurs 6 months to 10 years or more after exposure to RT.
     - **1)** Incidence ranges from 0.2% to 5% of patients receiving spinal cord doses of 45 Gy in 180- to 200-cGy fractions.
     - **2)** Characterized by an asymmetric myelopathy progressing over weeks, months, or rarely years to paraparesis or quadriparesis.
     - **3)** Initially hemicord (Brown–Sequard) syndrome, eventually symmetric myelopathy develops.
     - **4)** Occasionally the myelopathy stabilizes, leaving the patient moderately to severely weak.
     - **5)** Imaging studies are usually normal, although swelling and enhancement may be seen in the acute stages and atrophy may occur at a later stage.
     - **6)** Differential diagnosis includes epidural SCC, intramedullary metastases, and the rare paraneoplastic necrotic myelopathy.
     - **7)** There is no effective treatment, although there are anecdotal reports of benefit from steroids, anticoagulation, and hyperbaric oxygen.
   - **b.** A second form of delayed radiation myelopathy involves injury to lower motor neurons and occurs especially after pelvic irradiation.
     - **1)** Etiology is unclear. It was originally thought to result from injury to anterior horn cells, but involvement of proximal nerve roots is also a possibility.
     - **2)** Three months to 14 years after irradiation, a flaccid asymmetric paraparesis develops, affecting both distal and proximal muscles, and associated with atrophy, fasciculations, and loss of reflexes. Sensory loss and sphincter disturbance are usually absent but may occasionally be a late complication. The syndrome usually stabilizes after a few months.
     - **3)** Sensory and motor NCS are normal, but EMG shows denervation.

The CSF protein is often elevated.

4) Imaging studies of the spine are usually normal, but nerve roots may show enhancement.
5) Differential diagnosis includes radiation plexopathy, LMs, GBS, acute myeloid leukemia (AML), and paraneoplastic subacute motor neuronopathy.
6) There is no effective treatment.

Cranial Neuropathy

1. Rare (fewer than 1% of patients).
2. Visual loss may follow irradiation of the eye or the brain. Caused by a radiation-induced "dry eye syndrome," glaucoma, cataracts, retinopathy, or optic neuropathy.
3. Optic neuropathy typically occurs months to years after irradiation, with a peak at 12 to 18 months. Two clinical syndromes are seen:
   a. Painless, progressive monocular or bilateral visual loss with mild papilledema or optic atrophy, which may at times lead to complete blindness.
   b. Sudden visual loss as a result of central retinal artery or vein thrombosis.
4. Risk of optic neuropathy may be increased with concomitant administration of chemotherapy, including bevacizumab.
5. Deafness may result from an otitis media and rarely from vascular damage to the cochlear or vestibular nerves.
6. Radiation damage to other CNs is usually associated with large doses of irradiation (6,500 cGy or more) and are uncommon.

Brachial Plexopathy

1. Brachial plexopathy occurs after radiation for breast cancer or lymphoma.
2. Early delayed brachial plexus reaction may develop several months after irradiation. Described mainly in patients with breast cancer. Characterized by paresthesias in the forearm and hand, and occasionally pain, weakness, and atrophy in C6–T1 muscles. Symptoms usually improve over several weeks or months. NCS show segmental slowing.
3. Late delayed radiation plexopathy involving the brachial plexus occurs 1 year or more (median, 40 months) after RT with doses of 6,000 cGy or more.

4. Clinically: Tingling and numbness of fingers, weakness in hand or arm.
5. Signs usually referable to the upper brachial plexus (C5–C6 dermatomes).
6. Pain later in the course.
7. Differential diagnosis includes infiltrating tumor of the brachial plexus (usually painful) with involvement predominantly of the lower brachial plexus (C7–T1 dermatomes).
8. EMG shows myokymic discharges in more than 50% of cases of radiation plexopathy and none in cancerous cases.
9. Contrast MRI may help distinguish radiation fibrosis from tumor infiltration.
10. Surgical exploration of brachial plexus occasionally necessary for diagnosis.
11. No specific treatment; anecdotal reports of improvement with anticoagulation.

Lumbosacral Plexopathy

1. Early delayed, generally transient lumbosacral plexopathy is rare. Usually develops several months (median, 4 months) after RT. Presents with distal bilateral paresthesias of the lower limbs. Neurologic examination is usually normal. Improvement in 3 to 6 months.
2. Clinical features of late delayed lumbosacral plexopathy are similar to those of brachial plexopathy. This condition develops 1 to 30 years (median, 5 years) after irradiation. The patient may stabilize after several months or years. There is usually asymmetric weakness of one or both legs, with less-marked sensory loss. The foot is frequently involved. Pain is usually mild or absent. Myokymic changes may be seen on EMG. The usual course of the disease is usually one of gradual progression, although some patients may stabilize after several months or years.
3. No specific treatment; anecdotal reports of improvement with anticoagulation.

Hematopoietic Stem Cell Transplantation

Background

1. Hematopoietic stem cell transplantation (HSCT) used with increasing frequency to treat patients with cancer.

2. In allogeneic HSCT, the replacement marrow or peripheral blood stem cells are obtained from HLA-compatible donors and infused into the patient after high doses of chemotherapy administered to treat the underlying neoplasm.
3. In autologous HSCT, the replacement marrow or peripheral blood stem cells are harvested from the patient and then reinfused into the patient after high-dose chemotherapy.
4. Neurologic complications are common, especially encephalopathy, CNS infections, and cerebrovascular disorders. More frequent with allogeneic HSCT.

Pathophysiology

1. High-dose chemotherapy and radiation results in
   a. Immunosuppression and infection
   b. Organ damage and metabolic encephalopathy
   c. Vascular injury and cerebrovascular complications
   d. Direct neurotoxicity
2. GVHD in allogeneic HSCT results in autoimmune disorders such as MG, polymyositis, and chronic inflammatory demyelinating polyneuropathy (CIDP).

Prognosis

Patients who undergo HSCT and develop neurologic complications tend to have worse prognosis.

Diagnosis

Clinical Presentation

1. Toxic/metabolic encephalopathy.
2. CNS infections.
3. Seizures.
4. Cerebrovascular complications (hemorrhages from thrombocytopenia, thrombosis from hypercoagulable state).
5. Complications of chemotherapy, RT, immunosuppressive agents.
6. GVHD-associated MG, polymyositis, CIDP.

Diagnostic Tests

Blood work, neuroimaging studies, LP, EEG, and NCS depending on the symptoms.

Differential Diagnosis

Frequently complex and varies depending on specific complication.

Treatment

1. Varies depending on the specific complication.
2. Complications associated with GVHD treated with immunosuppression

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7 Multiple Sclerosis and Related Disorders

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MULTIPLE SCLEROSIS

Background

1. Multiple sclerosis (MS) is the most common disabling neurologic condition of young adults in European and North American populations. It was first recognized as a disease entity in the latter part of the 19th century. The first description of "disseminated sclerosis" dates back to 1835 and is credited to French neurologist Cruveilhier. Jean Martin Charcot, at the Salpêtrière Hospital in Paris, France, described the ataxia and oculomotor abnormalities that are often observed in younger patients. The pathologic features at autopsy, described in the first few decades of the 20th century, are now well known.
2. The cause of MS remains unknown. Theories of the cause have reflected concepts that were popular in different eras. Lesions of MS are often found close to small venules, and thrombosis of these veins was at one time thought to be important. A search for viruses, as intact infective agents or as DNA fragments, has unsuccessfully continued for many decades. Epstein-Barr virus (EBV) may play a particular role in MS: The studies have found that antibodies to the viral proteins, Epstein-Barr nuclear antigens, viral capsid antigens, and diffuse early antigens are significantly raised in people with MS. One study found that people with the highest levels of antibodies to EBV were 33 times more likely to develop MS than people with the lowest levels. It is not clear whether there is a causative or temporal association between infection with a specific pathogen and MS onset. In the last few decades, genetic predisposition was determined to clearly pay a

role. We now define MS as a *T cell-mediated autoimmune central nervous system (CNS) disease triggered by unknown exogenous agents, such as viruses or bacteria, in subjects with a specific genetic background*.

3. In most patients, MS is a chronic disease. In 85% of patients, it begins with focal inflammatory lesion of the nervous system, developing over days and recovering after months. Further lesions develop and cause clinical relapses, usually at a rate of one or relapse every 2 years. Magnetic resonance imaging (MRI) data have shown us that in actuality lesions occur in the brain and spinal cord at a far more rapid pace, often 10 times as frequently as relapses that are clinically recognized. After a number of years, or even decades, most patients enter a slowly progressive phase of the illness, with increasing disability. Impairment of gait, reduced visual acuity, paresthesias and pain, loss of bladder control, and cognitive deficits dominate the clinical picture after the progressive phase has advanced further. In large registries of patients, for example, from France and from Denmark, it is found that reduction in life span because of MS is not common, but that most (75% to 80%) of the patients are disabled and unable to work by age 65 years.
4. Other variants of MS occur. About 10% of patients have primary progressive MS (PPMS) (i.e., no relapses are recognized and the patient steadily worsens from the onset). Another 10% have so-called benign MS, with few relapses and no disability even though they have been known to have the disease for many decades. A small number of patients have acute MS, with frequent and large lesions and poor recovery, and it is among this group that a fatal outcome is occasionally seen.

Epidemiology

1. MS is the most common neurologic disease among young adults.
2. Incidence is the highest from ages 20 to 40 years, but the disease can start even in childhood or after age 60 years.
3. In the United States alone, there are about 500,000 MS patients and about 10,000 new cases are diagnosed yearly.
4. Current estimates are that about 70% of patients with MS are female.
5. There are zones of high incidence and medium incidence, and there are places in the world where the disease is almost unknown.

a. Prevalence decreases with proximity to equator creating a so-called "North-South Gradient" of MS distribution.
b. High incidence includes all of Europe, North America, New Zealand, and southern Australia. In Minnesota and many of the northeastern states of the United States, one person of every 500 has MS (i.e., a prevalence of 200/100,000). In general, MS is more than twice as common in the northern tier of the United States as in the southern states.
c. Race plays an important role: U.S. residents who are of Japanese, Native American, or Sub-Saharan African descent have a much lower incidence of MS than do people of Irish, British, or Scandinavian background under equal geographic circumstances.
d. Incidence of MS in African Americans is 25% of that of persons with Caucasian background. However, the disease tends to be more rapidly disabling and resistant to therapies in this patient population.

5. If persons with ethnically and geographically low risk develop MS, the disease may be atypical in clinical manifestations and imaging findings.

Pathophysiology

1. The *pathologic hallmarks* of MS are demyelination and predominantly perivenular inflammation. Severe or advanced disease causes axonal disruption and loss and cortical atrophy leading to a process of neurodegeneration.
2. Historically, MS was considered a disease of cerebral white matter. Recent data provide evidence for gray matter involvement.
3. The immunologic mechanism involves activation of autoreactive CD4≤ cells in the peripheral immune system followed by their migration into the CNS via a disrupted blood–brain barrier (BBB). This is followed by reactivation of the cells by in situ myelin antigens, activation of B cells and macrophages, and secretion of proinflammatory cytokines and antibodies.
4. The typical lesion of MS is a few millimeters to a centimeter in size. Viewed three-dimensionally, a lesion is often ovoid or linear rather than circular. This is a feature of the MRI appearance. Activated T cells and macrophages are present. The cells express T helper 1 (T_H1) cytokines such as interferon gamma (IFN-γ), tumor necrosis factor (TNF), and interleukin-2 (IL-2). Cytokines of the T_H2 series such as IL-4, IL-10, and IL-13 are

reduced. Many kinds of proinflammatory molecules, such as integrins and other adhesion molecules, are upregulated.

a. *Microscopically*, lesions show destruction, swelling or fragmentation of myelin sheaths, proliferation of glial cells, variable axonal destruction (new and old plaques), and variable damage to neurons, but relatively good preservation of background structure, and cystic lesions are rare.

b. Early/acute lesions (days to weeks) show marked hypercellularity, macrophage infiltration, astrocytosis, perivenous inflammation with plasma cells and lymphocytes, and disintegration of myelin.

c. Active/nonacute lesions (weeks to months) show lipid-laden phagocytes with minimal inflammatory response at the center of lesions but prominent at the edges of lesions with increased numbers of macrophages, lymphocytes, and plasma cells.

d. Chronic inactive plaques (months to years) show prominent demyelination (almost complete loss of oligodendrocytes), extensive gliosis, and hypocellularity.

e. Remyelinating plaques may result from differentiation of precursor cells common to type II astrocytes and oligodendrocytes. They show uniform areas of aberrant and incomplete myelination (shadow plaques).

5. Chronic lesions with poor recovery have the appearance on biopsy, at autopsy, or on MRI of an empty astroglial scar. The term *multiple sclerosis* refers to these late-stage discolored plaques or scars.
6. Recent work has demonstrated the presence of meningeal lymphoid follicles and has linked the presence of these follicles to worsened disability progression.
7. Chronic oxidative injury may also occur and may be associated with neuronal mitochondrial damage.

Genetics

1. Children of a parent with MS have a 1% to 5% chance of developing MS—an approximately 20-fold increase.
2. A sibling of an affected person, including a nonidentical twin, has a 3% to 4% chance of having MS.
3. An identical twin has a 30% chance of having MS if one includes asymptomatic twins with only MRI or spinal fluid findings.

4. MS is associated with major histocompatibility complex II (MHC-II) and three specific alleles in the DR2 haplotype.
5. Genome-wide association studies have shown no convincing locus for an "MS gene." It is likely that a number of genes contribute liability by increasing immune reactivity to common viruses or to antigenic components of myelin to which other persons are nonreactive.

Diagnosis

1. *Radiologically isolated syndrome* (RIS): Describes patients with an absence of symptoms or exam findings who are incidentally found to have typical imaging for MS. Risk factors for conversion to MS in this patient population include younger age (<37 years) and the presence of infratentorial or spinal cord lesions.
2. *Clinically isolated syndrome* (CIS), that is, optic neuritis (ON), transverse myelitis (TM), or a brainstem syndrome as the first ever episode of neurologic dysfunction. The patient does not meet criteria for MS diagnosis. Specific clinical syndrome depends on location of lesion(s) within brain, spinal cord, or optic nerves. The attack typically progresses for several days, plateaus, and then improves over days, weeks, or rarely months. Improvement can be complete or partial.
3. *Most common presenting symptoms of MS* include visual/oculomotor problems (49%), leg paresis/paresthesias (42%), and cerebellar ataxia (24%). Other symptoms may include progressive or abrupt cognitive changes, Lhermitte phenomenon (electrical painful paresthesias induced by neck flexion), Uhthoff phenomenon (worsening symptoms with increased body temperature), neuropathic pain, and fatigue.
4. Clinically definite MS (CDMS): Patient meets revised (Dublin) McDonald criteria for MS diagnosis.
   a. Revised (Dublin) McDonald criteria for diagnosis (2010) of relapsing–remitting MS (RRMS)
      1) Patients must present with a clinical symptom and meet criteria for dissemination in space and time. Other alternate diagnoses must also be excluded.
      2) Dissemination in space: MRI demonstrated involvement in at least two of four regions of the neuraxis:

a) Periventricular
b) Juxtacortical
c) Infratentorial (brainstem/cerebellum)—does not count if lesion is causing symptoms
d) Spinal cord—does not count if lesion is causing symptoms

3) Dissemination in time: Satisfied by either
a) A single scan with enhancing and nonenhancing lesions.
b) An initial scan with presence of disease and a follow-up scan with new lesions.

b. Revised (Dublin) McDonald criteria for diagnosis (2010) of PPMS: One year of disease progression and two of the three following:
1) Greater than or equal to one T2 lesion in an area typical of MS (periventricular, juxtacortical, infratentorial or spinal cord)
2) Greater than or equal to two T2 lesions in the spinal cord
3) Positive oligoclonal bands in cerebrospinal fluid (CSF) or increased immunoglobulin G (IgG) index

5. Over the course of the disease, each attack may leave some residual deficits. Accumulation of such deficits results in increasing disability. After several attacks of various types, a patient may present with common "fixed" problems:
a. Mild reduction in vision in one eye
b. Dysconjugate eye movements, with diplopia
c. Extensor plantar responses and inability to walk heel-and-toe
d. Reduced vibration sense in the legs
e. Urgency of bladder function
f. Cognitive impairment

6. Common late-stage deficits include dementia, inability to stand or walk, slurred speech, ataxia, incontinence, and marked sensory loss in hands and legs.

Diagnostic Testing

Magnetic Resonance Imaging

1. Although technically a diagnosis of MS can be made without MRI, it would be exceedingly rare for this to occur in the modern era. MS lesions are usually easily detected on conventional MRI and often are characteristic.

Conventional MRI techniques are now widely accessible to community and academic neurologists. By scan:

a. Lesions are bright on T2-weighted and fluid-attenuation inversion recovery (FLAIR) images, indicating a higher than normal water content. These MRI sequences reflect the total burden of disease (Fig. 7-1A).

b. Lesions are usually isodense on T1-weighted images, indicating that the tissue itself is intact.

c. Lesions may be hypodense on T1-weighted images, indicating underlying axonal disruption (black holes) (Fig. 7-1B).

d. Lesions may be present in many areas of the brain, but most typically, they are found adjacent to the lateral ventricles, oriented perpendicular to them, and in the corpus callosum (best seen on midline sagittal FLAIR images [Fig. 7-2]), and in the cerebellar peduncles. MS plaques directly touch the ventricular wall following the location of the small venules. In contrast, small vascular lesions are usually seen several millimeters away from the ventricular wall.

e. Acute and subacute lesions (usually <4 weeks since formation) often show enhancement on T1 postgadolinium contrast sequences indicating inflammation, BBB disruption, and recent disease activity (Fig. 7-3).

f. Size of cerebral lesions varies from 5 to 10 to 100 mm or greater.

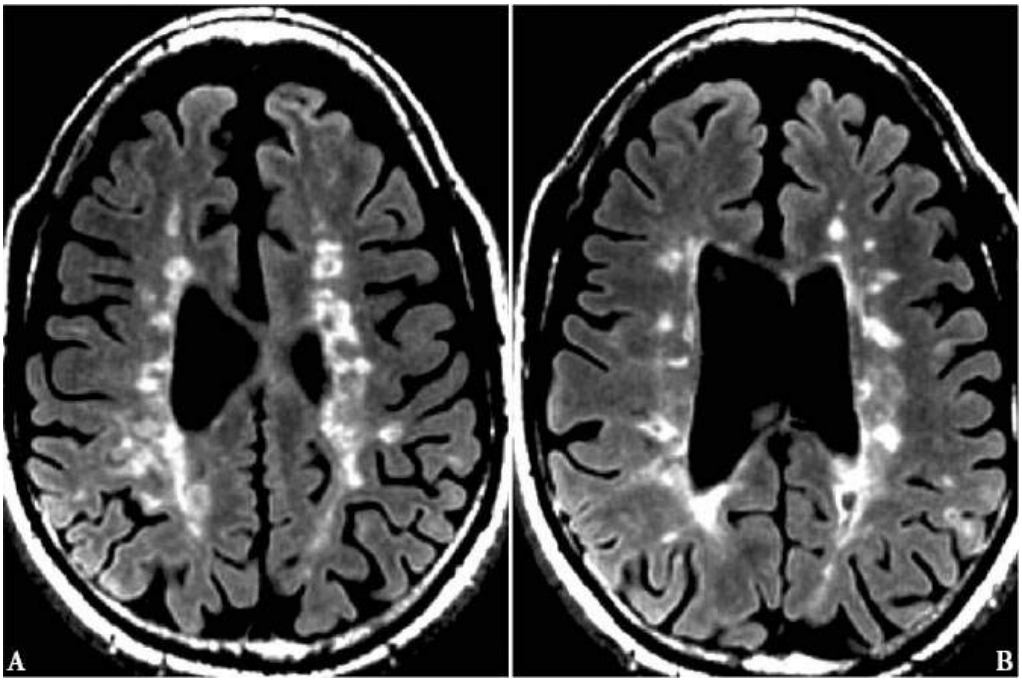

Figure 7-1. A: Axial FLAIR. This MRI was performed in a patient with secondary progressive MS. There are innumerable ovoid hyperintense lesions abutting lateral ventricles, involving the U-fibers and subcortical white matter. Cerebral atrophy is apparent: Lateral ventricles are enlarged, and cortical ribbon is thinned. **B:** "Black holes." T1 sequence shows hypointense lesions corresponding to some hyperintense lesions on FLAIR sequence. These are areas where severe axonal damage is seen pathologically. There is a correlation between axonal damage and neurologic disability.

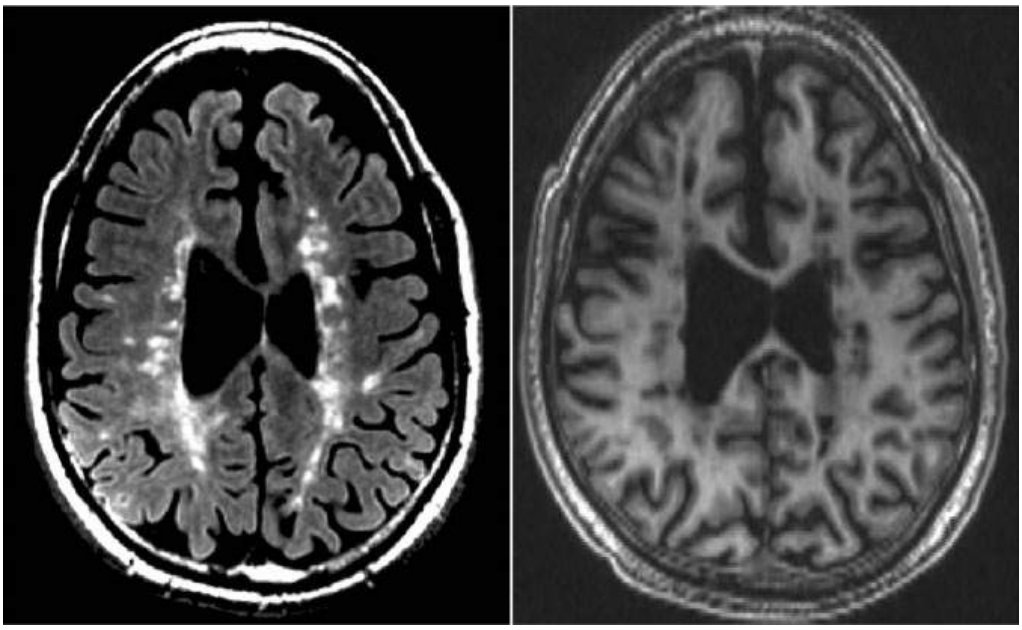

Figure 7-2. Sagittal FLAIR and T1. Typical "Dawson fingers" corresponding to areas of demyelination and inflammation are seen on sagittal FLAIR image. Atrophy of the corpus callosum is best appreciated on sagittal T1 precontrast sequence.

g. Lesions are common in the spinal cord, especially the cervical cord opposite the C2 or C3 vertebrae. They typically involve less than two contiguous segments of the spinal cord and less than half of the transverse diameter of the cord.

2. Most patients with MS have MRI scan findings that are characteristic of MS. Some may have atypical or nonspecific patterns of lesions. Only extremely rarely do patients with a typical clinical course suggestive of MS have normal MRI scans. Such patients present great diagnostic difficulty, and repeated scanning and other examinations may be required.

3. Other research techniques are being explored. High field MRI (7T) may better define whether a lesion is perivenular which may in turn enhance ability to accurately diagnose MS.

Other Tests

1. Lumbar puncture is needed in some patients with MS but is not performed routinely in cases of diagnostic certainty. Characteristic findings in the CSF in MS are a modest number of lymphocytes (fewer than 50/mm^3), total protein less than 0.8 g/L, elevated IgG synthesis levels (3.3 mg/day in 90% of patients), and high IgG index (0.7 or greater in 90% of patients). Myelin basic protein (MBP) is normally <1 ng/mL but increases in 80% of acute MS relapses. Presence of oligoclonal banding (OCB) on electrophoresis is the most sensitive of the CSF tests, being present in 75% to 80% of patients with established MS, and in 50% to 60% of patients with CIS. OCB may also be present in other infectious/autoimmune conditions such as Lyme disease, neurosarcoidosis, neurosyphilis, and HIV.
2. Evoked potentials testing—especially testing of visual evoked potentials—will occasionally help. It can establish evidence of prior damage to optic nerves in the absence of a clear clinical history by showing unilateral prolongation of P100 wave.

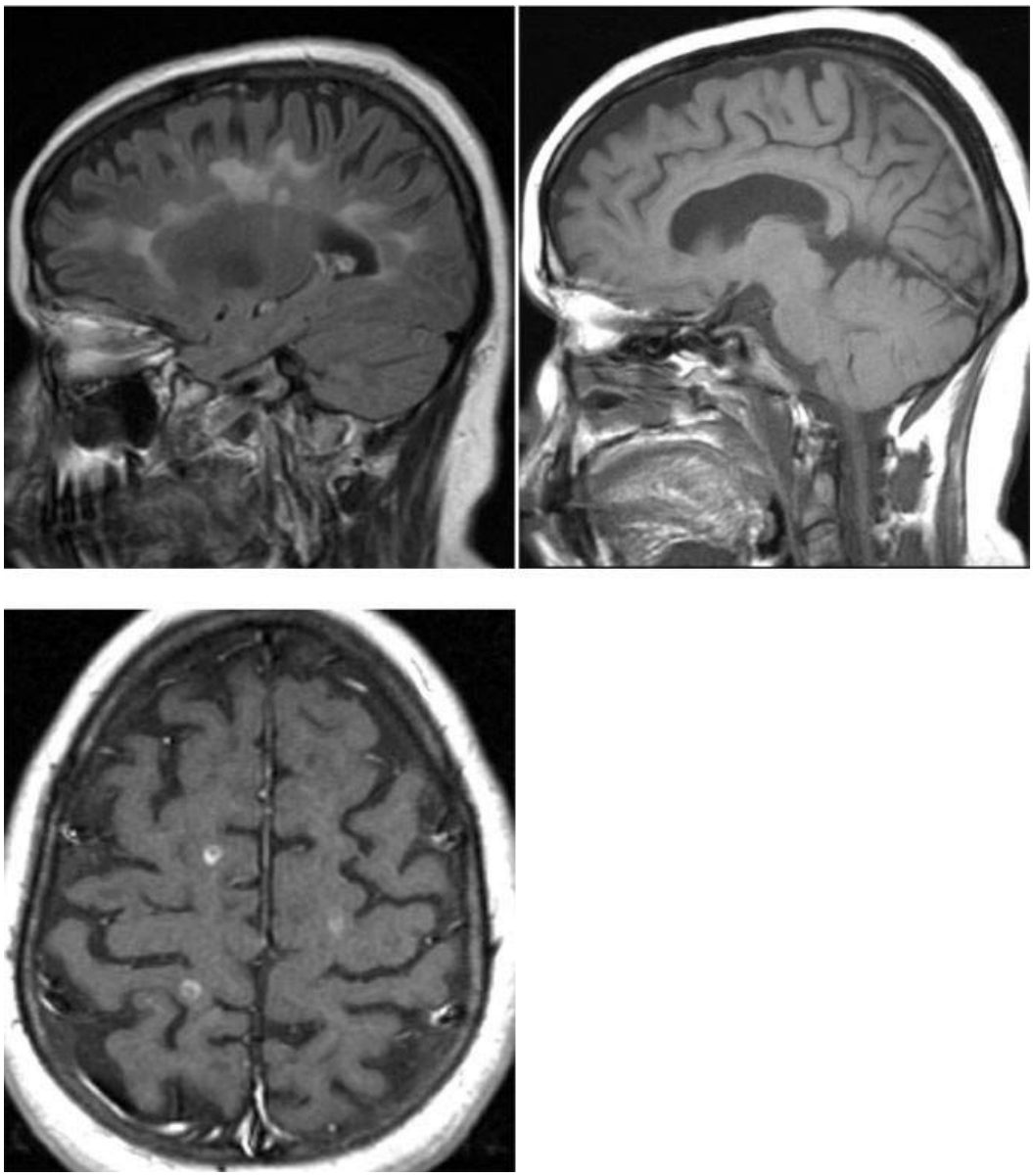

Figure 7-3. T1 postcontrast sequence. "Active" MS lesions are seen in this T1 postcontrast sequence. They appear as partially ring-enhancing or diffusely enhancing lesions. Pathologically, they correspond to areas of impaired blood–brain barrier.

3. Optic coherence tomography (OCT) can identify retinal nerve fiber layer thinning suggestive of prior optic nerve damage and fellow non-affected eye thinning correlates moderately with brain atrophy but is currently not commonly employed for clinical care.

Differential Diagnosis

Many other neurologic conditions may be confused with MS (Table 7-1). They

fall into two categories:

1. Relapsing diseases that look like MS clinically include other CNS inflammatory diseases such as lupus and sarcoidosis.
2. Primary progressive or secondary progressive disease clinically can mimic other degenerative processes such as hereditary ataxia, adrenoleukodystrophy, and motor neuron diseases such as amyotrophic lateral sclerosis (ALS).

Table 7-1 Diagnoses that Mimic Multiple Sclerosis

Infectious	Toxic-Metabolic	Inflammatory	Other
Lyme disease	Vitamin B_{12} deficiency	SLE	CADASIL
Neurosyphilis	Vitamin E deficiency	Sjögren disease	CNS lymphoma
HIV		Neuro-Behçet disease	Cerebrovascular disease
HTLV-1		Sarcoidosis	Leukodystrophies
PML		CNS vasculitis	Motor neuron disease
			Cervical spondylosis

SLE, systemic lupus erythematosus; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CNS, central nervous system; HTLV, human T-lymphocyte virus; PML, leukoencephalopathy.

3. Diseases that look like MS by MRI findings, including other causes of "white spots"
   - **a.** Vascular disease: Small-vessel disease in hypertension, migraine, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).
   - **b.** Infections: Lyme disease, HIV.
   - **c.** Granulomatous disease: Sarcoidosis, Behçet disease
   - **d.** Monosymptomatic demyelinating disease: TM and acute disseminated encephalomyelitis (ADEM)

Classification and Clinical Considerations

1. Several MS classifications are used.
   - **a.** Based on disability accumulation: Benign MS (approximately 10% of all

patients)—no or minimal neurologic disability after 10 to 15 years. Malignant MS (approximately 10% of all patients)—neurologic disability requiring ambulation assistance after ≤5 years.

b. Based on clinical course: RRMS. This subtype is the most common (85% of all patients fit into this disease category at diagnosis). It is characterized by relapses and remissions of neurologic disability over years to decades. Incomplete recovery from relapses often leads to disability accumulation. Secondary progressive MS (SPMS) follows RRMS in 10 to 25 years after the diagnosis in 60% to 80% of patients. This subtype is characterized by absence of relapses and progressive worsening of neurologic function involving the pyramidal system, cerebellar connections, dorsal columns, and cortical association fibers. Patients with progressive disease (PPMS and SPMS) most often present with unilateral leg weakness gradually evolving to a spastic paraparesis. Other symptoms that progressive patients frequently exhibit are ataxia, neuropathic pain symptoms, cognitive decline, and bowel and bladder symptoms. Ambulation assistance is often required. Careful history taking confirms absence of exacerbations of neurologic deficits. PPMS is more common in men, in the fourth and fifth decades of life. It presents in a similar way to SPMS, but there are no preceding relapses. Prognosis is worse for this group of patients. A recent clinical trial demonstrated a modest benefit in PPMS patients treated with ocrelizumab (see section on Treatment).

2. The combination of several epidemiologic, clinical, and imaging factors carry better prognosis for stable disease course. Favorable prognostic factors include

a. Younger age of onset
b. Female sex
c. Monosymptomatic onset
d. Sensory symptoms or ON at onset
e. Few T2 of FLAIR lesions on original MRI
f. Long interval between first and second attacks
g. Low attack frequency in the first 2 years
h. Full recovery of function after the first attack

3. There is no consistent evidence that the postpartum state, anesthesia,

surgical procedures, stress, or intercurrent illnesses worsen clinical outcome in MS patients. However, the aforementioned factors may temporarily aggravate preexisting neurologic deficit creating a "pseudo-exacerbation." These are not considered true relapses, and it is important to screen patients for infections in presence of transient or fluctuating neurologic worsening.

l. Expanded Disability Status Scale (EDSS): Ordinal 0 to 10 scale; most widely accepted measure of disability in MS.
   a. EDSS 0: No disability
   b. EDSS 6: Needs unilateral ambulation assistance (cane)
   c. EDSS 6.5: Need bilateral assistance with ambulation (walker)
   d. EDSS 7: Most often reliant on wheelchair
   e. EDSS 10: Death because of MS

Treatment

Treating Symptoms

Psychiatric Symptoms

l. Depression: Over the course of a year, about 20% of MS patients have depression. Symptoms of irritability, altered sleep pattern, and low self-esteem occur. Women are twice as likely as men to become depressed. There is little correlation with disability; in fact, depression may be more common in the earlier stages, with less disability. There is a causative connection in that some of the frontal lobe and limbic connections may be damaged by MS lesions.
   a. Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment of depression: fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), or second-generation drugs such as bupropion (Wellbutrin), citalopram (Celexa), or escitalopram (Lexapro) (Table 7-2). Care should be taken that the dose is sufficient. Most SSRIs reduce libido. The involvement of a psychiatrist should be considered in difficult cases.
   b. In addition to drug therapy, counseling or some other form of supportive psychotherapy is often beneficial. Ideal treatment is a combination of the two.
   c. Tricyclic antidepressants are helpful but have many side effects, such as

weight gain, dry mouth, and drowsiness. On the other hand, they may help insomnia or urinary urgency. Examples are amitriptyline, desipramine, or nortriptyline.

d. Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) are useful in treatment of depression, such as venlafaxine (Effexor) and duloxetine (Cymbalta). Duloxetine is also helpful in treating pain in MS patients.

Table 7-2 Medications for Depression in Multiple Sclerosis

Medication	Initial Dose	Final Dose Range
Fluoxetine (Prozac)	10 mg	10–80 mg
Paroxetine (Paxil)	10 mg	10–50 mg
Sertraline (Zoloft)	25 mg	25–200 mg
Citalopram (Celexa)	10 mg	20–60 mg
Venlafaxine (Effexor)	37.5 mg	75–300 mg, given twice a day

e. Fatigue can be a compounding issue and may be hard to distinguish from depression.

f. Depressed patients need to be followed, the success of treatment assessed, and risk of suicide should be considered at all times. In apathetic patients, thyroid deficiency, sleep apnea, and adverse effects of other medications should be considered.

2. Other common disorders

a. Bipolar disorder: Prevalence is 9% over the year in an MS population. Psychiatric consultation is advisable because bipolar disease requires a separate set of long-term preventive drugs such as lithium carbonate, carbamazepine, or valproate.

b. Anxiety disorders: Prevalence also increased. Can be treated with an SSRI, Wellbutrin, or a benzodiazepine (clonazepam, lorazepam, or valium are commonly employed). Psychological counseling can also be helpful.

Fatigue

The fatigue experienced by many MS patients may be disabling, pervasive, and not relieved by rest. Careful planning, avoidance of exhausting exercise, short rest periods, and other coping strategies may help. Different types of fatigue

may be present in patients. Motor fatigue relates to maintaining strength or ambulating for a distance. Patients may also complain of a general dearth of energy. The following medications are in use:

1. Amantadine (Symmetrel) 100 mg, two or three times a day. This medication has been in use for more than 20 years for MS. About a third of patients find it useful. Hallucinations, ankle swelling, and skin mottling may be seen, especially in older patients.
2. Modafinil (Provigil), 100 or 200 mg twice a day. This agent was approved for producing wakefulness in patients with narcolepsy. Despite a randomized controlled trial showing a lack of effect for fatigue in MS patients, we oftentimes find this compound helpful.
3. Methylphenidate (Ritalin), 5 to 10 mg/d, up to a maximum of 40 mg/d. A long-acting version (Concerta), at a dose of 18 mg once or twice a day, may be preferable. Other amphetamine-based preparations can be tried. They can cause hypertension, exacerbate anxiety disorders and cause insomnia.

Cognitive or Memory Problems

In some patients with MS, the lesions of the central white matter destroy nerve fibers and their coverings. The results of this axon loss are gradual atrophy of the white matter, enlargement of the ventricular system, and behavioral and cognitive deficits. Primary gray matter pathology is also known to play a role in this process. In minor form, cognitive dysfunction may be common and occur early in the disease course. Many patients with MS will note slowed processing speed, memory and recall problems, difficulty handling complex or multiple stimuli, or inability to concentrate well. When more severe, emotional lability, poor judgment, and personality change may occur.

1. Structuring of the environment may help: avoidance of complexity, doing "one thing at a time," asking for help.
2. Recognizing and treating fatigue or depression (see earlier) may provide a therapeutic option.
3. Acetylcholinesterase inhibitors failed to show an effect in a large randomized trial in MS patients. Some clinicians find that individual patients may benefit, however.
4. A phase II trial showed that lisdexamfetamine dimesylate (Vyvanse) improved processing speed and memory in cognitive impaired MS patients. Some patients trialed on this agent in clinic report an improvement in

cognition.

5. Cognitive-behavioral therapy is helpful for some patients.

Spasticity

1. Occurs with damage to descending motor fibers as part of the upper motor neuron syndrome. Walking may become slower and labored, with adduction of the hips and difficulty lifting the toes and ankles (foot drop). Spontaneous spasms may occur, especially at night, and may be painful. Usually these flexor spasms affect both legs. Spasticity is accompanied by varying degrees of weakness and clumsiness.
   a. Physiotherapy and exercise have a limited but important role. Maintenance of joint flexibility by stretching and range of motion can be accomplished by many techniques.
   b. Baclofen (Lioresal) blocks γ-aminobutyric acid (GABA), one of the major spinal cord inhibitory transmitters. A starting dose of 5 to 10 mg three times a day is typical, although sometimes it is taken only at night if the symptoms are bothersome before bed. The dose may be titrated to effect, although drowsiness typically provides a ceiling for most patients. At doses about 120 mg a day, we find further increases bring diminishing returns. Hypotonicity may also occur which can affect ambulation. At high doses, patients should be instructed not to suddenly discontinue the medication in order to avoid a potentially serious withdrawal syndrome.
   c. Tizanidine (Zanaflex), an α-2 adrenergic agonist, is used for the same indications. The drug is available as a 4-mg tablet. It must be increased very slowly from a starting dose of 2 mg at bedtime to a maximum of 16 to 20 mg/d. It can cause drowsiness but not hypotonicity.
   d. Benzodiazepines, such as clonazepam (Klonopin) 0.5 to 2.0 mg at bedtime, have some usefulness, but tachyphylaxis and dependency limit their value.
   e. Dantrolene (Dantrium) is used only rarely because of liver toxicity. However, it has a role for acute spasticity or muscle contracture.
   f. Nabiximols (Sativex), a cannabinoid, is approved for use in Canada, and some European counties for relief of neuropathic pain. A phase III trial showed benefit for MS-related spasticity. It is not currently approved in the United States, but many patients report that cannabinoids ameliorate spasticity.

2. For severe spasticity, an intrathecal pump system is available, consisting of a subcutaneous programmable reservoir and a tiny catheter into the spinal subarachnoid space, which delivers baclofen.
3. Botulinum toxin injections in isolated muscles may provide spasticity relief. The range of doses can be used to either improve ambulation quality or to relieve contracture-related pain.

Urinary Urgency

Many patients with MS have impairment of bladder function. The most common pattern is one of a small-capacity bladder, with urgent and involuntary contractions but incomplete emptying. Less commonly, MS patients may have a hypotonic bladder, with difficulty initiating urination and a large postvoiding urinary residual.

1. Oxybutynin (Ditropan), an anti-muscarinic drug, may be used empirically. It is effective in patients with hypertonic bladders in whom involuntary contractions and dyssynergy of sphincter function are the main problems. Dosages range from 2.5 mg to 10 to 15 mg/d. A long-acting version may be more convenient. Dry mouth and constipation are encountered at high dose levels.
2. Tolterodine (Detrol), another anti-muscarinic agent, is used in the same manner and may be substituted for oxybutynin. Dry mouth is less of a problem. Dosage is 2 mg, once or twice a day.
3. Other anticholinergic drugs, including tricyclic antidepressants, are sometimes useful.
4. Patients with symptoms indicative or bladder spasticity not benefitting from the aforementioned drugs should be referred to a urologist for further evaluation. Some patients experience improvement after administration of botulinum toxin into the wall of the urinary bladder.
5. For severe hypotonicity with retention, and especially with frequent urinary tract infections (UTIs), self-catheterization is indicated. For men, external drainage systems may be used, but they will not empty the bladder well. Referral to a urologist for assessment is usually required.

Pain

1. Pain is a common component of MS, particularly in mid-stage disease. Pain may be dull or burning and is often located in a large region, such as an arm,

a leg, one side of the body, a band-like sensation over the trunk, or in the face. Sharp lancinating pain in the face may be very reminiscent of idiopathic trigeminal neuralgia.

2. Consideration should always be given to the possibility of non-MS pain including various forms of nerve root compression, visceral pain, and depression will often worse pain. Various medications may be helpful:
   a. Gabapentin (Neurontin) may be used at dosages up to 3,600 mg/d. Above that dose level, little further medication is absorbed by active intestinal transport. Some patients are drowsy or lethargic at dosages of 600 to 900 mg/d and are unlikely to achieve much benefit.
   b. Tricyclic antidepressants, such as amitriptyline 50 to 75 mg/d or nortriptyline at 100 to 150 mg/d, are helpful, but dry mouth, urinary retention, drowsiness, confusion, and other symptoms because of anticholinergic side effects may occur.
   c. Carbamazepine (Tegretol) at dosages of 400 to 1,000 mg/d is helpful. The long-acting form of the medication is preferable. Other antiepileptic drugs may be tried as well, including valproate (500 to 1,500 mg/d) or topiramate (Topamax) (50 to 150 mg/d).
   d. Referral to a pain specialist is indicated if a patient is not achieving benefit from multimodality medical therapy. Sometimes interventional procedures, such as nerve blocks, can help.

Alternative or Complementary Medicine

1. In the United States, about half the patients with MS are involved in some type of nontraditional treatment in addition to conventional medical therapies. These nontraditional treatments may be classified as follows:
   a. Biologically based therapies, such as herbs, diet, bee venom, or bee stings
   b. Non-Western medical systems, such as Chinese, Tibetan, or homeopathic approaches
   c. Mind–body intervention, including meditation, yoga, and prayer
   d. Manipulative or body-based treatments including chiropractic manipulation or massage
   e. Energy therapies, such as magnets, Reiki, and therapeutic touch

2. Most of these treatments are complementary to standard conventional approaches and should not replace them. A nonconfrontational approach can

lessen the risk that patients will abandon or avoid important avenues of treatment. Some of these treatments are helpful, a few may be promising, and most are unproven.

Treatments that Alter the Course of the Disease

1. The six principles of treatment are listed in Table 7-3 and discussed in detail in the following text. Drug safety during pregnancy is considered in Table 7-4.
2. Disease-modifying therapy in MS aims to alter the natural course of the disease and maximize the quality of life by decreasing:
   - **a.** Frequency of relapses
   - **b.** New brain and spinal cord lesions (overall lesion burden and active lesions)
   - **c.** Progression of brain atrophy
3. Physical and cognitive disability progression. As of this writing, 13 medications are now approved in the United States for use in patients with MS to affect the course of the disease. Doses, frequency, and mode of administration are outlined in Table 7-5. All medications partially reduce the number of relapses and the activity of the disease as visualized on MRI scans. The average relapse reduction rate is between 30% and 50% annually, except for natalizumab which reduced the relapse rate by 68% per year in placebo-controlled trial. Five of the medications are β-interferons, two are monoclonal antibodies, one is synthetic polypeptide designed to resemble MBP, and the three oral agents have varied mechanisms of action, explained later in this chapter.

Table 7-3 Six Principles of Management in Multiple Sclerosis

1. Relapses with significant impairment of function should be treated with high-dose intravenous corticosteroids.
2. All relapsing–remitting patients should be offered long-term immunomodulatory disease modifying treatment.
3. Secondary progressive patients need aggressive treatment early. Late treatment (more than a few years after the onset of the progressive phase) accomplishes little.
4. Primary progressive patients cannot be expected to respond to any disease-altering treatmen in the current treatment landscape. Ocrelizumab when approved may be a good option fo these patients.
5. Multiple sclerosis is a lifelong illness, and there is no current guidance for therapy

discontinuation. If one treatment is not tolerated, or fails, another should be sought. Treatmen can possibly be discontinued on trial basis based on patient's strong preferences and afte more than 5–10 years of disease stability.

6. Patients need to be watched for signs of disease activity by clinical and/or magnetic resonance imaging monitoring. Changes or additions in treatment need to be started before there is irreversible loss of function.

Table 7-4 Safety of Multiple Sclerosis Drugs When Used During

Category B: Animal data show no fetal harm; no human data available
- Glatiramer (Copaxone)
- Oxybutynin (Ditropan)
- Antidepressants such as SSRIs

Category C: Animal data show fetal harm; no human data available
- Corticosteroids
- Interferon-β 1α
- Interferon-β 1β
- Fingolimod
- Dimethyl fumarate
- Alemtuzumab
- Baclofen
- Amantadine (Symmetrel)
- Tizanidine (Zanaflex)
- Carbamazepine (Tegretol) and most other antiepileptic drugs

Category D: Known to cause fetal harm when administered to humans
- Mitoxantrone (Novantrone)
- Cyclophosphamide (Cytoxan)
- Methotrexate

Category X: Absolute contraindication in pregnancy; known human teratogen
- Teriflunomide (rapid elimination protocol with cholestyramine 8 g q8h for 11 days if early pregnancy exposure)

SSRIs, selective serotonin reuptake inhibitors.

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4. One drug, mitoxantrone, is approved for SPMS. It is a chemotherapy agent administered at relatively low dose.
5. The precise mechanism of action of IFNs or glatiramer acetate is not known. IFNs are recombinant proteins. They do not cross BBB and exert their effects in the periphery, in the lymphoid organs, and not in the CNS. It is hypothesized from laboratory studies that they block T-cell activation, have antiproliferative effects on T cells and antiviral effects, and induce apoptosis of autoreactive T cells.

6. Glatiramer acetate is a polypeptide mixture. It acts in the periphery and in the CNS. Its mechanism of action is presumed to involve bystander suppression, induction of anergy, induction of anti-inflammatory T_H2 cells, and blockade of autoimmune T cells.

Table 7-5 Disease-Modifying Agents for Multiple Sclerosis

Name	Dose	Frequency	Route
Aubagio (teriflunomide)	7 or 14 mg	Once daily	PO
Avonex (IFN-β 1a)	30 μg	Once weekly	IM
Betaseron, Extavia (IFN-β 1b)	250 μg	Every other day	s.c.
Copaxone/Glatopa (glatiramer acetate)	20 mg	Once daily	s.c.
Gilenya (fingolimod)	0.5 mg	Once daily	PO
Lemtrada (alemtuzumab)	12mg/d × 5 d	Once annually × 2 y (second treatment given for 3 d)	IV
Novantrone (mitoxantrone)	12 mg/m^2 (maximum 140 mg/m^2)	Every 3 mo	IV
Plegridy (IFN-β 1a pegylated)	125 μg	Every 14 d	s.c.
Rebif (IFN-β 1a)	44 μg	Three times weekly	s.c.
Tecfidera (dimethyl fumarate)	240 mg	Twice daily	PO
Tysabri (natalizumab)	300 mg	Once monthly	IV

PO, orally; IM, intramuscular; s.c., subcutaneously; IV, intravenous.

7. Natalizumab is a recombinant monoclonal antibody. It is a selective adhesion molecule inhibitor directed against α4-β1 integrin receptor on lymphocytes. It prevents binding to the vascular adhesion molecule (VCAM)-1 on endothelial cells and stops lymphocyte migration across BBB. It acts in the periphery and does not cross the BBB into the CNS.
8. Fingolimod is a sphingosine-1-phosphate (S1P) receptor modulator. It is phosphorylated to active form and prevents lymphocyte egress from lymphoid tissue (primary effects on naïve, central memory T cells). Effector

T cells are spared. It penetrates into CNS and may have direct effects on neurons and glia.

). Dimethyl fumarate is a fumaric acid ester which may activate Nrf2 pathway; it decreases circulating lymphocytes with shift from T_H1 to T_H2 immune response. It restricts cell migration by decreasing intracellular adhesion molecule (ICAM)-1, VCAM-1, and E-selectin.

). Teriflunomide is an active metabolite of leflunomide and noncompetitively and reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), relevant for the *de novo* synthesis of pyrimidine. By inhibiting DHODH and diminishing DNA synthesis, teriflunomide has a cytostatic effect on proliferating B and T cells. It is also thought to reduce T cell proliferation and activation.

l. Alemtuzumab is a humanized monoclonal antibody directed against CD52. It produces rapid, long-lasting depletion of mobile T cells (CD4+ > CD8+) lasting several years as well as B cells and monocytes lasting several months.

2. Dalfampridine is a medication that does not modify disease course but is indicated to improve walking speed in MS patients with ambulatory difficulty. It is a potassium channel blocker, which may improve the speed of conduction across partially demyelinated nerve fibers.

3. Vitamin D_3 may have disease-modifying effects in MS patients and those with high risk for developing MS. The optimal blood levels and the dose of vitamin D for MS patients are not currently established. It is generally recommended to maintain vitamin D_3 blood levels above 35 ng/mL and to supplement all MS patients with 2,000 IU of daily vitamin D_3. Some physicians prefer higher supplementation doses and higher blood levels of vitamin D in their patients, with 3,000 to 5,000 IU of daily dose, and levels above 50 ng/mL.

4. Decisions about medication use should normally be executed by a practitioner with knowledge and experience in the field. Practice patterns are changing rapidly as further data are made available about these agents. Efficacy and side effect potential for some medications may change if other immunomodulators have been used previously.

a. Relapses with significant impairment of function should be treated with high-dose intravenous (IV) corticosteroids.

1) This principle is based on 30-year-old data, when

adrenocorticotropic hormone (ACTH) was the preferred form of steroid therapy, and more recently, on data from the Optic Neuritis Treatment Trial. Disability is shortened, and in some instances, the residual from an attack is lessened. Commonly used protocols now use methylprednisolone 1,000 mg/d administered IV over 1 to 2 hours for 3 to 5 days. Oral equivalents of the IV dose may have the same effect on relapse recovery (1,250 mg oral prednisone or 1,000 mg oral methylprednisolone). Dexamethasone, orally or IV, can also be used in instances of methylprednisolone allergy. Most authorities do not use an oral taper of prednisone after the IV steroid.

2) Acthar Gel (ACTH-containing preparation) can at times be used for acute relapses in settings where patient has contraindications to conventional steroids use. High cost and lack of data on superior efficacy, compared to steroids, limits its use.

b. All relapsing–remitting patients should be on treatment. This principle is based on data from longitudinal studies of patients followed up clinically and with serial MRI studies. Such studies, mainly from Canada and Britain, have shown the following:

1) Most relapsing patients will eventually develop disability. Only 10% of MS patients have benign MS and may not need therapy, but these patients are impossible to identify at the time of diagnosis, and the diagnosis of benign MS can only be made retrospectively.

2) After a single attack of demyelinating disease, the likelihood of a second attack is accurately predicted by the MRI findings. A patient with ON and more than two demyelinating lesions on an initial scan has 5 times the risk of a second neurologic event (thus acquiring a diagnosis of MS) compared to a patient with negative scan findings.

3) Although patients with short-lived, limited, or spontaneously clearing attacks have a less severe course, these clinical predictors are highly unreliable in predicting eventual outcome.

4) Also, while patients with less activity on their MRI scans (as measured by enhancement with gadolinium or increasing numbers of lesions) have a less severe course, these predictors are equally unreliable.

c. Therefore, because it cannot be known if there are patients who could forgo treatment, the current recommendation is for all to be treated.

5. Therapeutic efficacy: Currently available immunomodulating agents (IMAs)

decrease relapse rate annually by approximately 30% (IFNs and glatiramer acetate), by 30% to 54% for the oral agents, and by natalizumab by approximately 60%. They also significantly and beneficially affect MRI disease by decreasing new T2 lesions formation, new T1 Gd+ lesions, and, for some agents, have positive effects on reducing the rate of brain atrophy. Decreased disability progression is seen with most agents at the conclusion of clinical trial (most are 2 years long.) Long-term disability efficacy is not known, but open label extension trials with injectable agents report less disability in patients at 15 or 20 years than one would expect from natural history.

5. General side effects of IMAs
   a. IFNs: Injection-site reactions, flulike symptoms, neutropenia, liver function test elevation, formation of IFN-specific antibodies (partially inactivate effects of the drugs)
   b. Glatiramer acetate: Injection-site reactions, postinjection reaction, chest pain, facial erythema, tachypnea, fat necrosis at sites of prolonged injections
   c. Natalizumab: Infusion reaction, opportunistic infections with fatalities (progressive multifocal leukoencephalopathy [PML], disseminated varicella-zoster virus infection), antibody formation
   d. Fingolimod: Bradycardia, requiring a 6-hour first dose observation by physician, with vital signs monitoring; rare cases of atrioventricular (AV) conduction block, macular edema, liver enzyme elevation, lymphopenia, and increased risk of infections, including opportunistic infections and PML.
   e. Dimethyl fumarate: Prolonged lymphopenia in some patients, gastrointestinal distress, facial and body flushing, increased risk of PML, and, possibly, other infections.
   f. Teriflunomide: 17% incidence of hair thinning, elevation of liver enzymes, increased risk of serious infections, and possible teratogenicity.
   g. Alemtuzumab: Over 13 % risk of autoimmune thyroid disease several cases (0.01%) of immune thrombocytopenic purpura (ITP); profound lymphopenia in 97% of treated subjects and neutropenia in 77% of treated subjects. Patients should be on acyclovir prophylaxis for at least 2 months after each course of therapy. Although not specifically required, some providers also use trimethoprim/sulfamethoxazole prophylaxis for at least

2 months after each course of therapy. Cases of serious and opportunistic infections have been reported. Infusion reactions including urticaria, shortness of breath, fever, and malaise occur in most patients receiving treatment. Glomerulonephritis has rarely been reported. Monthly blood draws and urine screen every 3 months are required during therapy and for 48 months after cessation of therapy.

h. The approved injectable drugs for relapsing MS produce approximately the same 30% reduction in annual attack rate. There is no valid method to choose among them based only on effectiveness. They can be used as first-, second-, or third-line treatments and are generally considered to be less effective but likely safer than newer oral or infusions therapies. Exposure to these agents as first-line treatments does not limit future treatment choices for MS patients.

i. Natalizumab is a highly effective treatment. The use is limited by PML infection in John Cunningham virus (JCV)-exposed individuals. Exposure can be indirectly assessed by commercially available JCV antibody assay, measured in blood. In patients who have not been exposed to the virus, natalizumab can be used as first-, second-, or third-line agent. Generally, it is reserved for patients with highly active, inflammatory illness. Exposure to JCV should be periodically reassessed. Patients who test positive for JCV antibody should be warned about an increased risk of PML (between 1:500 and 1:100) with particularly high risk in patients treated beyond 2 years and with prior exposure to immunosuppressive medications, either for MS, or other comorbid conditions.

j. Alemtuzumab is a highly effective therapy. The use is limited by profound immunosuppression as a result of treatment, and the need for extensive and long-term safety follow-up. Although plasma concentration of alemtuzumab is close to 0 within 30 days of infusion treatment, biologic effects last for over a year, limiting future choice of therapy for this time period if alemtuzumab fails to optimally control the disease.

k. Dalfampridine is known to increase the risk of seizures and is contraindicated in patients with a known seizure disorder, or significant renal impairment. Caution should be used if combining it with any other medications known to lower the seizure threshold.

l. Oral agents vary in efficacy and are generally considered superior to (fingolimod, dimethyl fumarate) or equivalent to (teriflunomide) injectable

drugs. This information comes from phase III trials where oral agents were compared not only to placebo but also to an approved injectable MS therapy.

m. The clinical trials to establish effectiveness have varied in their inclusion criteria, follow-up details, duration of treatment, and other parameters and therefore cannot be easily compared.

n. Convenient prefilled syringes and automatic injection devices are available for injectable agents, and easy packaging is provided for oral tablets. All of these medications are costly, but an extensive network of financial and administration support services is readily available for patients.

o. Most patients and doctors choose among drugs on the basis of ease of administration and side effect profile. If side effects from one drug are limiting, a change can be made to another with the exceptions noted earlier.

7. As part of the natural history of most patients with MS, relapses slowly decline in number. In two IFN trials that contained a placebo arm lasting more than 2 years, the relapse rate in the placebo patients declined by about two-thirds. With successful treatment, the relapse rate goes even lower. The natural history of MS, unfortunately, also is that most relapsing patients will enter the secondary progressive phase of the illness, and disability will steadily increase from that point. Therefore, at any one time, about half the patients with MS will be in the secondary progressive phase. It is likely that there has been some change or evolution in the basic pathology in these patients. The change cannot be recognized on MRI scans, except by the fact that atrophy of white matter and gray matter structures and enlargement of the ventricular system are found as its consequence. Once disability because of SPMS is well established and present for more than a few years, it is very unlikely to be reversible. For this reason, if aggressive therapy is decided upon, it should be used relatively early. For a patient who has been wheelchair-dependent for 3 years, it is probably too late.

Treatment for Secondary Progressive Multiple Sclerosis

1. IFNs: A number of trials of IFN-β, for SPMS have been reported. One trial in Europe seemed to show a positive effect, but these patients were having

relapses in addition to steady progression, and the major effect seen was on the relapse rate. A trial organized in the United States probably contained fewer patients with "transitional" MS who were still having relapses. It showed no effect of IFN-β on disability. Accumulation of disability because of incomplete recovery from relapses can certainly occur, and this aspect of SPMS is preventable with IFN therapy.

2. Long-term IV steroids, usually given as a monthly bolus of 1,000 mg of methyl-prednisolone, are in use in many MS clinics. There has not been an adequate trial of such usage in either relapsing MS or SPMS. A more common usage is to give the steroid as a 3- to 5-day course, administered several times per year when apparent relapses are detected. If steroids are given frequently, bone density should be monitored and appropriate therapy instituted when osteopenia occurs.

3. Low-dose oral chemotherapy agents.
   - **a.** Azathioprine has been in use for decades, especially in Europe. Meta-analysis of a large amount of data, typically of dosage ranges of 100 to 200 mg/d, shows a very small positive effect. It is not often used.
   - **b.** Methotrexate has been used in dosages of 7.5 to 20 mg orally once a week. A sensitive assay of hand function in wheelchair patients showed a detectable minor effect of the drug. It is often used as an "add-on" in combination with Copaxone or an IFN. No class I or II data are available to support this usage.
   - **c.** Mycophenolate mofetil (CellCept), in doses typically used for transplantation recipients, has been reported in pilot studies.

4. IV chemotherapy agents: The rationale behind the use of these agents is that intense nonspecific immunosuppression will arrest the progressive phase of axon and myelin destruction. Two agents are now in widespread use, cyclophosphamide and mitoxantrone. They share the potential problems of infection, bone marrow failure, or other common difficulties with chemotherapy, and both have a lifetime total dose limitation. This means that even if effective, another strategy has to be available for the time when that limit is reached. Additional agents are entering the MS treatment armamentarium, including rituximab, a drug that selectively targets and depletes CD-CD-20+ B cells.
   - **a.** Mitoxantrone, commonly prescribed for myelogenous leukemia, is a

member of the anthracenedione group. It inhibits DNA repair and causes crosslinks and scissions in nucleic acids. In patients with MS, it has a striking suppression of enhancement in lesions seen on MRI. Based on a 1998 trial of two dose levels of the drug compared with placebo, which showed a statistically significant effect on disability, mitoxantrone (Novantrone) has been approved by the U.S. Food and Drug Administration for use in SPMS. The drug is given IV once every 3 months at a dose of 12 mg/m^2 to a maximum dose of 140 mg/m^2. The maximum dose is usually reached in about 2 years. It is well tolerated. Cardiac toxicity can occur.

b. Cyclophosphamide has been in use for over 20 years for progressive forms of MS. The drug is an alkylating agent with powerful cytotoxic and immunosuppressive effects. No adequately controlled study has been carried out, although there are extensive class II data. The drug is usually given as a monthly bolus infusion of 800 mg/m^2 or increased from that level to obtain a nadir in total white blood cells (WBCs). Each infusion produces some nausea, anorexia, and modest alopecia. One obvious long-term risk of the drug is that of metaplasia and eventual malignancy of bladder mucosa. Long-term oral cyclophosphamide carries a significant risk of induction of other neoplasms, which has not been observed with the IV bolus program. Ovarian and testicular functions are impaired; women in their 30s who are treated commonly enter the menopause.

c. Both these drugs, if used, should be given by an oncologist or specialist familiar with their use and the potential complications of the treatment. Unfortunately, their records of success are only modest. Even if there is a response, one is faced with the problem of subsequent therapy after the maximum has been reached.

d. Rituximab has been shown to decrease relapse rate and MRI disease activity in phase II double-blind, placebo-controlled trials in RRMS patients. Unfortunately, in a separate trial, it did not show an effect in PPMS patients. Ocrelizumab, a more humanized anti-CD20≦ antibody, has been shown to effectively decrease relapses in RRMS patients and to decrease disability progression in PPMS patients. This agent may be added to the MS treatment landscape within the next 1 to 2 years.

General Treatment Comments

1. PPMS, although certainly demyelinating, may not be the same disease as relapsing MS or SPMS. There is a preponderance of males, the lesions and clinical deficits are often located mainly in the spinal cord, and the lesions seen on MRI scans are often unimpressive. To make a firm diagnosis, additional evidence from evoked potentials testing or CSF examination is often required. Ocrelizumab, however, may offer a new hope to this patient population. Symptomatic treatment should be emphasized, and in this arena, some progress can often be made in the individual patient.
2. MS is a lifelong illness, and there is no current paradigm for discontinuation of treatment. The entity of benign MS does exist, and in every MS clinic, there are patients who have had several relapses years or decades ago, who have no disability, who have MRI scans showing inactive disease, and who do not need any form of treatment. Unfortunately, the current estimates are that only about 10% of patients have benign MS. If a patient is doing well on long-term IFN or Copaxone, the drug needs to be continued without interruption indefinitely. Treatment can be suspended if the patient expressed a strong desire to have a break in therapy and if they show no evidence of disease activity for a period of 5 to 10 years. These patients need to be carefully observed for disease reactivation while off treatment.
3. Many clinical trials can be criticized for their short duration and for measuring endpoints that are not important. In the end, a significant treatment effect will be seen if the drugs prevent disability.
4. Patients need to be observed for signs of disease activity by clinical and/or MRI monitoring. Because the therapies for relapsing MS are only partially effective, some patients will respond and others will not. It may be a matter of careful judgment to decide if a patient's disease has come under control. Patients should be encouraged to report new symptoms. Periodic examinations should be performed. The role of periodic MRI scanning is also important. Centers with access to frequent MRI scanning have shown that new lesions detected by MRI are about 10 times as frequent as clinically detected lesions.
5. When to switch or change?
   a. A patient with little or no disability and no relapses on treatment should remain on treatment unless the patient is experiencing side effects.
   b. A patient with some disability and still working or able to work, but with abnormal gait or balance, should be observed carefully for the

progressive disease. An MRI scan may be beneficial. A scan that reveals enhancement indicates that a change of therapy is needed. A patient beginning to use a cane is one at high risk for further progression.

c. A patient with major side effects from any of the medications should be considered for a change, because of concerns of decreasing compliance, even in a setting of good disease control.

d. Consideration should be given to switching a patient for efficacy reasons if a relapse or MRI activity occurs. Alternate therapy must be sought. Consultation or a second opinion is desirable.

Special Considerations

1. CIS: MS often presents for the first time with ON, an acute brainstem syndrome, or TM. This first episode is known as CIS. Not all patients with CIS develop CDMS. Treatment with MS-specific medications should be offered to CIS patients based on results of CHAMPS trial (Avonex), BENEFIT trial (Betaseron), and PreCISe trial (Copaxone). All three agents showed decreased rate of conversion to CDMS from CIS. It can be assumed that treatment with any disease-modifying agent will likely be beneficial to this group of patients.
2. ON can be an early symptom of MS (CIS event) or a separate disease entity. Patients typically present with acute/subacute unilateral decrease or loss of vision, impairment of color vision, and pain on eye movements. Examination may show reduced visual acuity on the affected side, relative afferent pupillary defect (RAPD), and inflamed optic nerve head. Visual evoked responses (VERs) often show prolonged latency of P100 wave; Goldmann Visual Field test shows central scotoma or other visual field defect. MRI may show T1 postcontrast enhancement of the optic nerve on the affected side. ON can be treated with IV methylprednisolone at a dose of 1,000 mg for 3 to 5 days. This treatment hastens visual recovery but does not improve the visual acuity (Optic Neuritis Treatment Trial). However, it decreases the rate of second clinical event over 24 months of follow-up, thus decreasing the probability of conversion to CDMS.
3. *TM* is an acute or subacute inflammation of the spinal cord. It is usually limited to two to three spinal segments and occupies less than two-thirds of cross-sectional cord diameter. Similarly to ON, it can be a precursor to MS

(CIS event) or occur independently (postinfectious, infectious, or idiopathic TM). Symptoms may include ascending numbness and paresthesias in the legs, trunk, or perineum, leg weakness, difficulty with or a loss of bladder and/or bowel control, or back pain. Exam findings depend on the level of spinal cord involvement and may show decreased sensation to various modalities in the legs and/or the arms, spinal sensory level, paraparesis, abnormal deep tendon reflexes, and pathologic reflexes. Involvement of the entire cross-sectional cord diameter and complete loss of sensation with paraplegia is seen more often in postinfectious or infectious TM rather than in MS. Treatment with IV methylprednisolone 1 g × 3 to 5 days is usually undertaken, although in contrast with ON, there are no trials with clear evidence of efficacy.

OTHER DEMYELINATING DISEASES

1. Baló concentric sclerosis is a rare variant of MS. It is characterized by alternating bands of demyelinated and myelinated white matter in concentric rings or irregular stripes. Lesions may be multiple or mixed with other, more typical MS plaques. It is often a feature of aggressive disease, but it can occur in chronic MS.
2. Marburg variant of MS is a severe, sometimes monophasic disease form leading to advanced disability or death within a period of weeks to months. It is usually a clinical diagnosis based on the speed and severity of progression of neurologic disability. No treatment has consistently proven effective. MRI shows extensive, diffuse, confluent cerebral involvement giving the appearance of "MS cerebritis." Sometimes, a large solitary expanding lesion (*tumefactive MS*; *tumorlike demyelination*) can be seen. These patients often undergo brain biopsy which shows extensive inflammatory infiltrates and demyelination. High-dose steroids are often ineffective, although they are usually tried. Transient improvement with aggressive chemotherapy regimens has been described. Some patients have a more benign course and are considered by some experts to represent a transitional demyelinating illness between MS and ADEM.
3. ADEM is a monophasic, acute, autoimmune demyelinating illness that typically occurs after an upper respiratory infection (URI) (50% to 75%) or

vaccination. First symptoms are seen 7 to 14 days postinfection, and most patients require a hospital admission within a week. Children are more prone to ADEM than adults. Clinical presentation varies by age: children often present with prolonged fever, headache, and brainstem syndrome (imbalance/gait instability, dysphasia/dysarthria, diplopia), while adults can have a milder illness with limb paresthesias and weakness. Suspect ADEM when:

a. There is a close temporal relation between infection/vaccination and multifocal CNS process.

b. MRI shows >50% involvement of white matter and may also involve deep gray matter with enhancement present in most/all lesions.

c. CSF analysis shows mild lymphocytic pleocytosis, protein elevation, and typically no oligoclonal bands.

d. Biopsy is performed (usually only for tumefactive or solitary lesions) because ADEM pathology shows perivascular infiltration with macrophages and T cells and demyelination restricted to perivascular area (unlike MS).

e. Examination hallmarks include confusion/disorientation, altered level of alertness, gait ataxia, dysmetria, dysarthria, brainstem signs, abnormal sensation, and pyramidal weakness.

f. Treatment options include IV corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIG), and cytotoxic chemotherapy. Efficacy is variable. Full recovery is expected in more than 70% of patients; 10% to 20% are left with mild to moderate disability; sudden severe polysymptomatic onset implies worse prognosis and there is 5% mortality in this group of patients.

4. Acute necrotizing hemorrhagic encephalopathy, or Weston Hurst disease, is a fulminant form of ADEM. Pathologic lesions are similar to ADEM. It is always preceded by respiratory infection (often, mycoplasma). Microscopic hemorrhages and perivascular neutrophilic infiltrates as well as necrosis of small blood vessels and surrounding brain tissue can be seen on pathology specimens. Response to treatment is very limited, and mortality is high in this disease, especially within the first 2 to 4 days after the diagnosis.

5. Neuromyelitis optica (NMO) (Devic disease) is a variant of MS predominantly affecting the spinal cord (myelitis) and bilateral optic nerves.

It can have a monophasic or a relapsing course. It is common in Africa and Asia as well as in African and Asian Americans. Japan has the highest incidence of NMO with at least 10,000 affected persons. Myelitis usually spans more than three spinal segments and often is accompanied by swelling of the spinal cord. Pathology in the spinal cord and optic nerves shows extensive demyelination, cavitating necrosis, acute axonal injury, and loss of oligodendrocytes. IgG anti-NMO antibodies, directed against the aquaporin-4 water channel, are positive in 73% of patients with NMO. Oligoclonal bands are present in 85% of these patients. Brain MRI may show few T2 hyperintense lesions, while spinal cord MRI usually shows extensive lesions. Natural history of NMO is that of a rapidly progressive and disabling neurologic illness: 50% of patients are wheelchair bound within 5 years of the diagnosis, and 60% of patients become functionally blind within the same time frame. Immunosuppression is partially effective in nonrandomized trials. IV methylprednisolone and plasma exchange can be used. Rituximab has showed efficacy in trials with significantly improved disability scores and decreased attack rate in NMO patients.

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8 Autoimmune Disorders

Ivana Vodopivec and Henrikas Vaitkevicius

BACKGROUND

1. Immune responses are traditionally classified as adaptive (acquired or specific) and innate (nonspecific). The adaptive immune system is specialized for development of an inflammatory response based on recognition of and memory for specific "foreign" target molecules (antigens). Its key players are antibodies, B lymphocytes (B cells), T lymphocytes (T cells), and antigen-presenting cells. Adaptive immune responses can be further divided into humoral (i.e., antibody-mediated) and T cell-mediated responses.
2. Autoimmune diseases are defined as diseases in which adaptive immune system erroneously targets self (autologous or autoantigens) resulting in tissue damage. The inappropriate, misdirected adaptive immune response results from a loss of self-tolerance. Autoimmune disorders of the nervous system are caused by an adaptive immune response directed against an autoantigen within the nervous system. The abnormal immune response is activated by either an autoantigen or foreign antigens. Based on the inciting mechanism, autoimmune disorders can be divided into autoimmune *sensu stricto*, paraneoplastic, and parainfectious.
   a. Autoantigens recruit immune response in *autoimmune* and *paraneoplastic* disorders. In *paraneoplastic* disorders, the immune response is generally directed against neuronal antigens that are inadvertently expressed by benign or malignant neoplasms (e.g., teratoma-induced limbic encephalitis).
   b. *Parainfectious* conditions are believed to be mediated by abnormal or enhanced immune response triggered by a foreign antigen (e.g., Guillain–Barré syndrome).

3. Some conditions, such as anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis, can be autoimmune (without an associated neoplasm or a preceding infection), paraneoplastic (related to ovarian teratoma), or parainfectious (post-herpes simplex virus [HSV] encephalitis). There are numerous individually named autoimmune diseases that are phenotypically diverse and difficult to study because of their low incidence. The management of these disorders often requires a multidisciplinary approach by rheumatologists, oncologists, and other specialists.
4. The treatment of neurologic autoimmune disorders is nonspecific. These disorders frequently remain untreated or undertreated because of difficulties with establishing the diagnosis, especially in cases when histopathologic evaluation is essential.
5. The organization of these disorders based on the pathophysiology of the underlying immune dysfunction delineated in this chapter allows expedited and more targeted interventions.

EPIDEMIOLOGY

1. Autoimmune disorders of the nervous system are generally diagnosed in young individuals.
2. The following gender differences have been recognized:
   - **a.** Female preponderance is observed in neuromyelitis optica (NMO; 5 to 10:1), multiple sclerosis (MS; 2:1), Susac syndrome (3.5:1), in the younger patient population with myasthenia gravis, Sjögren syndrome (9:10), Behçet disease in the United States and Northern Europe (2:1), and giant cell arteritis (3:1).
   - **b.** Male preponderance is observed in the older patients with myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, acute disseminated encephalomyelitis (ADEM; 0.6 to 0.8:1 in pediatric population), Guillain–Barré syndrome (0.7:1), and IgG4-related disease.
   - **c.** No gender predilection exists in sarcoidosis, primary angiitis of the central nervous system (CNS).

PATHOPHYSIOLOGY

1. Autoimmunity is caused by the loss of immunologic tolerance to self. Several mechanisms have been responsible including failure of what has been termed "central tolerance" (originating in dysfunction of germinal nodes in the thymus), failure of peripheral regulation (in lymph nodes and tissues), presentation of an autoantigen (through molecular mimicry, release of sequestered autoantigens), or by costimulation of T and B cells by antigen-presenting cells.
2. Distinct immune mechanisms are implicated in particular autoimmune disorders of the nervous system. In some instances, multiple immunologic pathways may be active:
   a. T-cell-mediated pathology
   b. B-cell-mediated pathology
   c. Granulomatous pathology
   d. Autoinflammatory pathology
   e. Unclear/not otherwise specified (NOS)

DIAGNOSIS

Clinical Presentation

1. Autoimmune disorders of the nervous system may be classified as
   a. Limited to (e.g., isolated neurosarcoidosis) or specific to the nervous system (e.g., MS)
   b. Manifestation of a systemic rheumatologic disease (e.g., Sjögren syndrome)
2. Autoimmune disorders are subacute (<3 months), monophasic, relapsing-remitting, or chronic progressive. Parainfectious disorders may present acutely or subacutely during or shortly after (within weeks of) an antigenic challenge (infectious disease or vaccination).
3. Diagnosis of autoimmune disorders is often established by exclusion once infectious, toxic/metabolic, neoplastic, and other processes are ruled out. Occasionally, specific clinical syndromes, the examples of which are listed in Table 8-1, can be identified. More frequently, the clinical findings are nonspecific, and additional evidence is sought through diagnostic testing.

Table 8-1 Well-Defined Autoimmune Syndromes of the Central Nervous System

Syndromes	Etiologies
Limbic encephalitis	Paraneoplastic (including anti-NMDA receptor antibodies), HSV, HHV-6, syphilis
Faciobrachial dystonic seizures	Anti-LGI1 antibodies
Motor cerebellar syndrome (subacute cerebellar degeneration)	Paraneoplastic, parainfectious
Opsoclonus-myoclonus	
Optic neuritis, myelitis	NMO, MS
Miller-Fisher syndrome	Anti-GQ1b antibodies
Stiff person syndrome	Anti-GAD, anti-GABAa, antiamphiphysin antibodies
Morvan syndrome (neuromyotonia, limbic encephalitis/encephalopathy, and autonomic dysfunction)	Anti-Caspr2 antibodies

NMDA, *N*-methyl-D-aspartate; HSV, herpes simplex virus; HHV-6, human herpesvirus 6; LGI1, leucine-rich, glioma inactivated 1; NMO, neuromyelitis optica; MS, multiple sclerosis; GQ1b, ganglioside Q1b; GAD, glutamic acid decarboxylase; GABA, γ-aminobutyric acid; Caspr2, contactin-associated protein-like 2.

Diagnostic Tests

1. Laboratory tests are used to demonstrate alternative, noninflammatory conditions or provide evidence of ongoing inflammatory/autoimmune dysfunction. Table 8-2 summarizes laboratory findings which may provide evidence of an underlying autoimmune disorder (e.g., anemia in systemic lupus erythematosus [SLE], hormonal dysfunction in patients with neurosarcoidosis with hypothalamic involvement) and identifies specific disease biomarkers that are associated with (e.g., anti-Ro and anti-La antibodies in Sjögren syndrome) or causing disease (e.g., NMO antibodies in NMO).
2. Neuroimaging is of great value in patients with suspected autoimmune disorders of the nervous system. Contrast-enhanced magnetic resonance imaging (MRI) of the brain and spine has become the cornerstone of advanced neurologic evaluation for these disorders. The diagnostic yield

from cranial computed tomography (CT) is poor but sometimes the only imaging available. CT angiogram is probably the method of choice in patients with suspected vasculitis. Patterns of T2/fluid-attenuated inversion recovery (FLAIR) abnormalities, diffusion restriction, contrast enhancement, and perfusion may be specific for certain autoimmune, infectious, parainfectious, toxic, metabolic (including mitochondrial), and neoplastic autoimmune conditions (Table 8-3).

Table 8-2 Suggested Laboratory Tests in Patients with Suspected Autoimmune Disorders of the Nervous System

Alternative Pathologies	Markers of Inflammation and/or Autoimmunity
CBC with differential[a]	ESR[a]
Electrolytes, glucose[a]	CRP[a]
BUN/Cr[a]	ANA[a]
Liver function tests[a]	Anti-dsDNA antibodies[a]
Ammonia	Extractable nuclear antigens (ENA)—anti-Ro, anti-La[a]
Vitamin B_{12}	ANCA[a]
Coagulation panel[a]	RF, ACPA
Thyroid function	Antiphospholipid antibodies
Cortisol	Myositis-specific antibodies
Toxicology screen	Complement levels
Urinalysis and culture	Cryoglobulins
Blood culture	IgG4 level
Serologies for syphilis	Anti-TPO antibodies
SPEP with immunofixation	ACE
Serum free light chains	HLA-B51
Blood flow cytometry	NMO (antiaquaporin 4) antibodies
β2 microglobulin	Paraneoplastic antibodies

[a]Denotes basic/screening laboratory evaluations.

CBC, complete blood count; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatine; ANA, antinuclear antibody; dsDNA, double-stranded DNA; ANCA, antineutrophil cytoplasmic antibody; RF, rheumatoid factor; ACPA, anticitrullinated peptide antibodies; IgG4, immunoglobulin G subclass 4; TPO, thyroid peroxidase; SPEP,

serum protein electrophoresis; ACE, angiotensin-converting enzyme; HLA-B51, human leukocyte antigen B51; NMO, neuromyelitis optica.

3. Advanced imaging, including spectroscopy and fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (FDG-PET/CT) of the brain, might be indicated to narrow the differential diagnosis.
4. Analysis of the cerebrospinal fluid (CSF) can be as valuable as neuroimaging. Table 8-4 lists CSF studies that may be requested in patients with suspected inflammatory disorders. CSF inflammation is most frequently identified by presence of one or more of the following: pleocytosis (>5 white blood cells), elevated protein (>50 mg/dL), the presence of oligoclonal bands (>1), and an elevated IgG index (>0.66). Hypoglycorrhachia is more typically seen in infectious (bacterial, fungal) and neoplastic conditions (leptomeningeal carcinomatosis) but can be observed not only in some inflammatory disorders such as neurosarcoidosis but also in primary angiitis of the CNS and neuro-Behçet disease. It is important to recognize that autoantibodies or oligoclonal bands may be present in CSF without CSF inflammation. The most frequent example of this configuration is MS, but oligoclonal bands in CSF are not unique to this disease and may be present in other autoimmune disorders.

Table 8-3 Magnetic Resonance Imaging Findings and Patterns of Contrast Enhancement

Location and Pattern	Autoimmune Etiologies	Alternative Diagnoses
FLAIR hyperintensity in the subarachnoid space	Elevated CSF protein/cells	Carcinomatosis, hyperoxygenation, propofol exposure, contrast extravasation
Mesial temporal T2/FLAIR hyperintensities	Limbic encephalitis	HSV, syphilis, HHV-6, seizures
Isolated white matter T2 hyperintensities (without contrast enhancement)*a*	Inflammatory/demyelinating conditions (MS, NMO, ADEM, neurosarcoidosis, Behçet disease, Sjögren syndrome)	Vascular pathologies (microvascular changes, CAA-related lesions, CADASIL, postradiation changes)

		Infections (PML, HIV encephalopathy) Neoplasms (glioma, gliomatosis cerebri, lymphomatosis cerebri, intravascular lymphoma, metastasis) Toxic exposures (methotrexate, cytarabine, toluene, heroin, alcohol) Leukodystrophies and mitochondrial diseases
Intra-axial rim enhancement*a*	Demyelination ("open" ring)	Metastasis, abscess, cerebritis, glioma, subacute infarction, contusion, radiation necrosis
Pachymeningeal/ Leptomeningeal enhancement*a*	Autoimmune granulomatous diseases (neurosarcoidosis, granulomatosis with polyangiitis) Nonspecific autoimmune conditions (IgG4-related disease, idiopathic hypertrophic pachymeningitis, Tolosa-Hunt, rheumatoid arthritis)	Infections (syphilis, tuberculosis, fungal) Neoplasms (meningioma, lymphoma, metastasis, histiocytic disorders) Other (intracranial hypotension)
Nerve root enhancement*a*	Guillain–Barré syndrome Autoimmune granulomatous diseases (neurosarcoidosis, granulomatosis with polyangiitis)	Infections (CMV, HSV, schistosomiasis, syphilis, tuberculosis, Lyme, fungal infections) Neoplasms (meningioma, lymphoma, metastasis, histiocytic disorders)

*a*Contrast enhancement, which results from the breakdown of blood–brain barrier.

FLAIR, fluid-attenuated inversion recovery; CSF, cerebrospinal fluid; HSV, herpes simplex virus; HHV-6, human herpesvirus 6; MS, multiple sclerosis; NMO, neuromyelitis optica; ADEM, acute disseminated encephalomyelitis; CAA, cerebral amyloid angiography; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PML, progressive multifocal leukoencephalopathy; IgG4, immunoglobulin G subclass 4; CMV, cytomegalovirus.

Table 8-4 Cerebrospinal Fluid Studies Consistent with Inflammation in the Central Nervous System

Cerebrospinal Fluid Study	Result

Glucose	Normal
Protein	Elevated
WBCs	5–100
IgG index	>0.66 (laboratory dependent)
Oligoclonal bands	>1 (laboratory dependent)
Paraneoplastic antibodies	Positive
HSV1/HSV2 PCR	Negative
VZV PCR, IgM and IgG	Negative
Next-generation sequencing of microbial DNA	Negative
Cytology	Normal
Flow cytometry	Normal
β2 microglobulin	Normal
IgH gene rearrangement	Absent

WBC, white blood cell; IgG, immunoglobulin G; HSV, herpes simplex virus; PCR, polymerase chain reaction; VZV, varicella-zoster virus; IgM, immunoglobulin M; IgH, immunoglobulin heavy chain.

a. Presence of oligoclonal bands or elevation of IgG index may represent activation of CNS-targeted humoral response (Table 8-5).
   1) The sensitivity of oligoclonal bands is laboratory-specific. Isoelectric focusing (IEF) on agarose gels followed by some form of immunodetection (immunoblotting or immunofixation) is now the accepted gold standard for detecting the presence of oligoclonal immunoglobulin bands (OCBs). There must be a parallel investigation of serum with a report on the relative band patterns in the CSF and serum.
   2) Quantitative IgG analysis (i.e., IgG index) is an informative complementary test but is not considered a substitute for qualitative IgG assessment (OCBs), which has the highest sensitivity and specificity.

b. In addition to CSF, cell counts with differential, cellular responses can be evaluated by analysis of T cell subsets and their cluster of differentiation 4 (CD4)/cluster of differentiation 8 (CD8) ratio. This is, however, of limited value, and the normal values are not standardized (see Table 8-5).

5. Electroencephalography (EEG) is usually nonspecific for autoimmune CNS diseases but is very informative in evaluating and guiding treatment of the

patients with altered level of consciousness. Occasionally, certain findings may be suggestive of specific disease processes (see Table 8-6 for details).

Table 8-5 Selected Markers of Adaptive Immune Response in Cerebrospinal Fluid (CSF)

CSF Constituents	Differential Diagnosis
Oligoclonal bands >1	Immunoglobulin generating CNS-focused autoimmune diseases (MS, ADEM, neurosarcoidosis, Behçet disease, SLE, Sjögren syndrome, paraneoplastic or autoimmune disorders caused by antineuronal antibodies) CNS infections (neurosyphilis, neuroborreliosis, HIV encephalitis) Lymphoma
IgG index 5 (CSF IgG/CSF albumin) / (serum IgG/serum albumin) >0.66 (laboratory-dependent value)	Immunoglobulin targeting antigens within CNS
CD4/CD8 ratio >3	Highly elevated in neurosarcoidosis Mildly elevated in MS Normal in infectious meningitis
Relative elevation of B cell counts	Paraneoplastic disorders

CNS, central nervous system; MS, multiple sclerosis; ADEM, acute disseminated encephalomyelitis; SLE, systemic lupus erythematosus; IgG, immunoglobulin G; CD4, cluster of differentiation 4; CD8, cluster of differentiation 8.

6. Additional investigations may be required to narrow the differential diagnosis, establish a definitive diagnosis, or determine the extent of a systemic disease (Table 8-7). For example, whole-body PET/CT can be used to determine appropriate sites for diagnostic biopsy in patients with multisystem involvement.
7. In patients with neurologic disease of unknown etiology, the value of stereotactic brain biopsy is sufficiently high and the morbidity sufficiently low to justify its use. Usually, the highest yield is achieved when specific and enhancing lesions are targeted. When random biopsy is considered, it is important to obtain a larger sample which includes white matter, grey matter with overlying leptomeninges, vessels, and dura. Demonstration of characteristic histopathologic findings is the method of choice for making

definitive diagnosis of vasculitis, sarcoidosis, IgG4-related disease, as well as neoplasms.

Table 8-6 Electroencephalography (EEG) Abnormalities in Patients with Suspected Autoimmune Conditions of the Nervous System

EEG Finding	Diagnosis
Extreme delta brush	Anti-NMDA receptor encephalitis
Periodic temporal discharges	HSV encephalitis
Diffuse slowing with triphasic waves	Metabolic encephalopathy

NMDA, *N*-methyl-D-aspartate; HSV, herpes simplex virus.

Table 8-7 Additional Imaging and Diagnostic Studies for Evaluation of Patients with Suspected Autoimmune Disorders of the Nervous System

Diagnostics	Finding	Potential Diagnosis
CT chest and abdomen/pelvis	Mass	Malignancy
Whole-body FDG-PET/CT	Areas of FDG avidity	Malignancy, inflammation
Transvaginal US	Ovarian mass	Anti-NMDA receptor encephalitis
Dilated funduscopic examination and fluorescein angiography	Branch retinal artery occlusions, hyperfluorescence of the vessel wall	Susac syndrome
	Uveitis	Sarcoidosis, Behçet disease, GPA, other rheumatologic conditions
	Vitreous opacities, subretinal pigment epithelial infiltrates	Intraocular–central nervous system lymphoma
Labial salivary gland biopsy	Focal lymphocytic sialadenitis	Sjögren syndrome
Temporal artery biopsy	Granulomatous inflammation	Giant cell arteritis

CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography; US, ultrasound; NMDA, *N*-methyl-D-aspartate; GPA, granulomatosis with polyangiitis.

TREATMENT

1. The treatment of immunologic diseases of the nervous system includes immunomodulation and symptomatic therapies for seizures, vascular events, cerebral edema, pain, psychiatric symptoms, etc. Treatment of paraneoplastic disorders should be focused on management of underlying neoplasms. Immunologic therapies should be selected based on distinct immune mechanisms implicated in particular autoimmune disorders of the nervous system summarized in Table 8-8.
   - **a.** Glucocorticoids, intravenous immunoglobulin, and plasma exchange (plasmapheresis) are reserved for induction (management of active disease to induce remission) because of their rapid onset and nonspecific effects on the immune system.
   - **b.** Maintenance immunotherapy includes agents that modulate immune responses more specifically.

Table 8-8 Autoimmune Central Nervous System Diseases and Treatments Classified by Mechanism of Underlying Immune Dysfunction

Predominant Pathophysiology	T-Cell-Mediated	B-Cell-Mediated	Granulomatous Disorders
Disorders	Multiple sclerosis	SLE	Sarcoidosis
	ADEM	Antiphospholipid syndrome	GCA
	PACNS (PCNSV)	NMO (anti-AQP4, anti-MOG antibodies)	GPA
	Aβ-related angiitis	Miller Fisher syndrome	—
	IgG4-related disease	Bickerstaff encephalitis	—
	Sjögren syndrome	SREAT	—
	Antibodies against intracellular antigens: Hu, Ma2, GAD, CV2, Ri, Yo, amphiphysin	Antibodies against cell-surface synaptic receptors (NMDA, LGI1, Caspr2, DPPX,	—

		AMPA, GABA, mGluR5, D2 receptor)	
	CLIPPERS	—	—
Treatments	Glucocorticoids	Glucocorticoids	Glucocorticoids
	Cyclophosphamide	Plasma exchange	TNF-α inhibitors (GCA does not respond)
	Anti-CD20 targeting therapies	IVIG	Anti-CD20 targeting therapies
	Natalizumab	Anti-CD20 targeting therapies	Cyclophosphamide
	—	Anti-C5 (eculizumab)	—
	—	Anti-IL-6R (tocilizumab)	—

NOS, not otherwise specified; SLE, systemic lupus erythematosus; ADEM, acute disseminated encephalomyelitis; GCA, giant cell arteritis; PACNS, primary angiitis of the central nervous system; PCNSV, primary central nervous system vasculitis; NMO, neuromyelitis optica; AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; GPA, granulomatosis with polyangiitis; IgG4, immunoglobulin G subclass 4; SREAT, steroid responsive encephalopathy associated with autoimmune thyroiditis; NMDA, *N*-methyl-D-aspartate; LGI1, leucine-rich, glioma inactivated 1; Caspr2, contactin-associated protein-like 2; DPPX, dipeptidyl-peptidase-like protein-6; AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GABA, gamma-aminobutyric acid; mGluR5, metabotropic glutamate receptor 5; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; TNF, tumor necrosis factor; IVIG, intravenous immunoglobulin; C5, complement component 5; IL-6R, interleukin receptor 6 receptor.

Table 8-9 Suggested Pretreatment Screening Studies and Baseline Evaluations Before Initiating Immunosuppressive Agents

Infectious Workup	Other Diagnostic Studies
Hepatitis B screening (HBsAg, anti-HBs, anti-HBc)[a]	CBC[a]
Hepatitis C screening (anti-HCV)[a]	BUN/Cr[a]
HIV antibodies,[a] PCR; T cell CD4 count	LFTs[a]
Tuberculosis testing (PPD/IGRA)[a]	hCG

JCV antibodies	Vitamin D
Strongyloides stercoralis, serology	Bone densitometry
Trypanosoma cruzi, serology	TMPT genotype
	CXR
	Ophthalmologic evaluation
	Immunoglobulin levels (IgM, IgG, IgA)

[a]Obtain in all patients.

HBsAg, surface antigen of the hepatitis B virus; HB, hepatitis B; HBc, hepatitis B core; CBC, complete blood count; HCV, hepatitis C virus; BUN, blood urea nitrogen; Cr, creatine; PCR, polymerase chain reaction; CD4, cluster of differentiation 4; LFT, liver function test; PPD, purified protein derivative; IGRA, interferon-γ-release assay; hCG, human chorionic gonadotropin; JCV, John Cunningham virus; TMPT, 5-thiopurine-methyltransferase; CXR, chest X-ray; IgM, immunoglobulin M; IgG, immunoglobulin G; IgA, immunoglobulin A.

2. The use of immunosuppressants carries a significant risk of systemic complications, which are infectious and noninfectious.

a. The potential risks of adverse reactions can be minimized by screening evaluations, patient monitoring, and preventative measures.

1) Baseline and screening laboratory testing that should be obtained prior to introducing immunomodulatory agents are listed in Table 8-9.

2) Subsequent routine monitoring should be individualized based on specific toxicities of individual medications (Table 8-10).

3) Vaccinations should be administered according to established guidelines (e.g., 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host).

4) Preventive measures for infectious and noninfectious complications are outlined in Table 8-10.

b. The risk-to-benefit ratio of any immunosuppressive drug should be discussed with the patient. Informed consent is required for certain immunosuppressants that are associated with significant adverse effects, such as cyclophosphamide, rituximab, and natalizumab.

c. Family planning should be addressed in patients of reproductive age. Fertility preservation measures may be instituted in patients who will receive cyclophosphamide. Adjustment or discontinuation of immunosuppression should be considered before a planned pregnancy.

d. Certain medications are compatible with pregnancy, including glucocorticoids, intravenous immunoglobulin, and azathioprine up to 2

mg/kg/d. TNF-α inhibitors are considered reasonably safe within first and second trimester and during lactation. Methotrexate, mycophenolate mofetil, and cyclophosphamide must be discontinued before conception because of proven teratogenicity. These medications are labeled by the U.S. Food and Drug Administration (FDA) as pregnancy category D, that is, drugs posing risks for human fetus, but benefits may outweigh risks in certain situations, and X, that is, drugs with proven fetal risks that outweigh any possible benefit. Most biologic agents have limited documentation on safe use in pregnancy and should be discontinued or replaced by other medication before conception.

Table 8-10 Immunomodulatory Therapies: Dosing Regimens, Key Risks and Adverse Effects, and Suggested Monitoring and Prophylactic Strategies

Immunotherapy (Mechanisms of Action)	Dosing	Major Risks	Prophy
Glucocorticoids (genomic effects, nongenomic effects: leukocyte adhesion and cytokine modulation)	Methylprednisolone 1 g IV qd for 3–5 d Prednisone start 1 mg/kg/d (60–80 mg p.o. qd) Dexamethasone 1–4 mg p.o. q6h	Hyperglycemia, psychiatric events, infections, adrenal suppression, osteoporosis, osteonecrosis, myopathy, glaucoma, cataracts	PPI, vita bisph altern TMP/SM
Intravenous immunoglobulin (autoantibodies, passive immunization, complement downregulation, cytokine modulation)	2 g/kg over 3–5 d	Hypersensitivity reactions, thromboembolic events, renal failure, aseptic meningitis, hemolytic anemia, neutropenia	Acetam Diphenh
Plasma exchange (removal of pathogenic antibodies from vascular compartment, cytokine modulation)	1–1.5 plasma volumes, typically 5 exchanges allowing for vascular compartment equilibration between	IV access complications, hypocalcemia, hypotension, arrhythmia, coagulopathy, medication removal	Not give gluco

	treatments (qod)		
Cyclophosphamide (DNA alkylation, T_H1 suppressor and T_H2 enhancer)	Protocols: Partners MS: 800 mg/m^2 IV q 4wk x 6 EULAR: 15 mg/kg IV q 2wk 3 3 SLE NIH: 0.5–1 g/m^2 q 4wk x 6 EURO lupus: 500 mg IV q 2wk x 6	Cytopenias, infections, hemorrhagic cystitis, malignancies (particularly bladder cancer), gonadal toxicity	Hydratic Mesna Antieme TMP/SM Fertility
Anti-CD20 antibodies (B-cell and plasmablast depletion)	Rituximab 1,000 mg IV q 2wk x 2 Rituximab 375 mg/m^2 IV qw x 4	Hypersensitivity reactions, hypogammaglobulinemia, CVID, infections, PML	HBV rea Acetam Diphenh Methylpr
TNF-a inhibitors (inhibition of macrophage activation via decrease in TNFR1/2 stimulation)	Infliximab 3–10 mg/kg IV q 2wk Adalimumab 40 mg s.c. q 2wk	Hypersensitivity reactions, hepatotoxicity, CNS and PNS demyelination, including optic neuritis, TB reactivation	Treat lat HBV rea Conside TMP/S Acetam
Azathioprine (DNA intercalation, inhibition of purine synthesis)	Start 1 mg/kg/d (50–100 mg p.o. qd) and then increase by 50 mg/wk to 2–3 mg/kg/d	Hepatotoxicity, leukopenia and other cytopenias, infections, GI toxicity (nausea, diarrhea)	None
Methotrexate (inhibition of thymidylate and purine synthesis)	p.o.: Start 7.5 mg qw and then increase to 15–25 mg qw. s.c.: Start 7.5 mg qw and then increase to 10–25 mg qw.	Nausea, diarrhea, mucositis, cytopenias, hepatotoxicity, (hypersensitivity pneumonitis)	Folic ac Sun pro
Mycophenolate mofetil (inhibition of guanosine synthesis)	Start 250 or 500 mg p.o. b.i.d. and then increase by 500 mg/d q 1–2 wk to 1,000–1,500 mg p.o. b.i.d.	Nausea, diarrhea, abdominal pain, hepatotoxicity, cytopenias, HTN, nephrotoxicity, cough, dyspnea, infections, HA,	Sun pro

		tremor	
Eculizumab (anti-C5 antibody)	Eculizumab 400–1,200 mg IV q 2wk	Hypersensitivity reactions, HTN, anemia	Acetam Diphenh
Tocilizumab (anti-IL-6R antibody)	Tocilizumab 8 mg/kg IV q 4wk	Hypersensitivity reactions, GI perforation, hepatotoxicity, neutropenia, thrombocytopenia, TB reactivation	Acetam Diphenh
Natalizumab (anti-a4–integrin antibody)	300 mg IV q 4 wk	PML, hypersensitivity reactions	Acetam Diphenh

IV, intravenous; PPI, proton pump inhibitor; TMP/SMX, trimethoprim/sulfamethoxazole; VS, vital signs; BUN, blood urea nitrogen; Cr, creatine; IVIG, intravenous immunoglobulin; qod, every other day; IVF, intravenous fluids; CBC, complete blood count; Ig, immunoglobulin; T_H1, type 1 T helper cells; T_H2, type 2 T helper cells; MS, multiple sclerosis; EULAR, European League Against Rheumatism; SLE, systemic lupus erythematosus; NIH, National Institutes of Health; EURO, Association of European Operational Research Societies; UA, urinalysis; CD20, cluster of differentiation 20; qw, every week; CVID, common variable immune deficiency; PML, progressive multifocal leukoencephalopathy; HBV, hepatitis B virus; CD19, cluster of differentiation 19; IgG, immunoglobulin G; IgM, immunoglobulin M; TNF, tumor necrosis factor; TNFR, tumor necrosis factor receptor; s.c., subcutaneous; CNS, central nervous system; PNS, peripheral nervous system; TB, tuberculosis; LFTs, liver function tests; GI, gastrointestinal; TMPT, 5-thiopurine-methyltransferase; CXR, chest X-ray; b.i.d., twice a day; HTN, hypertension; HA, headache; LDH, lactate dehydrogenase; JCV, John Cunningham virus.

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9 Neuromuscular Junction Disorders and Myopathies

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MYASTHENIA GRAVIS

Background

1. Myasthenia gravis is an autoimmune disease caused by an immunologic attack directed against the postsynaptic neuromuscular junction (NMJ).
2. The incidence of myasthenia gravis ranges between 1 and 9 per million, whereas the prevalence ranges between 25 and 142 per million. The incidence of myasthenia gravis is slightly greater in women than in men. The age of onset is bimodal for both men and women. Women demonstrate annual peak incidences at ages 20 to 24 years and 70 to 75 years, while men have peak rates between 30 and 34 years and 70 and 74 years.
3. Patients with myasthenia gravis can be classified according to the Osserman criteria:
   a. Group 1: ocular, 15% to 20%
   b. Group 2A: mild generalized, 30%
   c. Group 2B: moderately severe generalized, 20%
   d. Group 3: acute fulminating, 11%
   e. Group 4: late severe, 9%
4. As many as 70% of patients with myasthenia gravis have thymic hyperplasia, and approximately 10% have a thymoma. Thymomas are much more common in patients between the ages of 50 and 70 years. Importantly, the thymomas can be malignant and invasive. The role of the thymus in myasthenia gravis is unclear.

Pathophysiology

Myasthenia gravis is an acquired autoimmune disorder of neuromuscular transmission resulting from antibodies directed against the acetylcholine receptor (AChR), to a lesser extent, muscle-specific tyrosine kinase (MuSK), and, rarely, lipoprotein-related protein 4 (LRP4).

Prognosis

1. At least 50% of patients initially presenting with purely ocular symptoms eventually develop a more generalized form of the disease.
2. Most patients evolve to their weakest state within the first 3 years.
3. Patients may develop severe generalized weakness with respiratory failure or inability to swallow. Severe respiratory and bulbar weakness can develop in the absence of ocular or extremity weakness.
4. Patients with only mild weakness may respond to anticholinesterase medications. However, patients with moderate or severe weakness require immunosuppressive agents and immunomodulating therapies.

Diagnosis

Clinical Features

1. The clinical hallmark of myasthenia gravis is fluctuating weakness characterized by abnormal fatigability that improves with rest.
2. Patients often complain of drooping eyelids, blurred vision, or frank diplopia, particularly after prolonged reading or at the end of the day. Ptosis is the presenting symptom in 50% to 90% of patients, whereas 15% have blurred vision or frank diplopia. At some point, about 90% to 95% of patients complain of diplopia.
3. Dysphagia and dysarthria occur in as many as one-third of patients.
4. Proximal limb and neck weakness is a presenting symptom in approximately 20% to 30% of individuals. Importantly, approximately 3% of patients manifest with predominantly distal weakness. Head drop secondary to neck extensor weakness is not uncommon and can be the presenting feature. There may be fatigue after repetitive activities.
5. Occasionally, patients present with respiratory failure because of weakness

of the diaphragm and accessory muscles of respiration.

3. Patients with MuSK antibodies often manifest with bulbar or proximal weakness without ocular involvement.

Pharmacologic Testing

1. The edrophonium (i.e., Tensilon) test can be helpful in diagnosing myasthenia gravis. Edrophonium is an anticholinesterase and its ingestion will result in a transient increase in AChR in the NMJ.
   - **a.** Anticholinergic side effects of edrophonium include fasciculations, bradycardia, nausea, vomiting, increased tearing, and lacrimation.
   - **b.** Monitor the pulse and blood pressure of patients and be prepared to administer atropine to counteract the anticholinergic effects of edrophonium.
   - **c.** Place a butterfly needle in the antecubital vein and give a 2-mg test dose of edrophonium. If there is no response after 30 seconds, the other 8 mg is administered in increments (2 mg every 15 seconds).
   - **d.** It is most important to assess for objective sign of weakness, not the patient's subjective response. In this regard, evaluating improvement of measured ptosis or ophthalmoparesis is most useful.
   - **e.** A test is not considered positive solely if the patient states that he or she feels stronger.

Ice Pack Test

1. The ice pack test is useful in patients with ptosis. A bag of ice is placed over the eye of a ptotic eyelid for approximately 30 seconds. The cold temperature improves the ptosis in myasthenics.
2. In much the same way that cold temperature reduces decrement on repetitive nerve stimulation, cold may reduce the activity of acetylcholinesterase. This increases the safety factor of neuromuscular transmission by allowing more acetylcholine to be available after release into the NMJ.

Laboratory Features

1. AChR antibodies are detected in about 80% to 90% of patients with generalized myasthenia gravis, with a slightly lower occurrence (70% of patients) in the ocular form.
2. Antibodies directed against MuSK are seen in approximately one-third of

patients without AChR antibodies.

3. LRP4 antibodies are about half as common as MuSK antibodies.
4. Antistriatal muscle antibodies (also known as antititin antibodies) are evident in approximately 30% of adult patients with myasthenia gravis and 80% of patients who have thymomas.
5. Antinuclear antibodies (ANAs) and thyroid function tests may be abnormal in patients with other associated autoimmune conditions.

Electrophysiologic Findings

1. Repetitive stimulation is typically performed on an intrinsic hand muscle such as the abductor digiti minimi first; however, in patients with only proximal weakness, the trapezius can be assessed. In patients with only ocular or bulbar weakness, a facial muscle (orbicularis oculi, nasalis, or orbicularis oris) should be studied.
   a. First, perform a 2- to 3-Hz repetitive stimulation with the patient at rest. Normally, there should be less than a 10% decrement in muscle action potential amplitude.
   b. If an abnormal decrement is demonstrated, the patient is instructed to exercise the muscle for 10 seconds in order to assess for postexercise facilitation and the resulting improvement in the decrement on 2- to 3-Hz stimulation immediately postexercise.
   c. If no decrement is not seen at rest, the muscle is exercised for 1 minute to see if postexercise exhaustion will bring out an abnormal decrement. Repetitive stimulation at 2 to 3 Hz is performed immediately postexercise and once per minute for the next 5 to 6 minutes.
2. If repetitive nerve stimulation is normal, a single-fiber electromyogram (EMG) can be performed. Single-fiber EMG documents increased jitter in 77% to 100% of patients depending on disease severity and the muscle studied.

Treatment

1. There are various treatment strategies commonly used for myasthenia gravis.
   a. Acetylcholinesterase inhibitors (anticholinesterase drugs) (Table 9-1)
   b. Immunosuppressive/immunomodulating agents (see Table 10-1)
   c. Plasma exchange (PE)

d. Thymectomy

2. The regimen used in patients with myasthenia gravis is individualized and dependent on the severity of the myasthenia, age of the patient, the presence or absence of an enlarged thymus, and concurrent medical problems.
3. We try to treat patients with ocular myasthenia only with pyridostigmine bromide (Mestinon). If patients are still symptomatic on pyridostigmine bromide (Mestinon), we initiate prednisone in a slowly incrementing fashion (see the "start-low and go-slow approach" to prednisone treatment under "Specific Therapies" section).
4. Patients in myasthenic crisis (severe respiratory distress or bulbar weakness) represent the opposite end of the spectrum.
   a. These patients should be admitted to an intensive care unit (ICU) and followed closely, particularly for pulmonary function.
   b. When the forced vital capacity (FVC) declines to less than 15 mL/kg or the negative inspiratory pressure is less than 30 cm H_2O, consider elective intubation of the patient to protect the airway, and begin mechanical ventilation. Alternatively, bilevel positive airway pressure (BiPAP) may be initiated and may alleviate the need for intubation in patients who are not hypercapnic (i.e., $Paco_2$ above 50 mm Hg).

Table 9-1 Anticholinesterase Drugs Commonly Used for Myasthenia Gravis

Drug	Route	Adult Dose	Children's Dose	Infant Dose	Frequency
Neostigmine bromide (Prostigmin)	p.o.	15 mg	10 mg	1–2 mg	q2–3h
Neostigmine methylsulfate (Prostigmin injectable)	IM, IV	0.5 mg	0.1 mg	0.05 mg	q2–3h
Pyridostigmine bromide (Mestinon)	p.o. IM, IV	60 mg 2 mg	30 mg 0.5–1.5 mg/kg	4–10 mg 0.1–0.5 mg	q3–6h q3–6h
Mestinon Timespan	p.o.	180 mg			qhs

p.o., by mouth; q, every; IM, intramuscular; IV, intravenous; qhs, at bedtime.

c. Initiate PE and continue until the patient has had significant return of strength and can be weaned off the ventilator. Intravenous immunoglobulin (IVIG) may be an alternative treatment.

d. In addition to starting PE or IVIG, we usually begin high-dose corticosteroids at or around the same time.

5. Specific therapies

a. Acetylcholinesterase inhibitors

1) The acetylcholinesterase inhibitor pyridostigmine bromide (Mestinon) usually improves weakness in patients with myasthenia gravis.

2) Start pyridostigmine in adults at a dose of 30 to 60 mg every 6 hours. In children, start pyridostigmine at a dose of 1 mg/kg. The dosage is gradually titrated as necessary to control myasthenic symptoms and reduce side effects. Most adults require between 60 and 120 mg of pyridostigmine every 4 to 6 hours.

3) There is a timed-released form of pyridostigmine (Mestinon Timespan, 180 mg). A Mestinon Timespan tablet can be given at night to patients who have severe generalized weakness upon awakening. Alternately, in patients with only mild or moderate weakness, it is equally efficacious to have the patient set his or her alarm 30 minutes before he or she needs to arise from bed and take a regular pyridostigmine dose at that time.

4) Patients can develop cholinergic side effects secondary to the buildup of AChR at muscarinic and nicotinic receptors. Muscarinic side effects include nausea, vomiting, abdominal cramping, diarrhea, increased oral and bronchial secretions, bradycardia, and, rarely, confusion or psychosis. In patients with significant side effects, we pretreat with anticholinergic medications (e.g., hyoscyamine sulfate [Anaspaz] one tablet four times a day [q.i.d.]) 30 minutes prior to the pyridostigmine dose.

b. Corticosteroids

1) Most of our patients with moderate to severe generalized myasthenia gravis receive prednisone. There are two treatment strategies generally used when using prednisone in patients with myasthenia gravis.

Aggressive high-dose daily steroids at the onset of treatment.

b) "A start-low and go-slow approach."
c) The high-dose daily regimen leads to a much quicker improvement of strength, but there is about a 10% to 15% chance of early worsening. This transient worsening is typically not seen in the "start-low and go-slow" approach, but it generally takes longer for patients to improve.

2) In patients with moderate to severe generalized myasthenia, we generally initiate treatment with prednisone 0.75 to 1.5 mg/kg/d (up to 50 mg). We maintain the patients on this high dose of prednisone until their strength has normalized or there is a clear plateau in improvement. Subsequently, we slowly taper prednisone by 5 mg every 2 to 4 weeks, down to 20 mg daily. At this point, we taper even more slowly, by 2.5 to 5 mg every 4 weeks. At 10 mg daily, we taper no faster than 2.5 mg a month. It is usually at these low doses that patients may have a relapse.
3) Most patients will require some amount of immunosuppressive medication, but we try to find the lowest doses necessary to maintain their strength.
4) The addition of other immunosuppressive agents (e.g., azathioprine) may have a prednisone-sparing effect. Many authorities initiate treatment with one of these agents at the same time that prednisone is started in the hope that the prednisone may be tapered quickly and to a lower dose than could be achieved by prednisone monotherapy. We usually initiate treatment with a second-line agent along with prednisone in postmenopausal women, patients with known osteoporosis, or those with increased risk of adverse reaction to corticosteroids (e.g., patients with diabetes mellitus).
5) About 5% to 15% of patients experience a varying degree of initial worsening after they are started on high doses of steroids. If patients have moderate weakness, it is reasonable to hospitalize them for the first week after initiating treatment with high-dose corticosteroids.
6) Because of the risk of exacerbation with high-dose corticosteroids, some have advocated the start-low and go-slow approach. Patients are started at a dose of 10 to 20 mg/d, and the dose is slowly increased by 5 mg every 5 to 7 days or so until definite improvement is noted. Unfortunately, improvement takes much longer with this approach and is thus not very useful in patients with severe weakness.

We reserve this approach for patients with mild to moderate generalized disease not controlled with pyridostigmine bromide (Mestinon) or for patients with ocular myasthenia.

7) There is a multitude of potentially serious side effects to the chronic administration of corticosteroids (e.g., risk of infection, diabetes mellitus, hypertension, glaucoma, osteoporosis, and aseptic necrosis of the joints).

8) We obtain a chest radiograph and a purified protein derivative (PPD) skin test in at-risk populations prior to initiating immunosuppressive medications. Patients with a history of tuberculosis or those with a positive PPD result may need to be treated prophylactically with isoniazid.

9) Measure bone density with dual-energy x-ray absorptiometry (DEXA) at baseline and every 12 months while patients are receiving corticosteroids.

10) Calcium supplementation (1 g/d) and vitamin D supplementation (400 to 800 IU/d) are started for prophylaxis against steroid-induced osteoporosis. We usually recommend calcium carbonate (Tums) for calcium supplementation, because it can also help with the dyspepsia associated with steroid use.

11) Bisphosphonates are effective in the prevention and treatment of osteoporosis. If DEXA scans demonstrate osteoporosis at baseline or during follow-up studies, we initiate alendronate 70 mg/wk. In postmenopausal women, we start prophylactic treatment with alendronate 35 mg orally once a week if DEXA scans show bone loss at baseline (not enough to diagnose osteoporosis at that stage) or if there is significant loss on follow-up bone density scans. Alendronate can cause severe esophagitis, and absorption is impaired if it is taken with meals. Therefore, patients must be instructed to remain upright and not eat for at least 30 minutes after taking a dose of alendronate.

12) We do not prophylactically treat with histamine H_2 receptor blockers unless the patient develops gastrointestinal discomfort or has a history of peptic ulcer disease. Calcium carbonate (Tums) can help prevent any discomfort and also serve as a source of calcium.

13) Patients are instructed to start a low-sodium, low-carbohydrate, high-protein diet to prevent excessive weight gain.

14) Patients are also given physical therapy and encouraged to slowly

begin an aerobic exercise program.

15) Blood pressure is measured with each visit along with periodic eye examinations for cataracts and glaucoma. Fasting blood glucose and serum potassium levels are periodically checked. Potassium supplementation may be required if the patient becomes hypokalemic.

16) Steroid myopathy versus relapse of myasthenia gravis: High-dose, long-term steroids and lack of physical activity can cause type 2 muscle fiber atrophy with proximal muscle weakness. This needs to be distinguished from weakness caused by relapse of the myasthenia. Patients who become weaker during prednisone tapering and have worsening of their decrement repetitive stimulation or increasing jitter and blocking on single-fiber EMG are more likely experiencing a flare of the myasthenia. In contrast, patients with continued high doses of corticosteroids, normal repetitive stimulation and single-fiber EMG results, and other evidence of steroid toxicity (i.e., cushingoid appearance) may have type 2 muscle fiber atrophy and could benefit from physical therapy and reducing the dose of steroids.

c. Azathioprine

1) We prescribe azathioprine for patients with moderate to severe generalized myasthenia gravis whose disease is not well controlled by prednisone and pyridostigmine bromide (Mestinon). As noted previously, we will start azathioprine in patients most at risk of steroid complications at the initiation of treatment along with prednisone.

2) Prior to beginning azathioprine, patients can be screened for thiopurine methyltransferase (TPMT) deficiency. Patients who are heterozygous for mutation in TPMT may be able to tolerate azathioprine at lower dosages, but those who are homozygous should not receive the drug as they cannot metabolize it and may develop severe bone marrow toxicity.

3) We start azathioprine at a dose of 50 mg/d in adults and gradually increase by 50 mg/wk to every 2 to 4 weeks as tolerated up to a total dose of 2 to 3 mg/kg/d.

4) A systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia occurs in 12% of patients, requiring discontinuation of the drug. This reaction generally occurs within the first few weeks of therapy and resolves within a few days of

discontinuing the azathioprine.

5) A major drawback of azathioprine is that it takes a long time to see an effect. A double-blind, placebo-controlled trial of azathioprine did not show a statistically significant benefit in terms of cumulative corticosteroid dose reduction until 18 months of treatment.
6) Monitor complete blood counts (CBCs) and liver function tests (LFTs)—aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubins every 2 to 4 weeks until the patient is on a stable dose of azathioprine and then every 3 to 6 months.
7) If the WBC count falls below 3,000/mm^3, we decrease the dose. Azathioprine is held if the WBC count declines to 2,500/mm^3 or the absolute neutrophil count falls to 1,000/mm^3. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. The leukopenia usually reverses within 1 month, and it is possible to then rechallenge the patient with azathioprine without recurrence of the severe leukopenia.
8) Discontinue azathioprine if the LFTs increase to more than twice the baseline values. Liver toxicity generally develops within the first several months of treatment and can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after LFTs return to baseline without recurrence of hepatic dysfunction.
9) Allopurinol should be avoided because its combination with azathioprine increases the risk of bone marrow and liver toxicity.

d. Mycophenolate mofetil

1) Mycophenolate mofetil inhibits the proliferation of T and B lymphocytes by blocking purine synthesis in only lymphocytes.
2) The starting dose is 1 g twice daily and can be increased by 500 mg/mo up to 1.5 g twice a day (b.i.d.).
3) Mycophenolate is renally excreted; therefore, the dose should be no more than 1 g/d (i.e., 500 mg b.i.d.) in patients with renal insufficiency.
4) A benefit of mycophenolate compared to other immunosuppressive agents is the lack of renal or liver toxicity with the drug.
5) The major side effect is diarrhea. Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia.

6) Use of mycophenolate has been tempered by the results of two controversial double-blind, placebo-controlled trials that failed to demonstrate any benefit. Nevertheless, some authorities are still strong advocates and believe that it is beneficial in some patients. Given its high cost and lack of proven efficacy in two large trials, we no longer routinely prescribe it. However, we keep patients who are currently doing well with it on mycophenolate.

e. Cyclosporine

1) Cyclosporine inhibits primarily T cell–dependent immune responses. We reserve cyclosporine to patients who are refractory to prednisone and azathioprine.
2) Most patients notice improvement within 2 to 3 months of initiating treatment; thus, it works much faster than azathioprine.
3) We start cyclosporine at a dose of 3 to 4 mg/kg/d in two divided doses and gradually increase to 6 mg/kg/d as necessary.
4) The cyclosporine dose should initially be titrated to maintain trough serum cyclosporine levels of 50 to 150 ng/mL. Adjust the dose to keep the trough less than 150 ng/mL and the creatinine level less than 150% of baseline.
5) Blood pressure, electrolytes, renal function, and trough cyclosporine levels need to be monitored.

f. Tacrolimus

1) Tacrolimus is similar to cyclosporine but may be associated with fewer side effects. Therefore, many authorities prefer tacrolimus over cyclosporine.
2) The starting dose is 0.1 mg/kg and can be gradually increased up to 0.2 mg/kg (in two divided doses) as needed.
3) The dose is titrated to maintain a trough level of 5 to 15 mg/mL.
4) As with cyclosporine, it is important to monitor blood pressure, electrolytes, and renal function.

g. IVIG

1) Some studies have found that IVIG is equivalent to PE in the treatment of myasthenic crisis, whereas other studies have suggested that PE is more efficacious. We have successfully used IVIG in patients in myasthenic crisis and believe it is an equal alternative to PE until proven otherwise.
2) IVIG has not been compared to the aforementioned

immunosuppressive agents.

3) We usually use IVIG for patients with moderate to severe generalized myasthenia gravis in order to increase their strength before thymectomy. We also use IVIG in patients who are refractory prednisone and at least on other forms of immunotherapy (e.g., azathioprine, mycophenolate).
4) We initiate IVIG (2 g/kg) slowly over 2 to 5 days and repeat infusions at monthly intervals for at least 3 months. Thereafter, treatment is individualized. Some patient may need treatment (0.4 to 2 g/kg) every week, while others may go several months between IVIG courses.
5) Patients should have renal function checked, especially those with diabetes mellitus because of a risk of IVIG-induced renal failure. A serum IgA level can be checked prior to treatment because those with low IgA levels may be at risk for anaphylaxis.
6) Flulike symptoms—headaches, myalgias, fever, chills, nausea, and vomiting—are common and occur in as many as half the patients receiving IVIG. These symptoms can be reduced by premedication with a corticosteroid and lowering the rate of infusion.
7) Rash, aseptic meningitis, myocardial infarction, and stroke may also complicate IVIG infusions. IVIG should be avoided in patients with hypercoagulable states and significant atherosclerotic cardiovascular disease.

h. PE

1) PE is used in patients with myasthenic crisis or those with moderate weakness prior to thymectomy in order to maximize their preoperative strength.
2) The typical course involves exchange of 2 to 3 L of plasma three times a week until strength is significantly improved (usually five to six total exchanges). Improvement is noticeable after two to four exchanges.
3) PE lowers the serum concentration of anti-AChR antibodies, but it must be repeated at relatively regular intervals because of its limited duration of effect.
4) Within a week of PE, the autoantibodies begin to rebound. Therefore, patients will also need to be started on an immunosuppressive agent.
5) Some patients who are refractory or intolerant of prednisone, immunosuppressive agents, and IVIG may need to be managed with

intermitting PE (e.g., weekly PE).

i. Thymectomy

1) Thymectomy is clearly indicated in patients with a thymoma.

2) A recently single blind study of thymectomy (extensive transsternal approach) plus standard medical treatment (prednisone and pyridostigmine bromide [Mestinon]) versus standard medical treatment alone in nonthymomatous AChR antibody positive patients with generalized myasthenia gravis (age 18 to 65 years and myasthenia gravis <5 years) demonstrated that thymectomy improved myasthenia gravis scores, lowered cumulative prednisone dosage, and reduced need for second-line immunosuppressive agents.

3) It is not clear if thymectomy works in patients who are not AChR antibody positive, have only ocular myasthenia gravis, have had disease duration greater than 5 years, or are less than 18 years of age.

j. Rituximab

1) Rituximab is a monoclonal antibody directed against CD20 cell marker and will deplete B cells for 6 months to a year or more. As B cells are precursors to plasma cells, antibody production drops over time as well.

2) Several small reports have suggested that rituximab may be effective in patients with refractory myasthenia gravis, in particular those with MuSK antibodies who can be difficult to treat. A large National Institutes of Health (NIH)-sponsored double-blind, placebo-controlled trial is underway in patients with generalized AChR antibody positive patients.

3) We have used rituximab in refractory myasthenia gravis patients and also in patients who need frequent infusions of IVIG.

4) The dose of rituximab is 750 mg/m^2 (up to 1 g) IV. The dose is repeated in 2 weeks.

5) Alternatively, rituximab can be given at a dosage of 375 mg/m^2 weekly for 4 weeks.

6) Rituximab course treatment is generally repeated every 6 to 12 months, but we have had patients with sustained remission for 2 to 3 years between courses.

7) The main side effects are infusion reactions. Because rituximab depletes B cells, there is increased risk of infection. There have been a few reports of progressive multifocal leukoencephalopathy treated

with rituximab, but none to our knowledge had myasthenia gravis.

TRANSIENT NEONATAL AUTOIMMUNE MYASTHENIA GRAVIS

Background

Transient neonatal autoimmune myasthenia gravis develops in approximately 10% of infants born to mothers with AChR-positive myasthenia gravis but has also been reported in anti-MuSK myasthenia gravis.

Pathophysiology

Weakness results from the passive transfer through the placenta of the mother's autoantibodies.

Prognosis

1. Onset is usually within the first 3 days of life and manifests with a weak cry, difficulty feeding because of a poor suck, generalized weakness and decreased tone, respiratory difficulty, ptosis, and diminished facial expression (facial muscle weakness).
2. Weakness is usually temporary, with a mean duration of about 18 to 20 days.
3. Rare affected infants are born with arthrogryposis and have some degree of persistent weakness, perhaps related to damage to the NMJ by autoantibodies directed against components.

Diagnosis

1. The diagnosis should be suspected in any infant born to a mother with myasthenia gravis.
2. Mothers of floppy infants should be examined for signs of myasthenia gravis because not all mothers are symptomatic.
3. Diagnosis can be confirmed by demonstrating autoantibodies in the infant's serum or decremental response to repetitive nerve stimulation in child or mother.

Treatment

1. Infants with neonatal myasthenia and weakness may be treated with anticholinesterase medications for 3 to 6 weeks until antibody levels have diminished to the point where sufficient safety factors are reestablished at a significant number of NMJs.
2. Those infants with severe weakness may require mechanical ventilation and treatment with PE.

LAMBERT–EATON MYASTHENIC SYNDROME

Background

1. Lambert–Eaton myasthenic syndrome (LEMS) is the second most common NMJ disorder following myasthenia gravis.
2. LEMS is an immunologic disorder caused by antibodies directed against voltage-gated calcium channels (VGCCs).
3. Approximately 85% of patients with LEMS are older than 40 years, with mean age at presentation in the mid-50s.
4. In approximately two-thirds of cases, LEMS arises as a paraneoplastic disorder, usually secondary to small cell carcinoma of the lung. Small cell carcinoma of the lung is the culprit for approximately 90% of the paraneoplastic cases of LEMS. Other malignancies associated with LEMS include lymphoproliferative disorders, pancreatic cancer, and breast and ovarian carcinoma. The LEMS symptoms usually precede tumor diagnosis by an average of 10 months (can range from 5 months to 4 years).
5. In the other one-third of patients, LEMS occurs as an autoimmune disorder without an underlying cancer. Such cases are more common in females and younger patients and are associated with other autoimmune disorders.
6. The paraneoplastic and nonparaneoplastic forms of LEMS are otherwise clinically and electrophysiologically indistinguishable.

Pathophysiology

1. LEMS is caused by antibodies directed against VGCCs on presynaptic motor nerve terminals.

2. The antibodies bind to the VGCCs and subsequently inhibit the entry of calcium into the nerve terminal, which is required for the release of AChR. Additionally, the antibodies may cross-link neighboring calcium channels, thus precipitating the process of internalization and degradation of the calcium channels.

Prognosis

1. Patients generally improve with treatment.
2. Patients with primary autoimmune LEMS without underlying malignancy tend to do well. However, the prognosis in patients with an underlying cancer is more related to that of the malignancy, which generally is poor.

Diagnosis

Clinical Features

1. Patients with LEMS usually complain of proximal weakness and easy fatigability.
2. Ptosis and diplopia are often transient and mild. Some patients develop dysarthria or dysphagia, but these are more commonly secondary to dryness of the mouth.
3. Autonomic dysfunction as reduced saliva, dry eyes, blurred vision, constipation, decreased sweating, and impotence are commonly seen in patients with LEMS.
4. Although most patients do not have respiratory problems related to the NMJ defect (they may have dyspnea related to their lung cancer), rare cases of LEMS presenting with respiratory failure have been described.
5. Neurologic examination demonstrates symmetric, proximal greater than distal, weakness affecting the legs more than the arms. Mild ptosis, ophthalmoparesis, and bulbar weakness may be apparent, but these are not as common or as severe as in myasthenia gravis. Deep tendon reflexes may be diminished or absent but then become significantly easier to obtain once a slight contraction of the muscle has been performed.

Laboratory Features

1. Antibodies directed against the P/Q-type VGCCs of motor nerve terminals are detected in the serum in more than 90% of patients with LEMS (both paraneoplastic and non–cancer-related cases).
2. Antibodies directed against the N-type calcium channels, which are located on autonomic and peripheral nerves as well as cerebellar, cortical, and spinal neurons, are present in 74% of patients with LEMS and lung cancer and 40% of patients without cancer.
3. Some patients with paraneoplastic LEMS also have anti-Hu antibodies and the associated sensory ganglionopathy, cerebellar degeneration, and encephalopathy.
4. As many as 13% of patients with LEMS also have AChR-binding antibodies. The anti-AChR antibodies are not necessarily pathogenic in patients with LEMS and may just represent an epiphenomenon.

Electrophysiologic Findings

1. Motor nerve conduction studies (NCS) reveal a marked reduction in the compound muscle action potential (CMAP) amplitude.
2. With 10 seconds of exercise, repeated stimulation of the nerve elicits an increment in the CMAP amplitude because of postexercise facilitation.
3. If patients are unable to cooperate, high rates of repetitive stimulation at 20 to 50 Hz for up to 10 seconds will produce an incrementing response. We do not routinely use high rates of repetitive stimulation, unless necessary, as it can be quite painful.
4. Repetitive stimulation at 2 to 3 Hz demonstrates an abnormal decrement.
5. Single-fiber EMG demonstrates increased jitter.

Treatment

1. Patients with LEMS should undergo a thorough investigation for underlying carcinoma, particularly carcinoma involving the thoracic cavity (i.e., small cell lung cancer). Many other neoplasms have been responsible for the syndrome. In patients with paraneoplastic LEMS, muscle strength may improve with surgical removal of the tumor, radiation therapy, and chemotherapy.
2. In patients with and without tumor, a number of therapeutic medications can be given to assist with the symptoms of weakness and fatigue.

a. Acetylcholinesterase inhibitors

1) We generally treat patients with pyridostigmine bromide (Mestinon) 60 mg four to five times a day, as in patients with myasthenia gravis.

2) The response is variable and often modest in comparison to that seen in myasthenia gravis.

b. 3,4-Diaminopyridine (3,4-DAP)

1) The aminopyridines block voltage-dependent potassium conductance, thereby prolonging nerve terminal depolarization and facilitating AChR release.

2) Two recently clinical trials demonstrated the efficacy of 3,4-DAP, but it is not as yet approved by the U.S. Food and Drug Administration (FDA). The medication can be obtained on a compassionate-use basis for patients with LEMS or by utilizing a compound pharmacy.

3) Treatment with the 3,4-DAP compound from Jacobus Pharmaceutical Company (Princeton, NJ) is usually started at 5 to 10 mg three times daily and is gradually increased every 2 weeks as tolerated up 15 to 20 mg four or five times a day, as clinically needed and tolerated. The upper limit is 20 mg at a time and a total of 100 mg/d.

4) The other compound that has been shown to be effective is Firdapse (amifampridine phosphate, 3,4-DAP phosphate) by Catalyst Pharmaceuticals, Inc. (Coral Gables, FL). This is a 50-mg tablet, containing the equivalent of 10 mg 3,4-DAP. The starting dose is one tablet three times daily and increased as needed up to two tablets four or five times a day as needed and tolerated. Amifampridine phosphate should be taken with food.

5) 3,4-DAP appears to be well tolerated, with few patients experiencing perioral and acral paresthesias. It is recommended that the dosage not exceed 100 mg/d as higher doses may result in seizures.

c. Immunosuppressive agents and immunomodulating therapies (see Table 10-1)

1) Corticosteroids and other immunotherapies are helpful.

2) Dosing is similar to that described in the section on Myasthenia Gravis.

3) Unlike myasthenia gravis, there is no role for thymectomy in the treatment of LEMS.

4) Plasmapheresis may be beneficial in patients with LEMS, but the effect wears off after a few weeks, and it must be repeated.

5) IVIG has been noted to be beneficial in small, uncontrolled series of patients with LEMS. Dosing is similar to that outlined for myasthenia gravis.
6) It is unclear if rituximab may be of benefit, but it is worth considering in refractory patients.

BOTULISM

Background

1. Botulism is a serious and potentially fatal disease caused by one of several protein neuroexotoxins produced by the bacterium *Clostridium botulinum*.
2. There are eight immunologically distinct types of botulinum neurotoxins (BTXs) designated alphabetically in their order of discovery: A, B, C1, C2, D, E, F, and G.
3. Types A, B, and E account for most reported food poisoning cases; however, D, F, and G have been responsible for a few deaths. Toxin type C affects animals and not humans.
4. Five clinical forms of botulism have been described: (a) classic or food-borne botulism, (b) infant botulism, (c) hidden botulism, (d) wound botulism, and (e) inadvertent botulism.
   a. Classic or food-borne botulism
      1) The method of transmitting the botulinum toxin is usually through poorly prepared home-canned vegetables.
      2) The number of fatalities resulting from food-borne botulism has declined from about 50% prior to 1950 to approximately 7.5% from 1976 to 1984.
      3) Persons over 60 years of age are particularly prone to more serious complications, possibly less complete recovery, and certainly a higher mortality rate.
   b. Infant botulism
      1) This is the most common form of botulism in the United States, with an incidence of 1 per 100,000 live births.
      2) The mortality rate among recognized infants infected with botulinum spores is under 4%.
      3) Spores of *C. botulinum* inadvertently enter the infant's intestinal tract,

germinate and colonize this region, and then produce the toxin that is absorbed through the intestinal tract's lumen.

4) Epidemiologic studies reveal risk for botulism in infants consuming honey. As many as 25% of tested honey products contain clostridial spores. Because of this, honey should be avoided in infants.

c. Hidden botulism

1) Hidden botulism is believed to be a form of infantile botulism occurring in individuals older than 1 year.
2) Patients have a typical clinical presentation suggestive of botulinum intoxication with supportive laboratory findings but no obvious food or wound source for the disease.
3) The disorder manifests in individuals who have intestinal abnormalities (e.g., Crohn disease or following gastrointestinal surgery) that allow colonization by *C. botulinum*, leading to the in vivo production of the toxin.

d. Wound botulism

1) A wound is infected by *C. botulinum* with the subsequent production of toxin in vivo. The typical insult is some type of focal trauma to a limb with or without a compound fracture.
2) There have been increasing reports of wound botulism occurring in intravenous (IV) drug abusers. BTX type A is more often the offending agent; however, type B has also been implicated.

e. Inadvertent botulism

1) This is the most recent form of botulism and refers to iatrogenic cases. BTX is now commonly used to treat focal dystonias and other movement disorders.
2) Rarely, patients may develop distant or generalized weakness after focal injections of BTX. The mechanism is likely hematogenous spread of the toxin.

Pathophysiology

The net effect of BTX intoxication is the inhibition of release of AChR vesicles.

Prognosis

l. In the adult, the clinical presentation of botulinum intoxication is similar

regardless of whether the disease is acquired through the food-borne, wound, or hidden (i.e., suspected gastrointestinal) route.

a. Patients develop dysphagia, dry mouth, diplopia, and dysarthria beginning rather acutely and progressing over the course of 12 to 36 hours. The time course is dependent in part on the amount of toxin consumed.

b. Gastrointestinal symptoms of nausea, occasional vomiting, and initial diarrhea followed by constipation may occur just before or coincident with the earlier noted neurologic symptoms. Associated complaints of abdominal cramps, undue fatigue, and dizziness may also be described during the disease's evolution.

c. Then patients develop progressive weakness, affecting first the upper and then the lower extremities. The patient may begin to notice shortness of breath prior to extremity involvement.

2. In wound botulism, gastrointestinal complaints of nausea, vomiting, and usually abdominal cramps are less common than in food-borne botulism. The period of symptom development is longer in wound botulism as 4 to 14 days are required for the incubation period compared to hours for toxin or spore ingestion.

3. In infants, botulinum intoxication can manifest with an entire spectrum of disease, from mild symptoms to sudden death.

a. A relatively early sign is constipation.

b. The infant may later appear listless, with a diminution in spontaneous movements. Parents may note that the child has a poor ability to take in nutrition secondary to a diminished suck.

c. Respiratory function should be closely monitored as approximately 50% of infants require assisted mechanical ventilation. This necessity of respiratory assistance may be because of not only respiratory muscle weakness but also airway obstruction secondary to pharyngeal muscle weakness and loss of tonus.

d. Several weeks may be required before the patient shows any signs of recovery. The duration of required mechanical ventilation is dependent on the severity of the illness and the serotype of the infecting organism, with a mean of 58 days for type A and 26 days for type B botulism.

e. Recovery is usually satisfactory in all patients provided they are cared for in a hospital setting from the first manifestations of the disease. In the

elderly, associated complications can lead to unavoidable death. There are long-term sequelae of fatigue and mild reduction in respiratory capacity in selected patients.

Diagnosis

Clinical Features

1. Cranial nerve evaluation reveals ptosis, diminished gag reflex, dysphagia, dysarthria, and weakness of the face, jaw opening and closing, and tongue.
2. Depending on the length of time between presentation and examination, the upper and lower limbs may be involved to varying degrees. The upper limbs are typically more affected than the lower limbs, with an occasional asymmetry noted.
3. Deep tendon reflexes may be normal or diminished initially, with progression to complete loss in severely affected individuals.
4. Careful patient examination can reveal disturbances of autonomic function affecting both the sympathetic and parasympathetic systems. Pupils are often poorly reactive to light. In addition, there can be loss of vagal cardiac control, ileus, hypothermia, and urinary retention possibly requiring catheterization. In addition, hypotension without tachycardia may be present and a lack of vasomotor responses to postural change may be observed.
5. In cases of suspected wound botulism, the integument should be carefully searched for not only gross disruption and wound contamination but also for apparently minor bruises with or without signs of infection.

Laboratory Features

1. Stool and serum samples can be sent for toxin identification; however, this is a time-consuming process.
2. Less commonly, the organism can be cultured from the stool or a wound site.

Electrophysiologic Findings

1. CMAP amplitudes become reduced; however, it is not uncommon for patients examined relatively early after symptom onset to demonstrate normal amplitudes.
2. At low rates of repetitive stimulation (2 to 3 Hz), over 50% of patients

demonstrate a decremental response. Approximately 25% do not reveal a decrement at low stimulation rates, whereas 20% have an increment.

3. About 90% of infants with botulism demonstrate an increment on 20- to 50-Hz repetitive stimulation.
4. The needle EMG examination can be somewhat variable depending on the time of examination.
   - **a.** Early in the course of the disease, there is usually normal needle insertion activity and a lack of abnormal spontaneous activity.
   - **b.** Fibrillation potentials and positive sharp waves may be found in severely affected muscles.
   - **c.** The motor unit action potentials (MUAPs) have a myopathic appearance.
   - **d.** Abnormal increases in jitter can be observed very early in the disease in 40% to 50% of single-fiber EMG studies.

Treatment

1. Antitoxin should be administered within 24 hours of symptom onset, before toxin binding and entry into the nerve terminals. Once nerve terminal entry has been accomplished, the antitoxin is no longer capable of neutralizing the toxin.
2. The mainstay of care is supportive from the perspective of maintaining adequate ventilation and being prepared for prompt mechanical ventilation intervention.
3. Secretions must be handled and adequate nutrition provided.
4. Constipation must be kept under control.

TICK PARALYSIS

Background

1. There are three major families of ticks: Ixodidae (hard body ticks), Argasidae (soft body ticks), and Nuttalliellidae. Ticks belonging to the first two families are responsible for causing human paralysis. These creatures are found worldwide, primarily inhabiting rural and wilderness areas.
2. In North America, the tick *Dermacentor andersoni* (common wood tick)

usually causes the disease, but *Dermacentor variabilis* (dog tick) can also cause the disorder. Occasionally, ticks such as *Amblyomma americanum* and *Amblyomma maculatum*, as well as others, have been implicated in human paralysis.

3. In Australia, *Ixodes holocyclus* (Australian marsupial tick) causes especially severe disease in humans.
4. Peak occurrence of paralysis caused by ticks is in the spring and summer months. Children are 3 times as likely to be involved as adults.

Pathophysiology

1. Gravid female ticks are more commonly implicated because they feed for considerably longer times (days) and inject more toxin into their hosts compared to nongravid females and males.
2. In North American cases of tick paralysis, the toxin may block the sodium channel at the nodes of Ranvier and the distal motor nerve terminals.
3. Ixovotoxin released by the Australian *I. holocyclus* tick most likely interferes with the release of acetylcholine at the NMJ, perhaps similar to the effect of botulinum toxin.

Prognosis

1. Patients develop acute or subacute progressive weakness that may require ventilatory support.
2. Removal of the tick results in prompt improvement in strength, except for the Australian variety in which weakness may continue to progress to respiratory failure even after the tick is removed.

Diagnosis

Clinical Features

1. Patients typically present with ascending weakness, developing over the course of a few hours or days to flaccid paralysis that can mimic Guillain–Barré syndrome (GBS), myasthenia gravis, and botulism.
2. Early cranial nerve involvement including internal and external ophthalmoplegia, facial weakness, dysarthria, dysphagia, and respiratory

muscle weakness is a salient feature.
3. Patients may complain of pain, itching, burning, or numbness in the extremities.
4. Deep tendon reflexes are diminished or absent.
5. If there is a recent history of camping or other types of leisure activity involving wooded or high grassy areas, the suspicion of tick paralysis should be raised.

Laboratory Features

1. Cerebrospinal fluid (CSF) protein concentration is usually normal in tick paralysis.
2. AChR antibodies are absent.

Electrophysiologic Findings

1. The sensory NCS usually reveal normal amplitudes, latencies, and velocities.
2. Motor conduction velocity is usually slow or borderline in weak extremities. The CMAP amplitudes are borderline or decreased in size.
3. Removal of the tick within several days of clinical presentation results in the prompt resolution of amplitude and conduction velocity abnormalities.
4. Repetitive nerve stimulation at low and high rates usually fails to reveal either a significant decrement or increment.

Treatment

1. The treatment of tick paralysis is prompt removal of the tick, with hospitalization for observation of potential impending respiratory failure.
2. Begin supportive and respiratory therapies as outlined in the GBS section in Chapter 10.
3. A meticulous and comprehensive search for a tick is required. Common places for a tick to be present include the inferior hairline in the neck, periauricular area and the ear itself, the hair about the parietal scalp, the axillae, and the inguinal region.
4. Use a pair of tweezers or forceps and firmly grasp the tick as close to the patient's skin as possible (i.e., near the tick's mouth parts). A firm, steady pull should then be applied. The body of the tick should never be pierced as

more toxin may be released.

5. Within 24 to 48 hours of tick removal, most patients are well enough to be discharged from the hospital provided the tick is removed prior to profound functional loss.
6. An exception is the Australian variety of the tick, which produces such a virulent toxin that weakness may continue to progress to respiratory failure even after the tick is removed.
   a. An antitoxin in the form of polyclonal dog antiserum is available for the Australian form of the disease.
   b. The antiserum treatment is expensive and only effective if given in the early stages of paralysis, and it may be associated with serum sickness.
   c. Continued ventilator support is required for several additional hours or until the patient can once again sustain voluntary ventilation.

CONGENITAL MYASTHENIC SYNDROMES

Background

An increasing number of distinct congenital myasthenic syndromes (CMSs) are becoming better characterized. The individual types of CMSs are subdivided according to the previously used scheme of presynaptic, synaptic space, and postsynaptic locations of the presumed site for the abnormality. Unlike autoimmune myasthenia gravis, these disorders may manifest within the first year of life (Table 9-2).

Table 9-2 Congenital Myasthenic Syndromes

CMS Subtype	Gene/Protein Deficiency	Clinical Features	Electrophysiologic Features	Respons to AChE Inhibitor
Presynaptic Disorder				
CMS with paucity of ACh release	ChAT	AR; early onset, respiratory failure at birth, episodic apnea, improvement	Decremental response to RNS	Improve

		with age		
Synaptic Disorder				
AChE deficiency	ColQ	AR; early onset; variable severity; axial weakness with scoliosis; apnea; +/- EOM involvement, slow or absent pupillary responses	After discharges on nerve stimulation and decrement on RNS	Worsen
Postsynaptic Disorders Involving AChR Deficiency or Kinetics				
Primary AChR deficiency	AChR subunit genes	AR; early onset; variable severity; fatigue; typical MG features	Decremental response to RNS	Improve
AChR kinetic disorder: slow-channel syndrome	AChR subunit genes	AD; onset childhood to early adult; weak forearm extensors and neck; respiratory weakness; variable severity	After discharges on nerve stimulation and decrement on RNS	Worsen
AChR kinetic disorder: fast-channel syndrome	AChR subunit genes	AR; onset early; mild to severe; ptosis, EOM involvement; weakness and fatigue	Decremental response to RNS	Improve
Postsynaptic Disorders Involving Abnormal Clustering/Function of AChR				
	Dok 7	AR; limb girdle weakness with ptosis but no EOM involvement	Decremental response to RNS	Variable
	Rapsyn	AR; early onset	Decremental	Variable

		with hypotonia, respiratory failure, and arthrogryposis at birth to early adult onset resembling MG	response to RNS	
	Agrin	AR; limb girdle or distal weakness, Apnea	Decremental response to RNS	Variable
	MuSK	AR; congenital or childhood onset of ptosis, EOM land progressive limb girdle weakness	Decremental response to RNS	Variable
	LRP4	AR; congenital onset with hypotonia, ventilatory failure; mild ptosis and EOM weakness, proximal weakness	Decremental response to RNS	Worsen
Other Postsynaptic Disorders				
Limb-girdle CMS with tubular aggregates	GFPT1; DPAGT1; ALG2; ALG14	AR; limb girdle weakness usually without ptosis or EOM weakness; onset in infancy or early adult	Decremental response to RNS	Variable
Congenital muscular	Plectin	AR; infantile or childhood	Decremental response to RNS	Variable

	dystrophy with myasthenia	onset of generalized weakness including ptosis and EOM; epidermolysis bullosa simplex; elevated CK

CMS, congenital myasthenic syndrome; AChE, acetylcholinesterase; ACh, acetylcholine; ChAT, choline acetyl transferase; AR, autosomal recessive; RNS, repetitive nerve stimulation; 3,4-DAP, 3,4-diaminopyridine; ColQ, collagenic tail of endplate acetylcholinesterase; EOM, extraocular muscle; AChR, acetylcholine receptor; MG, myasthenia gravis; AD, autosomal dominant; Dok7, downstream of tyrosine kinase 7; MuSK, muscle-specific tyrosine kinase; LRP4, lipoprotein-related protein 4; CK, creatine kinase.

With permission from Amato AA, Russell J. *Neuromuscular Disease.* 2nd ed. New York, NY: McGraw-Hill; 2016:627–629.

Pathophysiology

1. Presynaptic disorders
   - **a.** Congenital paucity of synaptic vesicles and reduced quantal release (choline acetyl transferase [ChAT])
2. Synaptic disorder
   - **a.** Acetylcholinesterase (AChE) deficiency (ColQ)
3. Postsynaptic disorders
   - **a.** Slow-channel syndrome
   - **b.** Low-affinity, fast-channel syndrome
   - **c.** Primary AChR deficiency
   - **d.** Congenital myasthenia with mode-switching kinetics
   - **e.** Rapsyn deficiency
   - **f.** Plectin deficiency
   - **g.** MuSK deficiency
   - **h.** Downstream of kinase 7 (Dok-7) deficiency
   - **i.** Others: limb girdle CMS with tubular aggregates (GFT1, DPAGT1, ALG2, ALG14)

Prognosis

1. Weakness is stable or only slowly progressive.
2. Patients may develop respiratory failure at times of intercurrent illness.
3. Although patients may improve with various forms of treatment (see below), the improvement is not as dramatic as that seen in myasthenia gravis or LEMS.

Diagnosis

Clinical Features

1. Onset may be congenital or in early adulthood.
2. Ptosis and ophthalmoparesis are common.
3. Fatigable weakness of the extremities as well as ocular and bulbar muscles may be present.
4. Response to Tensilon is variable and dependent on the specific subtype of CMS. Patients with acetylcholinesterase deficiency and slow-channel syndrome may actually do worse with Tensilon.

Laboratory Features

1. Serum creatine kinase (CK) levels are normal.
2. AChR antibodies are absent.
3. Genetic testing is only available in a few laboratories.

Electrophysiologic Findings

1. Motor NCS demonstrates repetitive after-discharges in patients with acetylcholinesterase deficiency and slow-channel syndrome.
2. Repetitive NCS at 2 to 3 Hz reveals abnormal decrement.
3. EMG shows small myopathic MUAPs without abnormal insertional or spontaneous activity.
4. Single-fiber EMG demonstrates increased jitter.
5. Sophisticated electrophysiologic studies in intercostal muscles are used to define the different subtypes but are not readily available.
6. Genetic testing for some of the disorders is available at research laboratories (check www.genetest.com for listings).

Treatment

1. CMSs are not autoimmune in etiology, and thus, antibodies to AChR are not present. Therefore, treatments aimed at modulating the immune system (e.g., PE, IVIG, thymectomy, corticosteroids, and other immunosuppressive agents) are not effective in the CMS.
2. Pyridostigmine 1 mg/kg given 4 to 6 times per day may improve strength in patients with presynaptic defects, primary AChR deficiency, and fast-channel syndrome.
3. In patients with the fast-channel syndrome, 3,4-DAP starting at 1 mg/kg/d in divided dosages is helpful (see section on Lambert–Eaton Myasthenic Syndrome). In some studies, only a few of the patients with primary AChR deficiency responded, whereas the other patients with CMS failed to improve.
4. Pyridostigmine and 3,4-DAP may lead to worsening in patients with the slow-channel syndrome and end-plate acetylcholinesterase deficiency.
5. Albuterol starting at 2 mg b.i.d. and going up to 6 mg three times a day (t.i.d.) may be beneficial in cases of slow-channel syndrome, AChE deficiency, and those associated with mutations in Dok-7, agrin, MuSK, DPAGT1, and LAMB2.
6. Quinidine may help in slow-channel syndrome by shortening and even normalizing the duration of mutant channel openings. Administration of quinidine with serum levels of 0.7 to 2.5 μg/mL improved the clinical and electrophysiologic features in patients with slow-channel syndrome. However, the FDA has warned against the off-label of quinidine because of the risk of significant side effects (e.g., hemolytic uremic syndrome, cardiac arrhythmia).
7. Ephedrine may be beneficial in patients with Dok-7 mutations.
8. Patients with respiratory weakness may benefit from BiPAP treatment.

INFLAMMATORY MYOPATHIES

Background

1. Inflammatory myopathies are a heterogeneous group of disorders

characterized by muscle weakness, elevated serum CK levels, and inflammation seen on muscle biopsy.

2. The inflammatory myopathies can be divided into four groups: the more common idiopathic group, in which the etiology is unknown; myositis associated with connective tissue disease (CTD) and autoimmune disorders; myositis associated with cancer; and myositis because of various infections.
3. The major categories of idiopathic inflammatory myopathies include
   a. Dermatomyositis (DM)
   b. Polymyositis (PM)
   c. Inclusion body myositis (IBM)
   d. Autoimmune necrotizing myopathy (NM)
4. Overlap syndromes refer to DM, PM, and NM occurring in association with another autoimmune CTD such as systemic lupus erythematosus, mixed CTD, scleroderma, rheumatoid arthritis, and Sjögren syndrome.
5. The annual incidence of the idiopathic inflammatory myopathies is approximately 1 per 100,000.
   a. DM and IBM are the most common myositides.
   b. DM can occur in childhood through adulthood.
   c. IBM is the most common inflammatory myopathy in patients older than 50 years.
   d. PM is rare and is overdiagnosed. Many cases of PM turn out to be IBM, NM, DM with minimal rash, or muscular dystrophy with inflammation.

Pathophysiology

1. DM is associated with a microangiopathy. Previously, many investigators had felt that the myopathy was caused by complement-mediated destruction of capillaries resulting in ischemia/infarction of muscle. Recent studies suggest that overexpression of type 1 interferon-inducible proteins may be directly toxic to small blood vessels, muscle fibers, and skin.
2. PM is caused by an HLA-restricted, antigen-specific, cell-mediated autoimmune response directed against muscle fibers.
3. The pathogenic mechanism of the autoimmune NM is not known and is likely multifactorial.
4. IBM has an unclear pathogenesis.
   a. The inflammatory changes seen on muscle biopsy are similar to PM, and

some studies suggest the presence of an antigen-mediated autoimmune attack.

b. The lack of improvement with various immunosuppressive and immunomodulatory therapies suggests that IBM could be a primary degenerative myopathy with secondary inflammation.

Prognosis

1. DM, PM, and NM are responsive to immunotherapies.
2. IBM is refractory to immunotherapy.

Diagnosis

Clinical Features

1. DM
   - **a.** May present with acute or insidious onset of proximal greater than distal weakness.
   - **b.** Characteristic skin rash (e.g., heliotrope, scaling rash on forehead and malar regions, chest and neck, extensor surface of extremities/joints, Gottron sign and papules, periungual telangiectasias) usually accompanies or precedes muscle weakness.
   - **c.** Other organ systems may be involved: interstitial lung disease (ILD) in 10% to 20%, myocarditis, gastrointestinal bleed secondary to vasculopathy of gut, arthritis.
   - **d.** Increased incidence of malignancy.
2. PM
   - **a.** May present with acute or insidious onset of proximal greater than distal weakness.
   - **b.** No rash.
   - **c.** Other organ systems may be involved: ILD in 10% to 20%, myocarditis, arthritis.
   - **d.** May have increased risk of malignancy.
3. IBM
   - **a.** Presents with an insidious onset of proximal and distal weakness.
   - **b.** Early involvement of wrist and finger flexors in arms, with relative

sparing of the deltoids, and of the quadriceps and ankle dorsiflexors in the legs helps distinguish IBM from other myopathies.

c. Weakness is often asymmetric. Severe dysphagia can develop.

d. Other organs are not involved.

e. No increased risk of malignancy.

4. NM

a. May present with acute or insidious onset of proximal greater than distal weakness.

b. No rash.

c. Other organ systems may be involved: myocarditis, arthritis.

d. May have increased risk of malignancy.

e. Often develops in the setting of taking cholesterol-lowering agents (e.g., statins). However, patients do not improve and still have marked weakness and elevated serum CK months after stopping the cholesterol-lowering agent.

Laboratory Features

1. DM

a. Serum CK level can be normal in DM, particularly early in the course or with insidious onset but more commonly is moderately elevated up to more than 10 times normal.

b. Serum CK level is not a good indicator of disease activity.

c. ANAs may be detected in patients with overlap syndrome (e.g., myositis associated with and underlying CTD).

d. Anti–myositis-specific antibodies can be ordered as they may influence prognosis and treatment. For example, Jo-1 antibodies are associated with ILD, which is more difficult to treat (see below).

2. PM

a. Serum CK level is elevated, often more than 10 times normal.

b. Serum CK level is not a good indicator of disease activity.

c. ANAs may be detected in patients with overlap syndrome (e.g., myositis associated with and underlying CTD).

d. Anti–myositis-specific antibodies may be present.

3. IBM

a. Serum CK level is normal or only mildly elevated (<10 times normal).
b. Autoantibodies directed against cytosolic 5′-nucleotidase IA are present in one-third to two-thirds of patients with IBM and are very specific for the disorder.

4. NM
a. Serum CK level is elevated, often more than 10 times normal.
b. Serum CK level is not a good indicator of disease activity.
c. ANAs may be detected in patients with overlap syndrome.
d. Anti–signal recognition particle (SRP) antibodies may be found idiopathic cases. HMG-CoA reductase (HMGCR) antibodies may be found in cases triggered by statin use (usually patients over age of 50 years), as well as in cases without statiin use (typically younger patients). Both anti-SRP and anti-HMGCR myopathies can have smoldering courses and mimic limb-girdle muscular dystrophies.

Electrodiagnostic Features

1. EMG demonstrates increased insertional and spontaneous activity (fibrillation potentials and positive sharp waves).
2. MUAPs are usually small in amplitude, short in duration, polyphasic, and recruit early.
3. Long-duration units, which are often seen in neurogenic disorders, also may be seen, particularly in IBM. This abnormality reflects chronicity of the myopathic process as opposed to a superimposed neurogenic disorder.

Histologic Features

1. DM
a. The characteristic histopathologic abnormality is perifascicular atrophy, but this is not always evident and is seen for the most part in patients with long-standing weakness.
b. Inflammatory cell infiltrate, when evident, is seen in the perimysium and around blood vessels (perivascular). The predominant infiltrate is plasmacytoid dendritic cells, which are the body's natural producers of type 1 interferon.
c. Type 1 interferon–inducible proteins are overexpressed on capillaries and muscle fibers, particularly perifascicular muscle fibers.

d. Unlike PM and IBM, there are no endomysial inflammatory cells surrounding or invading nonnecrotic muscle fibers.

e. Immunoglobulin, complement, and membrane attack complex deposition (MAC) on small blood vessels may be appreciated.

f. Tubuloreticular inclusions in endothelial walls may be found on electron microscopy (EM).

2. PM

a. Muscle biopsy demonstrates endomysial mononuclear inflammatory cell infiltrate surrounding and sometimes appearing to invade nonnecrotic muscle fibers that express major histocompatibility antigen type 1 (MHC1).

b. Immune complex deposition on small blood vessels is not seen.

3. NM

a. Muscle biopsy demonstrates many necrotic and regenerating muscle fibers. However, inflammatory cell infiltrate is absent or scant.

b. There is scattered MHC1 and MAC expression on the sarcolemma of nonnecrotic muscle fibers.

c. Some biopsies may show capillaries with thickened basement membranes (so-called "pipe-stem capillaries") and MAC deposition.

4. IBM

a. Muscle biopsy demonstrates endomysial mononuclear inflammatory cell infiltrate surrounding and invading nonnecrotic muscle fibers expression MHC1, similar to PM.

b. Muscle fibers with one or more rimmed vacuoles are often but not invariably seen.

c. Increased number of ragged red and cytochrome oxidase–negative fibers are seen, indicative of mitochondrial abnormalities.

d. Amyloid deposition in vacuolated muscle fibers may be seen on frozen sections but not paraffin sections. These can be very difficult to appreciate. Much more common, the inclusions stain positive with p62 and to a lesser extent TDP-43 antibodies.

e. EM may demonstrate 15- to 21-nm tubulofilaments in the cytoplasm of vacuolated muscle fibers and less commonly in myonuclei.

f. Because of sampling error, as many as 20% to 30% of muscle biopsies will not demonstrate all these histologic abnormalities, leading to

erroneous diagnosis of PM unless the clinical pattern of weakness that is specific for IBM is not recognized by the clinician.

Treatment

Immunotherapy is recommended for DM, PM, NM, and overlap myositis (see Table 10-1). We do not recommend such treatment for IBM as this myopathy is refractory to such therapies.

I. Corticosteroids

- **a.** In patients with severe weakness (unable to ambulate) or with severe systemic involvement (myocarditis, dyspnea related to ILD), we usually initiate treatment with Solu-Medrol 1 g IV daily for 3 days and then start oral prednisone.
- **b.** In patients with mild or moderate weakness, we typically begin treatment with single-dose prednisone (0.75 to 1.5 mg/kg up to 60 mg) by mouth (p.o.) every morning.
- **c.** Patients are initially seen every 2 to 4 weeks, and we maintain the high-dose prednisone until the patients are back to normal strength or until improvement in strength has reached a plateau (usually 3 to 6 months). Subsequently, the prednisone dose is tapered by 5 to 10 mg every 2 to 4 weeks. Once the dose is reduced to 20 mg daily, prednisone is tapered no faster than 5 mg every 4 weeks. Once on 10 mg daily, prednisone is tapered no faster than 2.5 mg every 4 weeks
- **d.** If a patient does not significantly improve after 2 to 4 months of prednisone, or if there is an exacerbation during the taper, we add a second-line agent (e.g., methotrexate, azathioprine, mycophenolate mofetil, or IVIG) if not started one at the same time as the prednisone.
- **e.** Additionally, if the patient relapses during the taper, we generally double the prednisone dose (or at least put the patient back on a dose he or she was stable on in the past). Once a patient has regained his or her strength, we resume the prednisone taper at a slower rate.
- **f.** Although serum CK level is monitored, adjustments of prednisone and other immunosuppressive agents should be based on the objective clinical examination and not the CK level or the patient's subjective response.
  - **1)** An increasing serum CK level can herald a relapse, but without objective clinical deterioration, we would not increase the dose of

the immunosuppressive agent.

2) However, in such cases, we would hold the dose or the slow the taper.

g. A maintenance dose of prednisone is often required to sustain the clinical response.

h. High-dose, long-term steroids and lack of physical activity can cause type 2 muscle fiber atrophy with proximal muscle weakness that needs to be distinguished from weakness because of relapse of the myositis.

1) Patients who become weaker during prednisone taper, have increasing serum CK level, and have abnormal spontaneous activity on EMG are more likely experiencing a flare of the myositis.

2) In contrast, patients with normal serum CK level and EMG findings and other evidence of steroid toxicity (i.e., cushingoid appearance) may have type 2 muscle fiber atrophy and could benefit from physical therapy and reducing the dose of steroids.

2. Concurrent management with steroids

a. Obtain a chest radiograph and a PPD skin test in at risk patients before initiating immunosuppressive medications. Patients with prior history of tuberculosis or those with a positive PPD may need to be treated prophylactically with isoniazid.

b. Measure bone density with DEXA at baseline and yearly while patients are receiving corticosteroids.

1) A bone density less than 2.5 standard deviations below normal is considered positive for osteoporosis.

2) Calcium supplementation (1 g/d) and vitamin D supplementation (800 IU/d) are started for prophylaxis against steroid-induced osteoporosis.

3) Bisphosphonates are effective in the prevention and treatment of osteoporosis. If DEXA scans demonstrate osteoporosis at baseline or during follow-up studies, we initiate alendronate 70 mg/wk. In postmenopausal women, we start alendronate 35 mg orally once a week as prophylaxis for osteoporosis. The long-term side effects of bisphosphonates are not known, especially in men and young premenopausal women. In those patients, we start prophylactic treatment with alendronate 35 mg orally once a week if DEXA scans show bone loss at baseline (not enough to diagnose osteoporosis) or

if there is significant loss on follow-up bone density scans.

4) Alendronate can cause severe esophagitis and absorption is impaired if taken with meals. Therefore, patients must be instructed to remain upright and not to eat for at least 30 minutes after taking a dose of alendronate.

5) Alternative bisphosphonates can be used instead of alendronate.

c. We do not prophylactically treat with histamine H_2 receptor blockers unless the patient develops gastrointestinal discomfort or has a history of peptic ulcer disease. Calcium carbonate (Tums) can be used for calcium supplementation and dyspepsia.

d. Patients are instructed to start a low-sodium, low-carbohydrate, high-protein diet to prevent excessive weight gain.

e. Physical therapy is initiated and patients are encouraged to slowly begin an aerobic exercise program.

f. Blood pressure is measured with each visit along with periodic eye examinations for cataracts and glaucoma.

g. Fasting blood glucose and serum potassium levels are periodically checked.

1) Potassium supplementation may be required if the patient becomes hypokalemic.

2) Oral hypoglycemic agents or insulin may be required in patients who become hyperglycemic.

3. Second-line therapies

a. These agents are used in patients poorly responsive to prednisone or who relapse during prednisone taper as well as for their potential steroid-sparing effect. Furthermore, sometimes a second-line agent is started at the same time corticosteroids are initiated in hopes that improvement may be quicker and that there may be a long-term steroid-sparing effect.

1) The possible benefit may be offset by increased risk of immunosuppression and other adverse side effects of these agents. Patients should be counseled regarding the equipoise that exists in this regard.

2) No studies have demonstrated the risk–benefit ratio of adding any second-line agent at the onset of treatment of myositis.

3) In patients with severe myositis (particularly those with concomitant cardiac or lung involvement) and those with higher risks from chronic

steroids (e.g., postmenopausal women and patients with known osteoporosis or diabetes mellitus), we favor starting a second-line agent upfront.

b. Methotrexate is our second-line agent of choice unless the patient has ILD, as methotrexate can cause pulmonary fibrosis.

c. Mycophenolate mofetil or azathioprine is our second-line agent of choice in patients with ILD.

d. IVIG has been shown to be effective in a double-blind, placebo-controlled trial in DM, but no similar studies have been done in PM or NM. Small series suggest monotherapy with IVIG may be effective in some cases of anti-HMGCR myopathy. IVIG has not been shown to be beneficial in double-blind, placebo-controlled trials in IBM.

e. A large randomized, placebo-controlled trial failed to demonstrate efficacy of rituximab in myositis patients. However, there were problems with trial design and, in our experience, is efficacious in many patients who are refractory to other modes of immunotherapy, particularly in those with concomitant ILD.

l. Methotrexate

a. We usually begin methotrexate orally at 7.5 mg/wk given in three divided doses greater than 12 hours apart.

b. The dose is gradually increased by 2.5 mg every 2 to 4 weeks as needed, up to 25 mg/wk.

c. If there is no improvement after 1 month of 25 mg/wk of oral methotrexate, switch to weekly parenteral (intramuscular [IM] or IV) methotrexate and increase the dose by 5 mg/wk up to 50 mg/wk.

d. In patients with severe muscle weakness and/or myocarditis, we initiate methotrexate at 20 to 25 mg/wk (as opposed to 7.5 mg/wk) in combination with corticosteroids.

e. The dose of methotrexate needs to be adjusted in patients with renal insufficiency.

f. The major side effects of methotrexate are alopecia, stomatitis, ILD, teratogenicity, oncogenicity, risk of infection, and bone marrow, renal, and liver toxicities.

g. Folate is started at the same time.

h. Because methotrexate can cause ILD, we tend to avoid its use in patients

with myositis who already have the associated ILD. We also always check for an anti–Jo-1 antibody titer in the serum because of the risk of ILD in patients with these antibodies.

i. Baseline and periodic pulmonary function tests with diffusion capacity need to be checked for patients treated with methotrexate.

j. CBCs and LFTs (AST, ALT, and GGT) need to be followed closely. It is important to check the GGT, as its elevation is specific for hepatic dysfunction, whereas the AST and ALT may be elevated from myositis.

5. Mycophenolate mofetil

a. Mycophenolate mofetil inhibits the proliferation of T and B lymphocytes by blocking purine synthesis in only lymphocytes.

b. The starting dose is 1 g twice daily and can be increased by 500 mg/mo up to 1.5 g b.i.d.

c. Mycophenolate is renally excreted; therefore, the dose should be no more than 1 g/d (i.e., 500 mg b.i.d.) in patients with renal insufficiency.

d. A benefit of mycophenolate compared to other immunosuppressive agents is the lack of renal or liver toxicity with the drug. Therefore, it is the second-line agent we use most frequently after methotrexate in myositis patients.

e. The major side effect is diarrhea. Less common side effects include abdominal discomfort, nausea, peripheral edema, fever, and leukopenia.

6. Azathioprine

a. We start azathioprine at a dose of 50 mg/d in adults and gradually increase by 50 mg/wk every 2 to 4 weeks to a total dose of 2 to 3 mg/kg/d.

b. The major drawback is that it can take 9 months or more to see an effect from azathioprine.

c. Prior to beginning azathioprine, patients can be screened for TPMT. Patients who are heterozygous for mutation in TPMT may be able to tolerate azathioprine at lower dosages, but those who are homozygous should not receive drug as they cannot metabolize it and may develop severe bone marrow toxicity.

d. A systemic reaction characterized by fever, abdominal pain, nausea, vomiting, and anorexia occurs in 12% of patients, requiring discontinuation of the drug. This systemic reaction generally occurs within the first few weeks of therapy and resolves within a few days of

discontinuing the azathioprine. Rechallenge with azathioprine usually results in the recurrence of the systemic reaction.

e. Other major complications of azathioprine are bone marrow suppression, hepatic toxicity, pancreatitis, teratogenicity, oncogenicity, and risk of infection.

f. Allopurinol should be avoided because combination with azathioprine increases the risk of bone marrow and liver toxicity.

g. Monitor CBCs and LFTs every 2 weeks until the patient is on a stable dose of azathioprine and then monitor once a month.

h. If the WBC count falls below 3,000/mm^3, we decrease the dose. Azathioprine is held if the WBC count declines to 2,500/mm^3 or the absolute neutrophil count falls to 1,000/mm^3. Leukopenia can develop as early as 1 week or as late as 2 years after initiating azathioprine. The leukopenia usually reverses within 1 month, and it is possible to then rechallenge the patient with azathioprine without recurrence of the severe leukopenia.

i. Discontinue azathioprine if the LFTs increase to more than twice the baseline values. Liver toxicity generally develops within the first several months of treatment and can take several months to resolve. Patients can occasionally be successfully rechallenged with azathioprine after LFTs return to baseline without recurrence of hepatic dysfunction. It is important to check the GGT, which is specific for the liver, as opposed to just AST and ALT, which could be elevated secondary to hepatotoxicity or exacerbation of the myositis.

7. IVIG

a. A prospective, double-blind, placebo-controlled study of 15 patients with DM demonstrated significant clinical improvement with IVIG.

b. Patients should have IgA level checked before treatment. Patients with low IgA levels may be at risk for anaphylaxis.

c. We start IVIG (2 g/kg) slowly over 2 to 5 days and repeat infusions at monthly intervals for at least 3 months.

d. Patients should have renal functions checked, especially those with diabetes mellitus, because of a risk of IVIG-induced renal failure. IVIG is avoided in patients with renal insufficiency.

e. There is a low risk of thrombosis with subsequent myocardial infarction

or stroke. For this reason, we avoid IVIG in patients with significant atherosclerotic cardiovascular disease.

f. Flulike symptoms—headaches, myalgias, fever, chills, nausea, and vomiting—are common and occur in as many as half the patients. Rash and aseptic meningitis may occur.

g. We premedicate patients 30 minutes prior to IVIG infusions with hydrocortisone 100 mg IV, diphenhydramine (Benadryl) 25 mg IV, and acetaminophen (Tylenol) 650 mg p.o. This reduces the incidence of headaches and myalgias.

3. Rituximab

a. Rituximab is a monoclonal antibody directed against CD20 cell marker and will deplete B cells for 6 months to a year or more. As B cells are precursors to plasma cells, antibody production drops over time as well.

b. We have used rituximab in refractory myositis patients with success.

c. The dose of rituximab is 750 mg/m^2 (up to 1 g) IV. The dose is repeated in 2 weeks. This course of rituximab treatment is generally repeated every 6 to 12 months.

d. The main side effects are infusion reactions. Because rituximab depletes B cells, there is increased risk of infection. There have been a few reports of progressive multifocal leukoencephalopathy in patients.

). Third-line agents when the aforementioned treatments fail include cyclosporine, tacrolimus, and cyclophosphamide.

). Cyclosporine

a. We start cyclosporine at a dose of 3 to 4 mg/kg/d in two divided doses and gradually increase to 6 mg/kg/d as necessary.

b. The cyclosporine dose should initially be titrated to maintain trough serum cyclosporine levels of 50 to 200 ng/mL.

c. Blood pressure, electrolytes and renal function, and trough cyclosporine levels need to be monitored periodically.

d. Side effects of cyclosporine and tacrolimus are renal toxicity, hypertension, electrolyte imbalance, gastrointestinal upset, hypertrichosis, gingival hyperplasia, oncogenicity, tremor, and risk of infection.

l. Tacrolimus

a. Tacrolimus is similar to cyclosporine but may be associated with fewer side effects. Therefore, many authorities prefer tacrolimus over

cyclosporine.

b. The starting dose is 0.1 mg/kg and can be gradually increased up to 0.2 mg/kg (in two divided doses) as needed.

c. The dose is titrated to maintain a trough level of 5 to 15 mg/mL.

d. As with cyclosporine, it is important to monitor blood pressure, electrolytes, and renal function.

2. Cyclophosphamide

a. The efficacy of cyclophosphamide is controversial, and it has usually been reserved for patients refractory to prednisone, azathioprine, methotrexate, and IVIG.

b. Cyclophosphamide has also been advocated in patients with severe ILD, as improvement generally begins faster than is seen in treatment with azathioprine.

c. Cyclophosphamide can be given orally at a dose of 1 to 2 mg/kg/d or by IV at a dose of 1 g/m^2/mo for patients with severe myositis and ILD.

d. The major side effects are gastrointestinal upset, bone marrow toxicity, alopecia, hemorrhagic cystitis, teratogenicity, sterilization, and increased risk of infections and secondary malignancies.

e. It is important to maintain a high fluid intake to avoid hemorrhagic cystitis. Urinalysis and CBCs need to be followed closely (every 1 to 2 weeks at the onset of therapy and then at least monthly).

f. Cyclophosphamide should be decreased if the WBC count decreases below 4,000/mm^3. Cyclophosphamide is held if the WBC count declines below 3,000/mm^3, the absolute neutrophil count falls below 1,000/mm^3, or if there is evidence of hematuria. Cyclophosphamide can be restarted at a lower dose once the leukopenia has resolved, but we do not restart the medication in patients with hematuria.

3. Supportive therapy

a. Physical therapy

1) Range-of-motion exercises are started early to prevent contractures.

2) As the patient improves, exercises to improve strength, function, and gait should be done.

b. Speech therapy

1) Patients with dysphagia should undergo a swallowing study.

2) If severe dysphagia or recurrent aspiration is documented, a

percutaneous gastrostomy tube or cricopharyngectomy (in IBM) may be warranted.

4. Malignancy workup
   a. There is an increased risk of cancer in patients with DM, PM, and NM.
   b. The malignancies generally occur within 3 years of the presentation of the myositis.
   c. Patients should have a complete history and physical examination, including rectal, breast, and pelvic examinations.
   d. Chest, abdomen, and pelvic computed tomography (CT) are performed on every patient along with pelvic ultrasound and mammograms on women.
   e. Colonoscopy should be performed on everyone older than 50 years, patients with heme-positive stool, and those with gastrointestinal symptoms (e.g., abdominal pain, persistent constipation, blood in stool).

TRICHINOSIS

Background

Trichinosis is the most common parasitic disease of skeletal muscle.

Pathophysiology

1. Following ingestion of meat infected with encysted larvae, gastric juices liberate the larvae that infect the gut.
2. Maturation of the parasite occurs in the gut. Next, second-generation larvae migrate into the bloodstream and lymphatics to invade the muscle and provoke the inflammatory response.
3. The organism matures and remains within single muscle fibers until consumed by another organism, thereby completing the life cycle.

Prognosis

1. Myalgias and weakness peak in the third week of the infection but can last for several months.
2. Severe disease can be complicated by myocarditis and central nervous

system (CNS) infection.
3. In nonimmunocompromised patients, there is usually complete recovery within several months.

Diagnosis

Clinical Features

1. Two to 12 days following ingestion of inadequately cooked meat (usually pork), the larval form of the nematode disseminates through the bloodstream and invades the musculature.
2. The most frequent muscles invaded, in order of frequency, are the diaphragm, extraocular muscles, tongue, laryngeal muscles, jaw, intercostal muscles, trunk, and limbs.
3. Patients develop fever, abdominal pain, diarrhea, generalized myalgias, and weakness.
4. Periorbital edema, ptosis, subconjunctival hemorrhage, and an erythematous urticaria or petechial rash is often present.

Laboratory Features

1. Most patients have eosinophilic leukocytosis and elevated serum CK level.
2. Serum antibodies against *Trichinella spiralis* can be demonstrated 3 to 4 weeks after infection.

Histopathology

1. Infiltration of the muscle by inflammatory cells is more common.
2. Larvae, cysts, focal calcification of the cysts, fibrosis, and granulomas may be observed.

Treatment

1. Thiabendazole 25 mg/kg b.i.d. for 10 days is the treatment of choice for larvae and the mature nematode, but efficacy has not been established against the encysted larvae.
2. Mebendazole may be effective against both circulating and encysted larvae.
3. Because a Herxheimer-like reaction can develop following degeneration of

the larvae, concurrent corticosteroid administration is probably advisable. Prednisone is started at a dose of 60 mg p.o. daily for the first 2 days of treatment followed by a reduction by 10 mg every 2 days.

CRITICAL ILLNESS MYOPATHY (ACUTE QUADRIPLEGIC MYOPATHY)

Background

1. Weakness developing in a patient in the ICU may be secondary to critical illness polyneuropathy, prolonged neuromuscular blockage, or a special myopathy.
2. This myopathic disorder has been termed "critical illness myopathy" (CIM), acute quadriplegic myopathy, acute illness myopathy, and myopathy associated with thick filaments (myosin).
3. CIM is at least 3 times more common than critical illness polyneuropathy.

Pathophysiology

1. The mechanism of muscle fiber necrosis is not known.
2. Myosin is selectively lost in some patients.
3. Decreased muscle membrane excitability occurs with this myopathy.

Prognosis

1. The mortality is high, approximately 30% in one large series, secondary to multiple organ failure and sepsis rather than the myopathy.
2. The morbidity and mortality in CIM appears to be similar to that of critical illness neuropathy.
3. In patients who survive, muscle strength recovers slowly over several months.

Diagnosis

Clinical Features

1. CIM usually develops in patients who have received high-dose IV corticosteroids and/or nondepolarizing neuromuscular blockers.
2. The disorder has also been reported in critically ill patients with sepsis or multiorgan failure who have not received other corticosteroids or nondepolarizing neuromuscular blocking agents.
3. There may be a predilection for development of CIM in transplant recipients who receive high doses of IV corticosteroids during the perioperative period.
4. Patients with CIM exhibit severe generalized muscle weakness that develops over a period of several days. Occasionally, the weakness can be quite asymmetric and mimic a stroke.
5. The myopathy may be first recognized by the inability to wean the patient from the ventilator.
6. Sensory examination is usually normal, albeit sometimes difficult to interpret in an intubated patient with concurrent altered mental status. Deep tendon reflexes are decreased or absent.

Laboratory Features

Serum CK level can be normal but is moderately elevated in about 50% of patients.

Histopathology

1. Muscle biopsies often demonstrate type 2 muscle fiber atrophy with or without type 1 fiber atrophy, muscle fiber necrosis, and focal or diffuse loss of reactivity for myosin adenosine triphosphatase (ATPase).
2. A loss of thick filaments (myosin) is often apparent on immunohistochemistry and EM.

Electrophysiologic Findings

1. NCS demonstrate significantly diminished amplitudes of CMAPs with normal distal latencies and conduction velocities.
2. In contrast, sensory nerve action potential (SNAP) amplitudes are normal or mildly reduced (>80% of the lower limit of normal).
3. EMG frequently demonstrates prominent fibrillation potentials and positive sharp waves. Short-duration, small-amplitude, polyphasic MUAPs that

recruit early are evident. In severe cases, it may be difficult to recruit any MUAP.

Treatment

1. There is no medical therapy other than supportive care and treatment of underlying systemic abnormalities (e.g., antibiotics in sepsis, dialysis in renal failure).
2. If patients are still receiving high doses of corticosteroids or nondepolarizing neuromuscular blockers, the medications should be stopped.
3. Patients will require extensive physical therapy to prevent contractures and help regain muscle strength and functional abilities.

DUCHENNE AND BECKER MUSCULAR DYSTROPHY

Background

1. The best known of the muscular dystrophies is the X-linked, recessive Duchenne muscular dystrophy (DMD) (Table 9-3). The incidence is roughly 1 per 3,500 male births with a prevalence approaching 1 per 18,000 males. Approximately one-third of cases of DMD are a result of spontaneous mutations in the dystrophin gene located on chromosome Xp21.
2. Becker muscular dystrophy (BMD) (see Table 9-3) represents a form of dystrophinopathy that is milder and less common than the more severe DMD phenotype with which it is allelic. BMD can be distinguished from DMD primarily by its rate of progression combined with dystrophin analysis. Approximately 10% of cases are the result of spontaneous mutations.

Pathophysiology

1. Dystrophin is a structural protein that is intimately bound to the sarcolemma and provides structural integrity to the muscle membrane.
2. The large size of the gene accounts for the high mutation rate and the one-

third of cases caused by new spontaneous mutations. Large deletions, ranging from several kilobases (kbs) to more than 1 million base pairs, can be demonstrated in approximately two-thirds of patients with dystrophinopathy. Approximately 5% to 10% of DMD cases are caused by point mutation resulting in premature stop codons. Duplications are evident in another 5% of cases. Smaller mutations, which are not readily detectable, account for the remainder.

3. Mutations disrupting the translational reading frame of the gene result in near total loss of dystrophin and usually lead to DMD, while in-frame mutations result in the translation of semifunctional dystrophin of abnormal size and/or amount, typically resulting in outlier or BMD clinical phenotypes. Although there are exceptions to the "reading-frame rule," 92% of phenotypic differences are explained by in-frame and out-of-frame mutations.

Prognosis

1. Children with DMD are confined to a wheelchair by the age of 12 years, and most die from respiratory complications in their late teens or early 20s.
2. The severity of BMD is quite variable. Patients with BMD are ambulatory past the age of 15 years. The life expectancy is reduced, with the age at death ranging from 23 to 89 years (mean, 42 years) in some studies.

Diagnosis

Clinical Features

1. Most male children with DMD appear normal at birth and achieve the anticipated milestones of sitting and standing either normally or with only slight delay.
2. A "clumsy" walk and frequent falls are noted by about 2 to 6 years of age.
3. Weakness is characteristically worse proximally than distally and more so in the lower rather than upper limbs.
4. Children are confined to a wheelchair by the age of 12 years.
5. Cardiac dysrhythmias and congestive heart failure can occur late in the disease.

5. Smooth muscle is also affected, and patients can develop gastroparesis and intestinal pseudo-obstruction.

Table 9-3 Molecular Defects of Muscular Dystrophies

Disease	Inheritance	Chromosome	Affected Protein
X-Linked Dystrophies			
Duchenne/Becker	XR	Xp21	Dystrophin
Emery–Dreifuss	XR	Xq28	Emerin
Scapuloperoneal/reducing body myopathy	XR	Xq26.3	Four-and-a-half LIM domain 1 (FHL1)
Limb-Girdle Dystrophies (LGMD)			
LGMD1A	AD	5q22.3-31.3	Myotilin
LGMD1B	AD	1q11–21	Lamin A and C
LGMD1C	AD	3p25	Caveolin-3
LGMD1D	AD	6q23	DNAJB6
LGMD1E	AD	2q35	Desmin
LGMD1F	AD	7q32	Transportin 3
LGMD2A	AR	15q15.1–21.1	Calpain 3
LGMD2B	AR	2p13	Dysferlin
LGMD2C	AR	13q12	γ-Sarcoglycan
LGMD2D	AR	17q12–21.3	α-Sarcoglycan
LGMD2E	AR	4q12	β-Sarcoglycan
LGMD2F	AR	5q33–34	δ-Sarcoglycan
LGMD2G	AR	17q11–12	Telethonin
LGMD2H	AR	9q31–33	E3-ubiquitin-ligase (TRIM 32)
LGMD2I	AR	19q13	Fukutin-related protein (FKRP)
LGMD2J	AR	2q31	Titin
LGMD2K	AR	9q31	POMT1
LGMD2L	AR	11p14.3	Anoctamin 5

LGMD2M	AR	9q31–33	Fukutin
LGMD2N	AR	14q24	POMT2
LGMD2O	AR	1p32	POMGnT1
LGMD2P	AR	3p21	α-Dystroglycan
LGMD2Q	AR	8q24	Plectin 1
LGMD2R	AR	2q35	Desmin
LGMD2S	AR	4q35.1	TRAPPC11
Congenital Muscular Dystrophies (MDC)			
MDC1A	AR	6q22–23	Laminin-α2 chain
α7-Integrin-related MDC	AR	12q13	α7-Integrin
MDC1C	AR	19q13	FKRP
MDDGA1	AR	9q31	POMT1
MDDGA2	AR	14q24	POMT2
MDDGA3	AR	1p32	POMGnT1
MDDGA4	AR	9q31–33	Fukutin
MDDGA5	AR	19q13	FKRP
MDDGA6	AR	22q12.3	LARGE
MDDGA7	AR	7p21.2	ISPD
MDDGA8	AR	3p22.1	GTDC2
MDDGA10	AR	12q14.2	TMEM5
MDDGA11	AR	3p22.1	B3GALNT2
MDDGA12	AR	8p11.21	SGK196
MDDGA13	AR	11q13	B3GNT1
MDDGA14	AR	3p21.31	GMPPB
Rigid spine syndrome	AR	1p35–36	Selenoprotein N1
Ullrich/Bethlem	AR/AD	21q22.3 and 2q37	Collagens 6A1, 6A2, and 6A3
Distal Dystrophies/Myopathies			
Welander	AD	2p13	TIA1
Udd	AD	2q31	Titin
Markesbery–Griggs	AD	10q22.3–23.2	ZASP
Nonaka	AR	9p1–q1	GNE

Miyoshi 1*	AR	2p13	Dysferlin
Miyoshi 2	AR	11p14.3	Anoctamin 5
Laing (MPD1)	AD	14q11	MyHC 7
Williams	AD	7q32	Filamin C
Distal myopathy with vocal cord and pharyngeal weakness (VCPDM or MPD2)	AD	5q31	Matrin 3
Other Dystrophies			
Facioscapulohumeral type 1	AD	4q35	Deletion in D4Z4 region with secondary increase in DUX4
Facioscapulohumeral type 2	AD	18p11.32	SMCHD1 with secondary increase in DUX4
Scapuloperoneal dystrophy	AD	2q35	Desmin
	AD	14q11	MyHC 7
	XR	Xq26.3	Four-and-a-half LIM domain 1 (FHL1) protein
Emery–Dreifuss type 3	AD	6q24	Nesprin-1
Emery–Dreifuss type 4	AD	14q23	Nesprin-2
Emery–Dreifuss type 5	AD	3p25.1	TMEM43
Oculopharyngeal	AD	14q11.2–13	PABP2
Myotonic dystrophy 1	AD	19q13.3	DMPK
Myotonic dystrophy 2	AD	3q21	ZNF9
Myofibrillar myopathy	AD	5q22.3–31.3	Myotilin
	AD	10q22.3–23.2	ZASP
	AD	7q32.1	Filamin-c
	AD	11q21–23	αB-crystallin
	AD/AR	2q35	Desmin
	AR	1p36	Selenoprotein N1
	AD	10q25–26	BAG-3

Hereditary Inclusion Body Myopathies (hIBM)		
AR hIBM	AR	GNE
hIBMPFD	AD	VCP
hIBM 3	AD	MyHC IIa

XR, X-linked recessive; AD, autosomal dominant; AR, autosomal recessive; *POMT*, protein O-mannosyltransferase; *POMGnT1*, O-mannose-â-1,2-*N*-acetylglucosaminyl transferase; TRAPPC, trafficking protein particle complex 11; *MDDGA1*, muscular dystrophy-dystroglycanopathy with brain and eye anomalies (type A); *ISPD*, isoprenoid synthase domain-containing protein; *GTDC2*, O-linked mannose beta-1,4-N-acetylglucosaminyltransferase; *TMEM5*, transmembrane protein 5; *B3GALNT2*, beta-1,4-N-acetlyglucosaminyltransferase; *SGK196*, protein-O-mannose kinase; *B3GNT1*, beta-1,3-N-acetylglucosaminyltransferase 1; *GMPPB*, GDP-mannose pyrophosphorylase B; *TIA1*, T-cell restricted intracellular antigen; *ZASP*, Z-band alternatively spliced PDZ motif-containing protein; *GNE*, UDP-*N*-acetylglucosamine 2-epimerase/*N*-acetylmannosamine kinase; *MyHC*, myosin heavy chain; *hIBMPFD*, hereditary inclusion body myopathy, Paget disease and frontotemporal dementia; *VCP*, valosin-containing protein.

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7. The CNS is also involved in DMD, and the average IQ of the affected children is one standard deviation below the normal mean.
8. BMD has a milder course, with patients remaining ambulatory past the age of 15 years. The mean age of losing the ability to ambulate independently is in the fourth decade.
9. Some patients with BMD manifest with only myalgias, myoglobinuria, cardiomyopathy, and asymptomatic hyperCKemia.

Laboratory Features

1. The serum CK level is markedly elevated (as much as 50 to 100 times normal, or greater).
2. Patients with BMD with only exertional myalgias may have only slightly elevated serum CK level (three times normal).
3. The diagnostic gold standard now is genetic testing which is widely available.

Histopathology

1. Muscle biopsy is no longer required for diagnosis as genetic testing has become less expensive and widely available.
2. Muscle biopsies reveal evidence of muscle fiber degeneration and

regeneration. There is considerable fiber size variation, with scattered hypertrophic and hypercontracted fibers in addition to small, rounded, regenerating fibers. There is increased endomysial and perimysial connective tissue.

3. Immunohistochemistry demonstrates absence of dystrophin staining on the muscle membrane in most cases of DMD, but it can be normal or show only diminished dystrophin staining in BMD. A mosaic pattern of staining may be evident in manifesting women carriers.
4. Western blot analysis of muscle tissue assesses both the quantity and size of the dystrophin present. In DMD, there is a marked reduction in dystrophin (typically it is <3% of normal). In BMD, Western blot analysis reveals an abnormal quantity and/or size of the dystrophin to a lesser degree than seen in DMD.

Treatment

1. Steroids
   - **a.** Prednisone (0.75 mg/kg/d) is effective in improving strength and function, peaking at 3 months, and the subsequent slowing of the rate of deterioration in children with DMD. The beneficial effects are noted as early as 10 days and are sustained for at least 3 years. Lower doses of prednisone (<0.75 mg/kg/d) are not as effective.
   - **b.** Unfortunately, high-dose prednisone is associated with significant side effects including weight gain, stunted growth, cushingoid appearance, excessive hair growth, irritability, and hyperactivity. In addition, prednisone is associated with an increased risk of infections, cataract formation, hypertension, glucose intolerance, osteoporosis, and osteonecrosis.
   - **c.** Once the child is confined to the wheelchair, some authorities taper patients off the prednisone.
   - **d.** An analog of prednisone, deflazacort (not yet FDA-approved in the United States), has been studied in a few clinical trials. Deflazacort at doses of 0.9 mg/kg/d and 1.2 mg/kg/d may be as effective as prednisone 0.75 mg/kg/d and associated with fewer side effects.
   - **e.** A large international trial is underway to compare deflazacort to various regiments of prednisone.

2. Supportive therapy
   a. The best management should involve neurologists, physiatrists, physical therapists, occupational therapists, speech therapists, respiratory therapists, dietitians, psychologists, and genetic counselors to assess all the needs of individual patients.
   b. Physical therapy is a key component in the treatment of patients with muscular dystrophy. Contractures develop early in the disease particularly at the heel cords, iliotibial bands, and hips; therefore, stretching exercises must also be started early (i.e., at 3 to 4 years of age).

3. Bracing
   a. The appropriate use of bracing may delay the child's progression to a wheelchair by approximately 2 years.
   b. A major factor responsible for the child's inability to stand or walk is weakness of the quadriceps. The addition of a long-leg brace (knee–foot orthosis) may stabilize the knee and prevent it from flexing. The children walk stiff-legged, but they do not have the same problem with falling that they had previously. Generally, children are ready for bracing when they have ceased to climb stairs, are having great difficulty arising from the floor, and are having frequent daily falls.
   c. There may be some advantage to a lightweight, plastic knee–foot orthosis, but it is difficult to keep the foot straight with such a device, whereas the high-top boot worn with the double-upright brace provides excellent stability. The choice between plastic and metal often comes down to the personal preference of the patient and physician.
   d. A night splint to maintain the feet at right angles to the leg is important at an early age. Ankle contractures are almost never seen in patients who use these splints conscientiously.

4. Surgery
   a. Reconstructive surgery of the leg often accompanies bracing to keep the leg extended and prevent contractures of the iliotibial bands, hip and knee flexors, and ankle dorsiflexors.
   b. A simple way to maintain function in the legs with contractures beginning in the iliotibial bands, hip flexors, and knee flexors is to perform percutaneous tenotomies of the Achilles tendons, knee flexors, hip flexors, and iliotibial bands. This procedure often allows a child who is becoming

increasingly dependent on a wheelchair to resume walking.

c. Scoliosis is a universal complication of DMD and results in patient pain, aesthetic damage, and perhaps respiratory compromise. We consider spinal fusion in children with 35-degree scoliosis or more and who are in significant discomfort. Ideally, FVC should be greater than 35% to minimize the risk of surgery. Quality of life seems to be improved following spinal stabilization; however, scoliosis surgery does not appear to increase respiratory function.

5. Ventilatory failure

a. Most patients with DMD die as a result of respiratory failure; therefore, it is important to assess for symptoms or signs of respiratory impairment during each clinic visit.

b. Patients with FVCs below 50% or those with symptomatic respiratory dysfunction are offered noninvasive ventilator support, usually BiPAP.

c. Inspiratory and expiratory pressures are titrated to symptom relief and patient tolerability.

d. In our experience, only a few patients desire tracheostomy and mechanical ventilation. However, this is an individual decision that must be made by the patient. Tracheostomy needs to be offered to patients along with realistic counseling regarding what this entails for the patient and the family.

6. Genetic counseling

a. The daughters of males with BMD (males with DMD are usually infertile) and the mothers of affected children who also have a family history of DMD or BMD are obligate carriers of the mutated dystrophin gene.

b. Mothers and sisters of isolated DMD or BMD patients are at risk for being carriers.

c. It is essential to determine the carrier status of "at-risk" females for genetic counseling. There is a 50% chance that males born to carrier females will inherit the disease, whereas 50% of the daughters born will become carriers themselves.

d. Carrier females are usually asymptomatic, but, rarely, dystrophinopathies clinically manifest in females. Approximately 8% of DMD carriers have mild muscle weakness.

e. Serum CK level may be elevated in female carriers early in life.

However, a normal serum CK level does not exclude a carrier status. Elevated serum CK levels are identified in less than 50% of obligate carriers, and there is a false-positive rate of 2.5%.

f. The most reliable method of detecting carrier status is with DNA analysis.
   1) First, affected male relatives should be evaluated for mutations in the dystrophin gene. If a mutation is demonstrated in an affected male relative, at-risk females can be screened for the same mutation.
   2) Carrier status of the mother of a sporadic DMD case must be interpreted cautiously because of the potential for germ-line mosaicism. In a germ-line mosaic, the mutation involves only a percentage of the germ cells (i.e., oocytes) but is not present in the leukocytes in which DNA analysis is performed. An affected child may have an identifiable mutation on DNA analysis, whereas the mother could have no demonstrable mutation in the leukocytes, but she might still be a carrier. The recurrence rate in germ-line carriers is unknown and dependent on the number of mutated oocytes but has been estimated to be as high as 14%.

g. Prenatal diagnosis can be made with DNA analysis of chorionic villi or amniotic fluid cells when there is an identifiable mutation in the family.

h. When mutations are not evident in affected DMD cases, carrier detection depends on the less reliable linkage analysis of many family members using restriction fragment length polymorphisms.

LIMB-GIRDLE MUSCULAR DYSTROPHY

Background

1. The limb-girdle muscular dystrophies (LGMDs) are a heterogeneous group that clinically resembles the dystrophinopathies except for the equal occurrence in males and females (see Table 9-3).
2. The reported incidence and prevalence of LGMD are approximately 6.5 per 100,000 live births and 2 per 100,000 population, respectively.
3. These disorders are inherited in an autosomal recessive or, less commonly, autosomal dominant fashion. Autosomal dominant LGMDs are classified as type 1 (e.g., LGMD-1), while recessive forms are classified as type 2 (e.g.,

LGMD-2). Further alphabetic subclassification has been applied to these disorders as they have become genotypically distinct (e.g., LGMD-2A, LGMD-2B).

Pathophysiology

Mutations have been described in various genes encoding for sarcolemmal, sarcomeric, and nuclear structural proteins as well as enzymes.

Prognosis

Prognosis is similar to that for DMD and BMD.

Diagnosis

1. Patients can manifest with severe early childhood-onset weakness similar to DMD or with a more benign phenotype similar to BMD.
2. For the most part, the clinical, laboratory, and histopathologic features of the LGMDs are nonspecific.
3. Serum CK level is elevated.
4. Muscle biopsies demonstrate dystrophic features similar to those described with DMD and BMD.
5. Immunohistochemistry and immunoblotting demonstrate normal dystrophin. Immunostaining for sarcoglycans, α-dystroglycan, merosin, dysferlin, caveolin-3, and myotilin can be used for diagnosis in some subtypes of LGMD. Immunoblot (Western blot) can demonstrate reduced dysferlin in muscle or peripheral monocytes. Immunoblot can also reveal reduced calpain-3 in muscle, but because calpain-3 can be secondarily reduced in other dystrophies (e.g., dysferlinopathy), genetic testing is required for confirmation.
6. Genetic testing is available for many forms of LGMD and is the gold standard for definitive diagnosis (see www.genetest.com for a listing of laboratories that offer genetic testing).

Treatment

1. Treatment is largely supportive, similar to DMD and BMD.

2. Physical and occupational therapy are important to prevent contractures and improve function.
3. Whether corticosteroids can improve strength and delay progression similar to that observed in DMD is not known, although some patients with LGMD reported benefit from such treatment.

CONGENITAL MUSCULAR DYSTROPHY

Background

The congenital muscular dystrophies (MDCs) are a heterogeneous group of autosomal recessive inherited disorders characterized by perinatal onset of hypotonia with proximal weakness and joint contractures affecting the elbows, hips, knees, and ankles (arthrogryposis) (see Table 9-3).

Pathophysiology

Mutations in various genes have been identified (see Table 9-3). These mutations seem to affect the ability of sarcolemmal proteins to bind to the extracellular matrix.

Prognosis

The prognoses for the α-dystroglycanopathies are quite poor, with death in early childhood. Some patients with α-dystroglycanopathies can live to adulthood and manifest mild phenotypes similar to BMD as can the collagen VI disorders (Ullrich and Bethlem myopathy).

Diagnosis

1. The MDCs are classified according to clinical, ophthalmologic, radiologic, and pathologic features.
2. The major categories of MDCs are as follows:
   a. Those associated with mutations in genes encoding structural proteins of the basal lamina, extracellular matrix, or sarcolemmal proteins that bind to the basal lamina
   b. Those associated with impaired glycosylation of α-dystroglycan

c. That associated with selenoprotein 1 mutations

3. CK is elevated.
4. EMG and NCS are myopathic. In merosinopathies, mild slowing of motor and sensory nerve conductions may be apparent.
5. Magnetic resonance imaging (MRI) of the brain demonstrates migrational disturbances in the α-dystroglycanopathies.
6. Muscle biopsies appear dystrophic. Immunostaining for merosin is absent in merosin-deficient MDC. Immunostaining for merosin and α-dystroglycan is reduced in patients with mutations involving the α-dystroglycanopathies.
7. Genetic testing is available and the diagnostic gold standard (see www.genetest.com for laboratories).

Treatment

1. Treatment of congenital dystrophies is supportive.
2. Physical therapy is important to prevent contractures.
3. Antiepileptic medications are used for control of seizures.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Background

1. The incidence of facioscapulohumeral muscular dystrophy (FSHD) approximates 4 per million with a prevalence of roughly 50 per million.
2. The disease is inherited in an autosomal dominant fashion. However, there is a variable degree of penetrance of clinical findings within families.
3. Ninety-five percent of patients have FSHD type 1, while 5% have FSHD type 2.

Pathophysiology

1. FSHD1 is associated with an *Eco*RI polymorphism in the D4Z4 region of chromosome 4q35. This *Eco*RI polymorphism is variable in size but is reduced compared to normal (FSHD, 10 to 30 kb; normal, 50 to 300 kb).

The mutation results hypomethylation of D4Z4 region and the overexpression of the DUX4 gene which is not usually expressed. DUX4 alters transcription of the other genes.

2. FSHD2 is caused by a mutation in SMCHD1 gene. As in FSHD1, mutations in this gene lead hypomethylation of the D4Z4 region and the overexpression of the DUX4 gene.

Prognosis

1. Some patients with FSHD experience a late exacerbation of muscle weakness. They may only have mild weakness for years, followed by a marked increase of weakness in the typical distribution over the course of several years.
2. Approximately 20% of patients with FSHD eventually will require wheelchairs.
3. FSHD is usually associated with a normal life span.

Diagnosis

Clinical Features

1. The age of onset is usually between 3 and 44 years, although onset has been described as late as 75 years.
2. The muscles of facial expression are typically affected early. Patients are unable to fully close their eyes against resistance and sleep with incomplete eyelid closure.
3. Weakness of the scapula stabilizer muscles leads to upward and lateral rotation of the shoulder blades with scapular winging. There is also significant weakness and atrophy of the biceps brachii and triceps, with relatively normal bulk of the forearm muscles producing the so-called "Popeye arms." Wrist extensors are weaker than wrist flexors. The characteristic facial and upper torso appearance led to the designation of FSHD.
4. Some patients with FSHD manifest only with scapular winging.
5. The tibialis anterior muscles are the earliest lower limb muscle to manifest weakness, and occasionally patients present with foot drop.

6. The muscle involvement may progress to the pelvic musculature, producing a hyperlordotic posture and a waddling gait. As in the face, weakness in the arms and legs is often asymmetric.
7. Weakness can be strikingly asymmetric in the face and limbs.
8. Rare patients can manifest similar to an LGMD with sparing of facial muscles.
9. Ventilatory muscle weakness can occur.

Laboratory Features

1. Serum CK level may be only mildly to moderately elevated or may be normal in some persons.
2. It is important to assess pulmonary function tests for ventilatory muscle involvement.
3. Genetic testing is available to confirm the diagnosis. We start with FSHD1 testing and if negative, do FSHD2 testing.

Treatment

1. Treatment is largely supportive, with physical therapy to decrease contractures.
2. If the patient is unable to raise the arms above the head because of the lack of scapular fixation, surgical stabilization of the scapula to the thorax may be beneficial and increase range of motion and function of the arm. We reserve this for ambulatory patients.
3. Patients with severe biceps, triceps, and forearm weakness may benefit from a forearm orthosis or ball-bearing feeder device.
4. Ankle–foot orthotics are useful in patients with foot drop secondary to tibialis anterior and peroneal muscle weakness.
5. Surgical transposition of the posterior tibial tendon to the dorsum of the foot is particularly useful in patients who have a marked intorsion of the foot when walking.
6. BiPAP can be used in patients with ventilatory muscle weakness (see section on Duchenne and Becker Muscular Dystrophy).

EMERY–DREIFUSS MUSCULAR DYSTROPHY

Background

1. Emery–Dreifuss muscular dystrophy (EDMD) is characterized by the triad of the following:
   a. Early contractures of the Achilles tendons, elbows, and posterior cervical muscles.
   b. Slowly progressive muscle atrophy and weakness with a predominantly humeroperoneal distribution in early stages.
   c. Cardiomyopathy with conduction defects.
2. Prominent contractures are evident prior to the development of significant weakness.

Pathophysiology

1. EDMD is genetically heterogeneous and can be inherited in an X-linked or autosomal dominant fashion.
   a. X-linked EDMD is caused by mutations in a gene (*STA*) located on chromosome Xq28, which encodes for the protein emerin. Less commonly, an X-linked form of EDMD is caused by a mutation in FHL1.
   b. Autosomal dominant EDMD (also known as LGMD-1A) is usually caused by mutations in the lamin A/C gene.
   c. Other forms of autosomal dominant EDMD have recently been reported to be caused by mutations in genes that encode for nesprin-1, nesprin-2, and transmembrane protein 43 or (TMEM43) or LUMA.
2. Emerin, lamin A/C, and nesprin-1 and nesprin-2 are nuclear envelope proteins expressed in skeletal, cardiac, and smooth muscle fibers as well as skin cells.
3. Mutations in these genes result in the disorganization of the nuclear lamina and heterochromatin.

Prognosis

1. The disorder is slowly progressive and even severely affected patients are usually able to ambulate into the third decade.
2. There are potentially lethal cardiac abnormalities by the end of the second or beginning of the third decade. Conduction defects range from first-degree

atrioventricular (AV) block to complete heart block.
3. Although female carriers with emerin mutations typically do not manifest muscle weakness or contractures, they may develop cardiomyopathy.
4. Patients with lamin A/C mutations may manifest only with a cardiomyopathy and may represent the most common form of hereditary cardiomyopathy.

Diagnosis

Clinical Features

Clinical features are as noted in the section on Background.

Laboratory Features

1. The serum CK level is either normal or only mildly to moderately elevated.
2. Electrocardiograms (ECGs) frequently reveal sinus bradycardia, prolongation of the PR interval, or more severe degrees of conduction block.
3. Genetic testing is available and the gold standard.

Histopathology

1. Muscle biopsies reveal dystrophic or nonspecific myopathic features.
2. Muscle and skin biopsies reveal absence of emerin on the nuclear membrane in patients with X-linked EDMD.

Treatment

1. It is important to monitor cardiac function because of the risk of arrhythmias and sudden death.
2. We obtain yearly ECGs in all patients (as well as on possible female carriers) and cardiology consultations for patients with significant abnormalities.
3. Patients may require pacemakers/defibrillators, and some authorities have even recommended prophylactic implantation.
4. Stretching exercises are indicated to minimize contractures.
5. Otherwise, there is no specific medical therapy.

OCULOPHARYNGEAL MUSCULAR DYSTROPHY

Background

1. Oculopharyngeal muscular dystrophy (OPMD) is inherited in an autosomal dominant fashion and usually manifests in the fourth to sixth decades of life.
2. There is an increased incidence in French Canadians and some Hispanics who may share common inheritance from the Basque region of France and Spain.

Pathophysiology

1. OPMD is caused by mutations involving expansions of a short GCG repeat within the poly(A) binding protein 2 gene (*PABP2*) on chromosome 14q11.
2. Normally, there are six GCG repeats encoding for a polyalanine tract at the N-terminus of the protein. Approximately 2% of the population has a polymorphism with seven GCG repeats.
3. In OPMD, there is an expansion to 8 to 13 repeats.
4. The function of *PABP2* and how the mutation in the gene leads to muscle degeneration are unknown.

Prognosis

The late onset of the disease in most patients combined with slow progression usually does not alter the patient's life span provided adequate medical attention is sought with regard to the nutritional aspect of this disease.

Diagnosis

Clinical Features

1. Most patients present with bilateral ptosis. As many as 25% present initially with difficulty swallowing.
2. The extraocular muscles are affected in approximately 50% of patients, but diplopia is not a common symptom.
3. Mild weakness of the neck and proximal limbs can be detected in some

patients.

Laboratory Features

1. Serum CK level is normal or only mildly elevated.
2. Diagnosis can be confirmed by genetic testing.

Treatment

1. Eyelid crutches on glasses or even taping the eyelids open can be used to treat the ptosis.
2. Ptosis surgery can also be performed if patients have sufficient orbicularis oculi strength to allow complete closure of the eyelids postoperatively.
3. Swallowing studies should be obtained to delineate the degree of pharyngeal and esophageal dysmotility.
4. Patients with severe dysphagia may benefit from cricopharyngeal myotomy.
5. Some patients will require percutaneous endoscopic gastrostomy (PEG) tube placement secondary to severe dysphagia.

MYOTONIC DYSTROPHY TYPE 1

Background

1. Myotonic dystrophy type 1 (DM1) is inherited in an autosomal dominant manner.
2. The incidence of this disorder is 13.5 per 100,000 live births, and the prevalence is 3 to 5 per 100,000.
3. DM1 can present at any age; onset in infancy is known as congenital myotonic dystrophy.

Pathophysiology

1. DM1 is caused by the expansion of an unstable polymorphic cytosine-thymine-guanine (CTG) trinucleotide repeat in the 3′ untranslated region of the myotonin protein kinase gene on chromosome 19q13.2.
2. Nuclear retention of mutant messenger RNA (mRNA)–containing expanded CTG repeats sequesters RNA-binding proteins, which impairs normal

transcription and splicing of other mRNAs, leading to abnormal translation of many different proteins.

Prognosis

1. The severity of DM1 directly correlates with the size of the CTG repeat.
2. The size of the repeat is unstable and typically expands from one generation to the next, which accounts for the anticipation phenomena (i.e., the earlier presentation and/or more severe disease in each generation).
3. Life expectancy is reduced. The higher mortality is reflective of death from the associated respiratory weakness and cardiomyopathy.

Diagnosis

Clinical Features

1. Frontal balding, posterior subscapular cataracts, ptosis, and wasting of the facial and masseter/temporalis muscles are characteristic.
2. Limb weakness begins distally and progresses rather slowly to affect proximal muscles.
3. The myotonia is most prominent in the hands.
4. The smooth muscles of the gastrointestinal tract are also involved, leading to dysphagia and chronic pseudo-obstruction.
5. Involvement of the diaphragm and intercostal muscles is common, leading to alveolar hypoventilation.
6. Decreased central drive contributes to hypoventilation, leading to symptoms suggestive of sleep apnea: frequent nocturnal arousals, excessive daytime hypersomnolence, and morning headaches.
7. Cardiac abnormalities are common with approximately 90% of patients having conduction defects on ECG.
8. Sudden cardiac death secondary to arrhythmia is well documented; however, the severity of the cardiomyopathy does not necessarily correlate with the severity of skeletal muscle weakness.
9. Cognitive impairment, particularly in memory and spatial orientation, may be evident, although these abnormalities are not as severe in adult-onset cases as they are in the congenital form of the disorder.

Laboratory Features

1. Serum CK level may be normal or mildly increased.
2. EMG demonstrates myotonic discharges.
3. Genetic testing is the gold standard for diagnosis.

Treatment

1. There is no treatment available that has been clearly shown to improve muscle strength.
2. Myotonia rarely warrants treatment. In fact, some drugs that improve myotonia (i.e., quinine, procainamide, and tocainide) can potentiate cardiac arrhythmias and should be avoided.
3. If myotonia is severe enough to require treatment, phenytoin 100 to 300 mg daily or mexiletine 150 mg daily to 300 mg t.i.d. may be tried.
4. Obtain yearly ECGs to monitor for evidence of conduction defects/arrhythmias and right-sided heart failure because of pulmonary hypertension.
5. Cardiology consultation, 24-hour Holter monitoring, and echocardiograms are ordered in patients with significant ECG abnormalities.
6. Some patients will ultimately require antiarrhythmic medication or pacemaker insertion.
7. Patients with myotonic dystrophy are at risk for pulmonary and cardiac complications from general anesthesia and neuromuscular blocking medications. These agents should be avoided if possible.
8. Pulmonary function tests are routinely performed.
9. Obtain overnight polysomnography in patients with symptoms and signs of cor pulmonale or sleep apnea.
10. Patients with significant hypoventilation or sleep apnea may benefit from noninvasive ventilatory assistance with BiPAP.
11. Modafinil 200 to 400 mg/d has been demonstrated to improve hypersomnolence.
12. Some patients require excision of their cataracts.
13. Ankle braces are indicated in patients with foot drop to assist their gait.
14. Genetic counseling
    a. Patients need to know that the risk of passing the disease on to their

children is 50% with each pregnancy.

b. The disease severity is generally worse from one generation to the next, especially in children born to mothers with DM1.

c. Prenatal diagnosis is possible via amniocentesis or chorionic villous sampling.

MYOTONIC DYSTROPHY TYPE 2 OR PROXIMAL MYOTONIC MYOPATHY

Background

1. Myotonic dystrophy type 2 (DM2) or proximal myotonic myopathy (PROMM) is a multisystem, autosomal dominant disorder characterized by proximal muscle weakness, myotonia, myalgias, and cataracts.
2. Some patients have features almost identical to DM1.

Pathophysiology

1. DM2 is caused by mutations in the gene that encodes for CCHC-type zinc finger, nucleic acid binding protein (CNBP), also called zinc finger 9 (*ZNF9*), on chromosome 3q21.
2. The mutations are expanded CCTG repeats in intron 1.
3. As with DM1, this expanded repeat likely leads to the expression of a toxic pre-mRNA that sequesters RNA-binding proteins, which impairs the splicing of other mRNA species, including those of ion channels.

Prognosis

Slowly progressive proximal weakness develops in most patients.

Diagnosis

1. Clinical features are similar to DM1 except that weakness is much less severe and predominantly affects proximal muscles, and patients with PROMM more often complain of muscle stiffness and aching.
2. Cardiac involvement is also much less common.

3. Onset is in middle or late adulthood.
4. Serum CK level is mildly elevated.
5. EMG demonstrates myotonic discharges.
6. Genetic testing is the gold standard for diagnosis.

Treatment

1. Treatment is similar to that described in the section on Myotonic Dystrophy Type 1, although cardiac and pulmonary complications are less frequent.
2. Genetic counseling.

MYOTONIA CONGENITA

Background

There are autosomal dominant (Thomsen disease) and autosomal recessive (Becker disease) forms of myotonia congenita.

Pathophysiology

Both the autosomal dominant and autosomal recessive forms of myotonia congenita are caused by mutations in the muscle chloride channel gene (*CLCN1*) on chromosome 7q35.

Prognosis

The life span is not adversely affected.

Diagnosis

1. Autosomal dominant myotonia congenita
   - **a.** There is muscle stiffness that usually manifests in early childhood.
   - **b.** Patients have generalized muscle hypertrophy leading to Herculean physique.
   - **c.** Action and percussion myotonia are evident.
   - **d.** Patients are generally not weak.
   - **e.** Serum CK level is normal or only slightly elevated.

f. EMG demonstrates myotonic discharges.
g. Genetic testing is available and the gold standard for diagnosis

2. Autosomal recessive myotonia congenita
   a. The severity of the myotonia is worse in the recessive form and gradually increases during the first two decades of life.
   b. Patients develop proximal muscle weakness.
   c. Action and percussion myotonia are evident.
   d. Patients are generally not weak.
   e. Serum CK level is usually increased 2 to 4 times normal.
   f. EMG demonstrates myotonic discharges. After-discharges may be evident on NCS. Short exercise NCS test may be abnormal.

Treatment

1. Most patients with myotonia congenita do not require medical treatment.
2. When the myotonia is severe and limits function, antiarrhythmic and antiepileptic medications, which interfere with the muscle sodium channel, can be beneficial.
3. We initiate treatment with mexiletine 150 mg daily and gradually increase as tolerated and as necessary to control the symptoms to a maximum of 300 mg t.i.d. The major side effects of mexiletine are light-headedness, diarrhea, and dyspepsia.
4. If mexiletine is ineffective, phenytoin 100 to 300 mg daily is the next step.

POTASSIUM-SENSITIVE PERIODIC PARALYSIS

Background

1. Primary hyperkalemic periodic paralysis is transmitted in an autosomal dominant fashion, and there is a high degree of penetrance in both females and males.
2. "Potassium-sensitive periodic paralysis" is the preferred term because attacks of weakness are not necessarily associated with hyperkalemia in all patients. However, all patients are sensitive to potassium, as they can

become weak when given potassium.

Pathophysiology

Potassium-sensitive periodic paralysis is caused by mutations in the α-subunit of the voltage-dependent sodium channel (*SCN4A*).

Prognosis

The frequency of attacks tends to diminish with time, although fixed proximal weakness may also develop.

Diagnosis

Clinical Features

1. In most patients, symptoms manifest within the first decade of life.
2. Attacks of weakness usually develop in the morning but can occur at any time and are precipitated by rest following exercise or fasting.
3. Unlike hypokalemic periodic paralysis (hypoKPP) (discussed later in the chapter), there is rarely generalized flaccid paralysis.
4. The duration of weakness is usually less than 2 hours, although mild weakness can persist for a few days.
5. The frequency of attacks is highly variable, with some persons afflicted several times a day, whereas others experience difficulty once a year.
6. Some patients have clinical myotonia.
7. Secondary hyperkalemia can cause generalized weakness mimicking primary hyperkalemic periodic paralysis and must be excluded, particularly in patients with no family history. Patients with secondary causes of hyperkalemia do not exhibit clinical or electrical myotonia.

Laboratory Features

1. Between attacks of weakness, serum potassium levels are normal.
2. The attacks of weakness are usually associated with an increase in serum potassium levels (up to 5 to 6 mmol/L). Secondary causes of hyperkalemia need to be excluded.
3. Serum CK level can be normal or mildly elevated in patients even between

attacks of weakness.

4. Genetic testing is the gold standard.

Electrophysiologic Findings

1. Both motor and sensory NCS are normal between and during attacks of weakness. During an attack, the CMAP amplitudes may be reduced or absent in patients with severe weakness. CMAP amplitudes may also decrease in response to brief exercise. The long exercise NCS test may be abnormal.
2. The needle EMG may reveal myotonic discharges that may also be seen in patients without apparent clinical myotonia.

Histopathology

Muscle biopsy frequently reveals vacuoles.

Treatment

1. Preventive therapy with a low-potassium, high-carbohydrate diet and avoidance of fasting, strenuous activity, and cold is recommended.
2. The acute attacks of weakness are often mild in severity, short lasting, and do not require treatment.
3. Ingestion of simple carbohydrates (e.g., fruit juices, glucose-containing candies) results in insulin excretion, which diminishes serum potassium levels, and can improve strength.
4. β-Adrenergic agonists (e.g., metaproterenol, albuterol, salbutamol) can be effective in improving strength and used safely, provided there are no associated cardiac arrhythmias.
5. Only rarely with severe attacks is treatment with IV glucose, insulin, or calcium carbonate indicated.
6. Prophylactic treatment with acetazolamide (125 to 1,000 mg/d), chlorothiazide (250 to 1,000 mg/d), and dichlorphenamide (50 to 150 mg/d) may be beneficial in reducing the frequency of attacks and may help with myotonia as well.

PARAMYOTONIA CONGENITA

Background

1. Paramyotonia congenita is an autosomal dominant disorder with high penetrance that, as noted earlier, is allelic to hyperkalemic periodic paralysis.
2. Some kinships have clinical features of both hyperkalemic periodic paralysis and paramyotonia congenita.
3. The name derives from the "para"-doxic reaction to exercise. In contrast to the warm-up phenomena observed in the other myotonic syndromes, repeated exercise worsens the muscle stiffness in patients with paramyotonia congenita.

Pathophysiology

Paramyotonia congenita with and without episodes of periodic paralysis are caused by mutations in the α-subunit of the voltage-gated sodium channel (*SCN4A*).

Prognosis

Some patients develop attacks of weakness and mild fixed proximal weakness over time.

Diagnosis

Clinical Features

1. Muscle stiffness with or without attacks of periodic paralysis is evident within the first decade of life.
2. Cold temperature also precipitates myotonia and weakness.
3. Percussion myotonia can be demonstrated, although usually is not prominent.
4. Paramyotonia, particularly of the eyelids, is typically evident in most patients. Myalgias are not a common complaint.
5. Muscle strength is normal in patients between attacks of paralysis.

Laboratory Features

1. Serum CK level can be mildly to moderately elevated.
2. Serum potassium levels may be elevated in some patients during an attack of

paralysis.
3. Genetic testing is the gold standard.

Electrophysiologic Findings

1. Both motor and sensory NCS are normal between and during attacks of weakness. During an attack, the CMAP amplitudes may be reduced or absent in patients with severe weakness.
2. Between attacks, CMAP amplitudes also diminish if the limb is cooled with cold water. NCS may reveal after-discharges. The short exercise NCS test is abnormal and worsens with repetition and with cold.
3. The needle EMG may reveal myotonic discharges that can also be seen in patients without apparent clinical myotonia.

Treatment

1. Mexiletine 150 mg daily to 300 mg t.i.d. has been used to prevent weakness and myotonia induced by cold in patients with associated paramyotonia congenita.
2. Chlorothiazide 50 to 100 mg daily is also sometimes effective in relieving the myotonia.

POTASSIUM-AGGRAVATED MYOTONIAS

Background

This group of disorders includes acetazolamide-responsive myotonia congenita, myotonia fluctuans, and myotonia permanens.

Pathophysiology

These disorders are also caused by mutations in the α-subunit of the voltage-gated sodium channel.

Prognosis

Acetazolamide-responsive myotonia is usually responsive to acetazolamide.

Diagnosis

Clinical Features

1. Patients develop myotonia that can be painful. Severity and frequency increase with age, at least into early adulthood.
2. Myotonia is provoked by fasting, potassium, and to a lesser extent by exercise. Myotonia is eased by ingestion of high-carbohydrate meals.
3. Examination reveals normal muscle strength.

Laboratory Features

Serum CK level can be normal or mildly elevated. Genetic testing is available.

Electrophysiologic Findings

1. Routine motor and sensory studies are normal. Short exercise NCS is usually normal.
2. Needle EMG examination demonstrates significant runs of myotonic potentials, but MUAP morphology and recruitment are normal.

Treatment

1. Acetazolamide is effective in reducing myotonia and associated muscle pain in acetazolamide-responsive myotonia. It is started at 125 mg/d and titrated as tolerated to 250 mg t.i.d.
2. Mexiletine 150 mg daily to 300 mg t.i.d. may also be beneficial

FAMILIAL HYPOKALEMIC PERIODIC PARALYSIS

Background

1. hypoKPP type 1 is the most frequent form of periodic paralysis, with an estimated prevalence of 1 per 100,000.
2. It is an autosomal dominant disorder, with reduced penetrance in women (a male-to-female ratio of 3:1 or 4:1).

3. It is genetically heterogenic.

Pathophysiology

1. Most cases of familial hypoKPP type 1 are caused by mutations in the skeletal muscle VGCC α-1 subunit gene (*CACNA1S*).
2. Mutations in *SCN4A* cause less common hypoKPP type 2.

Prognosis

The frequency of attacks generally decreases after the age of 30 years, and some patients become free of attacks in their 40s or 50s.

Diagnosis

Clinical Features

1. Symptom onset is usually in the first two decades when patients note the development of episodic weakness.
2. Most patients note that some form of unaccustomed strenuous exercise or exertion followed by rest or sleep usually precipitates an attack.
3. Other aggravating factors include heavy meals rich in carbohydrates and sodium, alcohol consumption, exposure to cold, and emotional stress. The bouts of weakness can occur at any time of day, although early morning hours appear to have a slightly higher propensity for being associated with weakness.
4. Severity of an attack can range from mild weakness of an isolated muscle group to severe generalized paralysis.
5. The frequency of these attacks of weakness is also highly variable, and they can occur several times a week or once a year.

Laboratory Features

1. Attacks of weakness are associated with decreased serum potassium levels usually below 3.0 mEq/L. Secondary causes of hypokalemia periodic paralysis need to be excluded.
2. Between bouts of weakness, the serum potassium is normal.
3. During severe attacks of weakness, there is oliguria with urinary retention of

sodium, potassium, chloride, and water.

4. Genetic testing is available to confirm the diagnosis.
5. The ECG may demonstrate bradycardia, flattened T waves, prolonged PR and QT intervals, and, notably, U waves secondary to the hypokalemia.
6. Serum CK level is normal or only mildly elevated between attacks and increased during an attack of weakness.
7. Genetic testing is the gold standard to confirm the diagnosis

Histopathology

1. The muscle biopsy may demonstrate multiple or single intracellular vacuoles, tubular aggregates, and dilatation of the sarcoplasmic reticulum.
2. Patients with the typical *CACNA1S* mutations are more likely to have vacuoles, while tubular aggregates are more commonly seen in patients with *SCNA4* mutations.

Electrophysiologic Findings

1. Routine sensory and motor NCS are normal between attacks of weakness. However, a decrement of the CMAP amplitude may be appreciated with the long exercise test.
2. During the paralytic attack, the CMAP amplitude declines precipitously secondary to muscle membrane inexcitability. CMAP amplitudes may also decrease following brief exercise.
3. The needle EMG examination between attacks of muscle paralysis usually reveals no abnormalities.
4. Early in an attack of weakness, a slight increase in spontaneous potentials (fibrillation potentials and positive sharp waves) and insertional activity may be noted. As the paralytic attack progresses, one observes a decrease in the amplitude and duration of voluntary MUAPs as well as an overall decrease in the number of MUAPs contributing to the interference pattern.

Treatment

1. Preventive measures include avoidance of provocative factors (e.g., ingestion of high-carbohydrate meals, strenuous exercise).
2. Acetazolamide (125 to 1,500 mg/d) and potassium salts (0.25 to 0.5 mEq/kg) can also be prophylactically administered to prevent hypokalemia

and attacks of weakness. However, acetazolamide may exacerbate attacks of weakness in patients with hypoKPP type 2 caused by *SCNA4* mutations.

3. Dichlorphenamide (50 to 150 mg/d) appears to be at least as effective at reducing attack frequency and severity as acetazolamide.
4. Triamterene (25 to 100 mg/d) and spironolactone (25 to 100 mg/d) may be used to prevent attacks and improve inter-attack weakness when acetazolamide and dichlorphenamide are not effective.
5. Acute attacks of weakness are treated with oral potassium salts (0.25 mEq/kg) every 30 minutes until strength improves.
6. If the patient's condition precludes oral potassium, IV potassium (potassium chloride [KCl] bolus 0.05 to 0.1 mEq/kg or 20 to 40 mEq/L of KCl in 5% mannitol) may be administered.
7. Cardiac monitoring is essential during treatment.

KLEIN–LISAK–ANDERSEN OR ANDERSEN–TAWIL SYNDROME

Background

Klein–Lisak–Andersen syndrome, also known as Andersen–Tawil syndrome, is a distinct autosomal dominant disorder characterized by the triad of periodic paralysis, ventricular dysrhythmias, and dysmorphic features.

Pathophysiology

Mutations in the potassium channel gene (*KCNJ2*) located on chromosome 17q23 are evident in some affected individuals.

Prognosis

Some patients develop mild fixed proximal weakness. Life-threatening cardiac dysrhythmias can also occur.

Diagnosis

Clinical Features

1. This form of periodic paralysis could be associated with hypokalemia, normal kalemia, or hyperkalemia.
2. The cardiopathy ranges from an asymptomatic long QT interval to potentially fatal ventricular tachyarrhythmias.
3. The major dysmorphic features described include short stature, scaphocephaly, hypertelorism, low-set ears, broad nose, micrognathia, high arched palate, clinodactyly and short fingers, syndactyly, and scoliosis.
4. The episodes of periodic weakness and cardiac arrhythmia can manifest in early childhood.
5. There is no evidence of myotonia or paramyotonia.

Laboratory Features

1. Serum CK level is normal or only mildly elevated (less than 5 times normal).
2. Serum potassium levels can be normal, elevated, or decreased during attacks of weakness.
3. A prolonged QT interval is present in 80% of patients, while some have even more ominous ventricular tachyarrhythmias.
4. Genetic testing can be done to confirm the diagnosis.

Histopathology

Muscle biopsies frequently reveal tubular aggregates similar to those observed in other forms of periodic paralysis.

Electrophysiologic Findings

1. Motor and sensory NCS are normal.
2. Likewise, EMG is normal interictally. Importantly, there are no myotonic discharges.

Treatment

1. Early recognition of the potential cardiac conduction abnormalities is important because they may be treated with antiarrhythmic agents or insertion of a pacemaker/defibrillator.

2. Acetazolamide (125 to 1,500 mg/d) may prevent paralytic attacks in some patients.
3. Medications that prolonged the QT should be avoided or used with extreme caution.

MALIGNANT HYPERTHERMIA

Background

1. The incidence of malignant hyperthermia (MH) in patients exposed to general anesthesia ranges from 0.5% to 0.0005%.
2. At least 50% of patients with MH have had previous anesthesia without clinically manifesting the disorder.

Pathophysiology

1. MH is thought to arise secondary to excessive calcium release by the sarcoplasmic reticulum calcium channel, the ryanodine receptor.
2. Increased intracytoplasmic calcium leads to excessive muscle contraction, increased utilization of oxygen and ATP, and overproduction of heat.
3. MH susceptibility is genetically very heterogenic with at least six different genes identified.

Prognosis

Patients and family members should be warned of increased risk of subsequent episodes of MH with anesthesia.

Diagnosis

Clinical Features

1. MH is an autosomal dominant disorder characterized by severe muscle rigidity, myoglobinuria, fever, tachycardia, cyanosis, and cardiac arrhythmias precipitated by depolarizing muscle relaxants (e.g., succinylcholine) and inhalational anesthetic agents (e.g., halothane).

2. MH usually occurs during surgery, but it can manifest in the postoperative period. Rarely, attacks of MH have developed following exercise, ingestion of caffeine, or stress.

Laboratory Features

1. Serum CK level can be normal or mildly elevated interictally in patients susceptible to MH.
2. During attacks of MH, serum CK levels are markedly elevated and myoglobinuria can develop.
3. Hyperkalemia and metabolic and respiratory acidosis are evident.
4. Genetic testing is available to identify many of the subtypes of MH.

Treatment

1. Patients at risk for MH should not be given known triggering anesthetic agents.
2. MH is a medical emergency requiring several therapeutic steps.
   - **a.** The anesthetic agent must be discontinued while 100% oxygen is delivered.
   - **b.** Dantrolene 2 to 3 mg/kg every 5 minutes for a total of 10 mg/kg should be administered.
   - **c.** The stomach, bladder, and lower gastrointestinal tract are lavaged with iced saline solution, and cooling blankets are applied.
   - **d.** Acidosis and hyperkalemia are treated with sodium bicarbonate, hyperventilation, dextrose, insulin, and occasionally calcium chloride.
   - **e.** Urinary output must be maintained with hydration, furosemide, or mannitol.
   - **f.** The patient must be monitored and treated for cardiac arrhythmias.

CONGENITAL MYOPATHIES

Background

The term "congenital myopathy" refers to myopathic disorders presenting preferentially, but not exclusively, at birth (Table 9-4).

Pathophysiology

A variety of mutations have been identified for the specific forms of congenital myopathy.

Prognosis

The congenital myopathies were initially considered nonprogressive, although it is now clear that progressive weakness can occur. Some forms are particularly associated with a poor prognosis and death in infancy or early childhood (e.g., X-linked myotubular myopathy, infantile-onset nemaline rod myopathy). Some "congenital myopathies" present in adult life, even in late adulthood (late-onset ryanodine receptor mutations)

Diagnosis

1. Congenital myopathies can be inherited in an autosomal dominant, autosomal recessive, or X-linked pattern.
2. The serum CK level is either normal or only mildly elevated.
3. NCS are normal. EMG demonstrates increased muscle membrane instability and myopathic motor units in myotubular/centronuclear and occasionally nemaline and central core myopathies.
4. Definitive diagnosis of congenital myopathies usually requires muscle biopsy.
5. Genetic testing is now available and the gold standard for diagnosis for most forms (see www.genetest.com).

Treatment

1. There are no medical treatments available to improve strength or slow deterioration.
2. Treatment is largely supportive as discussed with the muscular dystrophies.
3. Physical and occupational therapies are important to reduce contractures and improve mobility and function.
4. Patients may benefit from bracing and other orthotic devices.
5. It is important to advise patients and families of the risk of MH in central core and multicore myopathies.

Table 9-4 Congenital Myopathies

Disease	Inheritance	Protein (Gene)
Central core myopathy	AD (rare AR)	Ryanodine receptor (*RYR1*)
	AR	Muscle slow/b cardiac myosin heavy chain 7 gene (*MYH7*)
	AD	α-Actin 1 (*ACTA1*)
	AR	Titin (*TTN*)
	AD	Coiled-coil domain-containing 78 (*CCDC78*)
Multiminicore myopathy	AR	Selenoprotein N1/(*SEPN1*)
	AD/AR	Ryanodine receptor (*RYR1*)
	AR	Titin (*TTN*)
	AD	Muscle slow/b cardiac myosin heavy chain 7 gene (*MYH7*)
	AR	Multiple epidermal growth factor-like domains protein 10 (*MEGF10*)
Core-rod myopathy	AD/AR	α-Actin 1 (*ACTA1*)
	AR	Nebulin (*NEB*)
	AD	Kelch repeat and BTB/ (*KBTBD13*)

Nemaline rod myopathy	AR	Nebulin (*NEB*)
	AD/AR	α-Actin (*ACTA1*)
	AD/AR	α-Tropomyosin (*TMP3*)
	AD/AR	β-Tropomyosin (*TPM2*)
	AR	Slow troponin T (*TNNT1*)
	AR	Cofilin-2 (*CFL2*)
	AD	Kelch repeat and BTP domain containing 13 (*KBTKT13*)
	AR	Kelch-like family member 40 and 41 genes (*KLHL40* and *KLHL41*)
Centronuclear/myotubular myopathy	X-linked	Myotubularin (*MTM1*)
	AD	Dynamin 2 (DYN2)
	AR	Ryanodine receptor (*RYR1*)
	AR	Amphiphysin 2 (*BIN2*)
	AR	Titin (*TTN*)

Congenital fiber-type disproportion	AD AD AR	α-Tropomyosin (*TMP3*) Ryanodine receptor (*RYR1*) Rarely caused by mutations in *ACTA1*, *SEPN1*, *MYL2*, *TPM2*, and *MHC7*
Reducing body myopathy	X-linked AR	Four-and-a half LIM (*FHL1*) Desmin (*DES*)
Fingerprint body myopathy	Unknown	Unknown
Sarcotubular myopathy (allelic to LGMD 2H)	AR	Tripartite motif-containing protein 32/(*TRIM 32*)
Trilaminar myopathy	Unknown	Unknown
Hyaline body myopathy/familial myopathy with lysis of myofibrils/myosin storage myopathy	AD	Muscle slow/b cardiac myosin heavy chain 7 gene (*MYH7*)
H-IBM 3/myosin storage myopathy	AD	Myosin heavy chain type IIa (*MYH2*)

Cap myopathy	AD AD AD	β-Tropomyosin (*TPM2*) α-Tropomyosin (*TMP3*) α-Actin (*ACTA1*)
Zebra body myopathy	AR	α-Actin (*ACTA1*)
Tubular aggregate myopathy	AD AD	Stromal interaction molecule 1 (*STIM1*) Orai1 (*ORAI1*)
	AR	UDP-*N*-acetylglucosamine-dolichyl-phosphate *N*-acetylglucosaminephosphotransferase 1 (*DPAGT1*)
	AR	Glutamine-fructose-6-phosphate transaminase 1 (*GFPT1*)

AD, autosomal dominant; AR, autosomal recessive; EOM, extraocular muscle; MH, malignant hyperthermia; LGMD, limb-girdle muscular dystrophy.

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POMPE DISEASE

Background

1. Pompe disease (acid maltase deficiency) is an autosomal recessive disorder caused by defects in the lysosomal acid maltase (α-glucosidase) pathway.
2. There are three recognized clinical subtypes of Pompe disease:
   a. A severe infantile, or classical form
   b. A milder infantile form
   c. A late (childhood or adolescent) onset variant
3. The incidence is less than 1 per 100,000 newborns.

Pathophysiology

The disorder is caused by mutations encoding for acid maltase (α-glucosidase) on chromosome 17q21–23.

Prognosis

Classical infantile Pompe is progressive and invariably fatal by 2 years of age secondary to cardiorespiratory failure. Rare infantile-onset patients have a more slowly progressive course, but the process is still invariably fatal. Life expectancy is reduced in late-onset patients because of ventilatory failure.

Diagnosis

Clinical Features

1. Infantile Pompe disease
   a. The cardinal features of the disease include profound cardiomegaly, macroglossia, and mild to moderate hepatomegaly.
   b. Infants demonstrate progressive weakness and hypotonia within the first 3 months of life. Feeding difficulties and respiratory muscle weakness are common.
2. The late-onset form can present anytime during childhood to late adult life. The typical age of onset of symptoms is in the third or fourth decade with generalized proximal greater than distal muscle weakness and ventilatory muscle weakness. Some patients manifest with only ventilatory muscle weakness (e.g., dyspnea).

Laboratory Features

1. Deficiency of α-glucosidase activity can be demonstrated in muscle fibers, fibroblasts, monocytes, and urine. The fastest and probably easiest way to screen for Pompe disease is to assess α-glucosidase activity on a dried blood spot. The dried blood spot testing need not be done in your laboratory. Blood can be sent to a specialty laboratory that can perform the blood spot test (see www.genetest.com for a list of laboratories that offer this testing).
2. Genetic testing is available to look for mutations in the α-glucosidase gene. Some laboratories can even perform this test on residual blood that was sent for dried blood spot analysis.
3. Serum CK level is elevated to variable degrees in infantile Pompe disease but can be normal in adult-onset Pompe.
4. ECGs can demonstrate left axis deviation, a short PR interval, large QRS complexes, inverted T waves, ST depression, or persistent sinus tachycardia.
5. Echocardiograms can show progressive hypertrophic cardiomyopathy.
6. Pulmonary function tests may show a restrictive defect with decreased FVC, reduced maximal inspiratory and expiratory pressures, and early fatigue of the diaphragm.

Electrophysiologic Findings

1. Sensory and motor nerve conduction findings are typically normal.
2. Needle EMG reveals abundant fibrillation potentials, positive sharp waves, and myotonic or pseudomyotonic potentials. Voluntary MUAPs demonstrate the typical alterations noted in chronic myopathic disorders.

Histopathology

1. The characteristic light microscopy feature is the formation of vacuoles within type 1 and type 2 fibers.
2. The vacuoles react strongly to periodic acid–Schiff (PAS) and are sensitive to diastase. These vacuoles also stain intensely to acid phosphatase, confirming that the vacuoles filled with glycogen are secondary lysosomes.
3. However, muscle biopsy in late-onset Pompe disease may not demonstrate PAS-positive vacuoles and may show only nonspecific myopathic features.

Additionally, sometimes the biopsies look more neurogenic (owing to glycogen accumulation in the anterior horn cells) and may even look normal.

4. α-Glucosidase activity and glycogen content can be measured from a frozen piece of the muscle biopsy tissue.

Treatment

1. Enzyme replacement therapy (ERT) with alglucosidase alfa (Myozyme) has a beneficial effect in infantile Pompe and is now FDA-approved. It is unclear if ERT is effective in late-onset Pompe disease. The dose is 20 mg/kg IV every 2 weeks. The main side effects are infusion reactions.
2. Ventilatory muscles can be affected preferentially and therefore one must follow the pulmonary functions closely. Ventilatory insufficiency may be managed by noninvasive mechanical ventilatory support (e.g., BiPAP).
3. Prenatal diagnosis is possible with amniocentesis or chorionic villous sampling.

DEBRANCHER ENZYME DEFICIENCY

Background

Debrancher enzyme deficiency, also known as Cori–Forbes disease, accounts for approximately 25% of glycogen storage diseases.

Pathophysiology

The disease is caused by mutations in the debrancher enzyme gene located on chromosome 1p21.

Prognosis

The course is slowly progressive but mild, and life span is not affected.

Diagnosis

Clinical Features

1. Onset of muscle weakness is usually in the third to fourth decade of life and is slowly progressive.
2. Approximately, one-third of the cases begin in infancy or early childhood, and motor milestones can be delayed.
3. There is prominent atrophy and weakness of distal limb muscles in about 50% of patients.
4. Cardiomyopathy can also complicate debrancher deficiency.

Laboratory Features

1. Debrancher enzyme deficiency can be demonstrated with biochemical assay of muscle, fibroblasts, or lymphocytes.
2. Serum CK level is elevated 2 to 20 times normal.
3. ECGs can reveal conduction defects and arrhythmias.
4. Echocardiogram may reveal findings suggestive of hypertrophic obstructive cardiomyopathy.
5. Genetic testing is available and is the gold standard.

Electrophysiologic Findings

1. Sensory and motor nerve conduction findings are typically normal.
2. Needle EMG reveals abundant fibrillation potentials, positive sharp waves, and myotonic or pseudomyotonic potentials. Voluntary MUAPs demonstrate the typical alterations noted in chronic myopathic disorders.

Histopathology

1. Muscle biopsies demonstrate a vacuolar myopathy with abnormal accumulation of glycogen in the subsarcolemmal and intermyofibrillar regions of muscle fibers.
2. These vacuoles stain intensely with PAS but are partially diastase resistant. Furthermore, in contrast to α-glucosidase deficiency, these vacuoles do not stain with acid phosphatase, suggesting that the glycogen does not primarily accumulate in lysosomes.

Treatment

1. There is no specific medical therapy for the muscle weakness.
2. Patients are best managed by preventing fasting hypoglycemia through

frequent low-carbohydrate feedings and maintaining a high-protein intake.
3. Supportive therapy is required for patients with clinical manifestations of congestive heart failure.

BRANCHING ENZYME DEFICIENCY

Background

Branching enzyme deficiency, also known as Andersen disease or polyglucosan body disease, is caused by the deficiency of the enzyme capable of creating the branched glycogen molecule, which results in an accumulation of polysaccharide in the liver, CNS, and skeletal and cardiac muscles.

Pathophysiology

It is caused by mutations within the gene for glycogen branching enzyme located on chromosome 3.

Prognosis

The course is variable.

Diagnosis

Clinical Features

1. There is a neuromuscular form of the disease in which patients manifest primarily with muscle weakness and cardiomyopathy.
2. Weakness and atrophy can be predominantly proximal or distal.
3. There is also a form of branching enzyme deficiency that manifests mainly in adults as progressive upper and lower motor neuron loss, sensory nerve involvement, cerebellar ataxia, neurogenic bladder, and dementia.

Laboratory Features

1. Deficiency of branching enzyme may be demonstrated in muscle.
2. The serum CK level may be normal or slightly elevated.

3. ECG can demonstrate progressive conduction defects leading to complete AV block.
4. Echocardiogram may reveal a dilated cardiomyopathy.
5. Genetic testing is available and the gold standard for diagnosis.

Electrophysiologic Findings

1. Sensory and motor nerve conduction findings are typically normal.
2. Needle EMG reveals abundant fibrillation potentials, positive sharp waves, and myotonic or pseudomyotonic potentials. Voluntary MUAPs demonstrate the typical alterations noted in chronic myopathic disorders.

Histopathology

1. Routine light and EM reveal deposition of varying amounts of finely granular and filamentous polysaccharide (polyglucosan bodies) in the CNS, peripheral nerves (axons and Schwann cells), skin, liver, and cardiac and skeletal muscles.
2. These polyglucosan bodies are PAS-positive and diastase-resistant.

Treatment

1. Liver transplantation has been performed in some children.
2. Long-term follow-up (mean, 42 months) has shown that most of the patients became free of liver, neuromuscular, and cardiac dysfunction.
3. No other medical therapies have been demonstrated to be effective.
4. Treatment is otherwise supportive.

DYNAMIC GLYCOGEN STORAGE DISORDERS

Background

1. Dynamic glycogen storage disorders include deficiencies in myophosphorylase (McArdle disease), phosphofructokinase, phosphorylase b kinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, and β-enolase. They are very similar to and are associated with exertional cramps and occasionally myoglobinuria with mild exercise.

2. Thus, these are considered the dynamic glycogen storage disorders as opposed to the previously described Pompe disease and debrancher and branching enzyme deficiencies, which are associated with nondynamic, fixed weakness.

Pathophysiology

These disorders are caused by mutations in the respective genes.

Prognosis

1. Approximately 50% of patients experience myoglobinuria related to exercise, while a third of these individuals have various degrees of renal failure.
2. As many as one-third of patients develop mild, fixed proximal weakness as a result of recurrent bouts of rhabdomyolysis.

Diagnosis

Clinical Features

1. The major symptom is exercise intolerance that usually starts in childhood. Exertional muscle pain, cramps, and myoglobinuria develop later, and the diagnosis is usually made by the second or third decades of life.
2. Some patients note a second-wind phenomenon in which, after the onset of mild exertional myalgias or cramps, the individual may continue with exercise at the previous or a slightly reduced level following a brief period of rest.
3. Overt myoglobinuria is rarely noted in children and primarily manifests in the second or third decades.
4. Most patients essentially have normal physical examinations between attacks of muscle cramping.

Laboratory Features

1. Serum CK level is invariably elevated at baseline.
2. The forearm exercise test can be used to diagnose various disorders of glycolysis.

a. The forearm muscles are exercised by having the patient rapidly and strenuously open and close the hand for 1 minute. Immediately after exercise and then 1, 2, 4, 6, and 10 minutes after exercise, blood samples are again taken and analyzed for lactate and ammonia.
b. The normal response is for lactate and ammonia levels to rise to three to four times the baseline levels.
c. If neither the lactate nor the ammonia levels increase, the test is inconclusive and implies that the muscles were not sufficiently exercised.
d. A rise in lactate levels but not ammonia is seen in myoadenylate deaminase deficiency (probably nonpathogenic deficiency).
e. In myophosphorylase, phosphofructokinase, phosphoglycerate mutase, phosphoglycerate kinase, phosphorylase b kinase, β-enolase, and lactate dehydrogenase deficiencies, the ammonia level rises appropriately, but the lactic acid level does not.
f. Genetic testing is available for most.

Electrodiagnostic Findings

EMG and NCS are usually normal.

Histopathology

1. Excessive accumulation of glycogen in the subsarcolemmal and intermyofibrillar areas may be observed on light microscopy and EM.
2. Staining for myophosphorylase and phosphofructokinase can be routinely performed and shows absence in cases of respective deficiency.
3. Enzyme activities can be assayed in muscle tissue for definitive diagnosis of the specific subtype of glycogen storage disease.

Treatment

1. Intense isometric exercises such as weight lifting and maximum-aerobic exercises such as sprinting should be avoided.
2. Patients may benefit from a mild to moderate aerobic conditioning. A mild to moderate exercise program improves exercise capacity by increasing cardiovascular fitness and the supply of necessary metabolic substrates to muscle.
3. Patients with McArdle disease should be instructed on moderating their

physical activity and obtaining a "second-wind" response. Any bout of moderate exercise should be preceded by 5 to 15 minutes of low-level warm-up activity to promote the transition to the second wind.

4. Oral glucose or fructose loading before activities may be effective in McArdle disease but may be deleterious in phosphofructokinase deficiency.
5. Patients with myoglobinuria should be admitted to the hospital and hydrated to prevent acute tubular necrosis.

CARNITINE DEFICIENCY

Background

1. Carnitine deficiency is the most common muscular disorder of lipid metabolism.
2. It is systemic or only evident in muscle. Muscle carnitine deficiency may be primary or secondary to some other myopathic disorder.

Pathophysiology

Primary carnitine deficiency has been linked to mutations in the sodium-dependent carnitine transporter protein gene (*OCTN2*) located on chromosome 5q33.1.

Prognosis

The course and response to replacement therapy with carnitine are variable.

Diagnosis

Clinical Features

1. Primary muscle carnitine deficiency usually manifests in childhood or early adult life, but infantile onset has also been described.
2. Progressive proximal muscle weakness and atrophy develop.
3. Cardiac involvement with ventricular hypertrophy, congestive heart failure, and arrhythmias occurs in some patients.

4. A secondary deficiency of carnitine may result from a variety of disorders, including respiratory chain defects, organic aciduria, endocrinopathies, dystrophies, renal and liver failure, and malnutrition, or as a toxic effect of certain medications. It is not clear whether patients with secondary carnitine deficiency truly develop myopathic symptoms.

Laboratory Features

1. Plasma and tissue carnitine levels are severely decreased in the primary systemic carnitine deficiency, whereas the deficiency is much less (25% to 50% of normal) in secondary forms of carnitine deficiency.
2. Only muscle carnitine levels are decreased in primary muscle carnitine deficiency.
3. Serum CK level is normal in approximately 50% of patients with the myopathic form of the disease but can be elevated to as much as 15 times normal.
4. Genetic testing is available.

Electrophysiologic Findings

1. Motor and sensory NCS are normal.
2. Needle EMG is often normal, but some patients with profound weakness have increased insertional activity. Short-duration, small-amplitude, polyphasic MUAPs that recruit early can be observed.

Histopathology

1. Muscle fibers contain numerous vacuoles and abnormal accumulation of lipid.
2. Muscle carnitine level is dramatically decreased (<2% to 4% of normal).

Treatment

1. Oral L-carnitine (2 to 6 g/d) has benefited some, but not all, patients with carnitine deficiency.
2. Treatment is otherwise supportive.

CARNITINE PALMITOYLTRANSFERASE

DEFICIENCY

Background

Carnitine palmitoyltransferase (CPT) deficiency is the most common cause of myoglobinuria.

Pathophysiology

1. CPT deficiency is caused by mutations in the *CPT2* gene located on chromosome 1p32.
2. Deficiency of CPT impairs the transport of acylcarnitine across the inner mitochondrial membrane.
3. Thus, the generation of ATP from fatty-acid metabolism is impaired.

Prognosis

Persistent weakness after attacks of myoglobinuria is uncommon but may occur.

Diagnosis

Clinical Features

1. The typical clinical presentation is muscular pain and cramping following intense or prolonged exertion. Symptoms may also be triggered by fasting or recent infection.
2. Myoglobinuria is a common feature of this disease, and renal failure can occur.
3. Most patients become symptomatic by the second decade.
4. Between attacks, the physical examination is usually normal.

Laboratory Features

1. Serum CK level is usually normal, except when the patient performs intense physical activities or fasts for prolonged periods.
2. Exercise forearm test is normal.
3. Genetic testing is available.

Electrophysiologic Findings

EMG and NCS findings are typically normal between attacks of myoglobinuria.

Histopathology

1. There is usually no gross abnormality noted on light microscopic examination of muscle tissue.
2. Enzyme analysis on muscle tissue can confirm the deficiency.

Treatment

1. Patients with CPT deficiency should be cautioned to avoid any situation that provokes muscle pain and puts them at risk for myoglobinuria.
2. The physiologic effect of fasting should be explained, and the patient should be warned not to attempt exercise under such conditions.
3. The use of glucose tablets or candy bars during exercise may raise exercise tolerance slightly.
4. If myoglobinuria is noted, the patient should be admitted to the hospital and renal function should be monitored.

MULTIPLE ACYL DEHYDROGENASE DEFICIENCY

Background

Multiple acyl dehydrogenase deficiency (MADD) is another rare lipid storage disease that can manifest in childhood or adulthood with progressive weakness.

Pathophysiology

The disorder can result from deficiency of any of three subunits of the enzyme complex: the α or β subunits of electron-transferring flavoprotein (ETF) (ETFA or ETFB) and ETF dehydrogenase (ETF-QO). These genes map as follows: ETFA to 15q23–q25, ETFB to 19q13.3, and ETF-QO to 4q32-qter. ETF

transfers electrons from reduced forms of acyl-CoA dehydrogenase to the respiratory chain via ETF-QO. ETF-QO transfers electrons from ETF to ubiquinone. Defects in these enzymes result in the inability to oxidize the reduced forms of various dehydrogenases including VLCAD, LCAD, MCAD, and SCAD (very long, long, medium, and short chain acyldehydrogenase deficiencies).

Prognosis

The course is variable. Stopping secondary causes (e.g., valproic acid) when evident can help as has riboflavin in a few patients.

Diagnosis

Clinical Features

1. Usually manifests with progressive proximal weakness and atrophy associated with episodes of confusion, ataxia, tremor, nausea, vomiting, hypoketotic hypoglycemia, lethargy, and hepatomegaly in infancy or early childhood.
2. Some patients present with recurrent episodes of exercise-induced myoglobinuria later in childhood or adult life similar to CPT2 deficiency or with proximal or distal weakness.

Laboratory Features

1. Serum acylcarnitine analysis usually reveals increased concentrations of all-chain-lengths but mainly medium- and long-chain acylcarnitines. The plasma free carnitine level is usually decreased but can sometimes be normal. Urine organic acid demonstrates C5 to C10 dicarboxylic aciduria and acylglycine derivatives.
2. Reduced ETF-QO activity can be demonstrated in cultured fibroblasts.
3. Genetic testing is available to confirm a mutation.

Electrophysiologic Findings

NCS demonstrate an axonal sensory neuropathy, while the EMG may reveal myopathic appearing MUAPs.

Histopathology

Muscle fibers contain numerous vacuoles and abnormal accumulation of lipid similar to primary carnitine deficiency.

Treatment

1. Fasting should be avoided.
2. Carnitine supplementation does not appear to help, although both low-fat diets and riboflavin have been reported to provide benefit.

MITOCHONDRIAL MYOPATHIES

Background

1. Mitochondrial myopathies can be caused by mutations in mitochondrial DNA (mtDNA) or in nuclear genes that code for mitochondrial proteins.
2. mtDNA encodes for 22 transfer RNAs (tRNAs), 2 ribosomal RNAs (rRNAs), and 13 mRNAs.
3. The 13 mRNAs are translated into 13 polypeptide subunits of the respiratory chain complexes.
4. Most mitochondrial proteins are encoded by nuclear DNA, and these proteins are translated in the cytoplasm and subsequently transported into the mitochondria.
5. There appears to be some nuclear control of replication of the mitochondrial genome.

Pathophysiology

1. Mutations have been identified in several mtDNA genes encoding for tRNA. Disorders because of these mutations (e.g., myoclonic epilepsy and ragged red fibers [MERRFs] and mitochondrial encephalomyopathy lactic acidosis and stroke [MELAS]) have a typical mitochondrial inheritance pattern (e.g., only from mother to both male and female children).
2. Some disorders are caused by mutations in nuclear genes responsible for replication of mtDNA (e.g., mtDNA-depletion syndromes, mitochondrial

neurogastrointestinal encephalomyopathy [MNGIE], and progressive external ophthalmoplegia [PEO]). These disorders may be inherited in an autosomal recessive or dominant manner.

3. Other disorders are associated with single, large deletions of mtDNA but occur sporadically (e.g., Kearns–Sayre syndrome [KSS]).

Prognosis

Prognosis is dependent of the specific subtype. A reduced life expectancy is associated with most of the disorders.

Diagnosis

Clinical Features

1. The clinical presentations of the different forms of mitochondrial myopathies are quite heterogeneous.
2. Findings include short stature, scoliosis, ptosis, ophthalmoparesis, proximal weakness, cardiomyopathy, neuropathy, hearing loss, optic neuropathy, pigmentary retinopathy, endocrinopathy, myoclonic seizures, ataxia, headaches, stroke-like symptoms (including cortical blindness), gastroparesis, and intestinal pseudo-obstruction.

Laboratory Features

1. Serum CK may be normal or elevated.
2. ECG may show conduction abnormalities in some disorders (e.g., KSS).
3. Serum and CSF lactate levels may be normal or elevated.
4. MRI scans of the brain may be abnormal (e.g., MELAS).
5. Genetic testing is available and the gold standard for diagnosis.

Histopathology

1. The histopathologic abnormalities on muscle biopsies of the various mitochondrial myopathies are nonspecific.
2. Mitochondrial abnormalities are reflected on the modified Gomori trichrome stain, in which subsarcolemmal accumulation of abnormal mitochondria stains red and gives the abnormal muscle fibers their

characteristic appearance (ragged red fibers).

3. Oxidative enzyme stains (NADH, SDH, and COX) are also routinely used to diagnose mitochondrial myopathies.
4. Ultrastructural alterations in mitochondria are apparent on EMG. These abnormalities include an increased number of normal-appearing mitochondria, enlarged mitochondria with abnormal cristae, and mitochondria with paracrystalline inclusions.
5. Specific mitochondrial enzymes (components of the respiratory chain) may show reduced activity.
6. Genetic testing: Mutations in mtDNA may be demonstrated in leukocytes, but specificity is increased by looking for the mutations in muscle tissue.

Treatment

1. There are no proven medical therapies for most mitochondrial myopathies.
2. We recommend that patients take coenzyme Q (children's dose is 30 mg daily; adults are given 150 to 1,200 mg daily).
3. Likewise, we tell patients to take creatine monohydrate (5 to 10 g/d).
4. Patients with MERRF and an associated myoclonic seizure disorder should be treated with antiepileptic medication.
5. Patients and their physicians need to be aware that patients with mitochondrial myopathies can be very sensitive to sedating medications and anesthetic agents that may lead to alveolar hypoventilation and respiratory failure.
6. Patients with FVCs below 50% or those with symptomatic respiratory dysfunction are offered noninvasive ventilator support, usually BiPAP.
7. Hormone replacement is given for associated specific endocrinopathies.
8. Pacemaker insertion may be required because of the associated cardiac conduction defects.
9. Eyelid surgery to correct ptosis can be performed provided there is sufficient facial strength to allow full eye closure.
10. Patients with severe gastrointestinal dysmotility may require PEG tube placement or parenteral feedings for nutritional support.
11. Ankle–foot orthoses may be beneficial in patients with distal lower limb weakness.

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10 Motor Neuropathies and Peripheral Neuropathies

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There is a vast number of neuromuscular disorders, some rare and others more common. This chapter presents disorders of the motor neurons and peripheral nerves, with neuromuscular junction disorders and myopathies covered in another chapter of the book.

SPINAL MUSCULAR ATROPHIES

Background

A number of spinal muscular atrophies (SMAs) have been identified on the basis of age of onset, degree of physical impairment, life expectancy, mode of inheritance, and genetic localization. Most are childhood diseases, and the most common, the infantile form, Werdnig–Hoffmann disease, is the main consideration in the differential diagnosis of the "floppy infant."

Pathophysiology

1. SMA types 1 through 3 are allelic and caused by mutations in the survival motor neuron gene (*SMN* gene) located on chromosome 5q13.
2. Kennedy disease, or X-linked bulbospinal neuronopathy, is caused by mutations (expanded CAG repeats) in the androgen receptor gene (*AR* gene) located on chromosome Xq12. Repeat lengths of 38 to 68 are reported in patients.

Prognosis

1. The major subtypes of autosomal recessive SMA are as follows:
   a. SMA type 1 (SMA-1), commonly known as Werdnig–Hoffmann disease,

manifests within the first 6 months of life, with generalized weakness, hypotonia, and poor head control. Affected children are not felt to achieve the ability to sit unassisted, and most do not survive past the second year of life.

b. SMA type 2 (SMA-2), the chronic infantile subtype, presents between the ages of 6 and 18 months. Patients are able to sit unassisted but never able to walk independently and generally survive into the second or third decade.

c. SMA type 3 (SMA-3), more frequently referred to as Kugelberg–Welander disease, manifests after the age of 18 months. The patients are able to walk unassisted at some point in their life and have a normal life expectancy.

d. SMA type 4 (SMA-4) represents less than 5% of SMA cases and have the mildest form of the disease. They are similar to SMA-3, but the onset is in adulthood.

2. Kennedy disease is another progressive form of SMA that may present in early or adult life (dependent on size of the mutation).

Diagnosis

Clinical Features

1. The age of onset and severity of weakness are variable in the different forms of SMA.
2. Most are characterized by generalized, symmetric proximal greater than distal weakness and atrophy, although there are rare forms associated with mainly distal extremity weakness.
3. Fasciculations are often evident in extremity and bulbar muscles.
4. Sensation is normal and deep tendon reflexes are reduced or absent.
5. Oral pharyngeal weakness leads to dysphagia and aspiration pneumonia.
6. Bulbar manifestations, including dysarthria and nasal speech, prominent tongue and facial muscle fasciculations, and signs of mild androgen insensitivity, such as gynecomastia, testicular atrophy, and reduced fertility, may be seen in Kennedy disease.
7. Death is often caused by respiratory failure related to diaphragmatic weakness.

Electrodiagnostic Features

1. Sensory nerve conduction studies (NCS) are usually normal except in Kennedy disease in which the sensory nerve action potential (SNAP) amplitudes may be reduced secondary to an associated sensory neuronopathy.
2. Motor NCS are normal or have diminished compound muscle action potential (CMAP) amplitudes.
3. Electromyography (EMG) shows increased insertional and spontaneous activity in the form of fibrillation potentials, positive sharp waves, and fasciculation potentials as well as large, polyphasic fast-firing motor unit action potentials (MUAPs) (i.e., decreased recruitment).
4. Grouped discharges may be seen in facial muscles in Kennedy disease.

Laboratory Features

1. Serum creatine kinase (CK) levels are normal or slightly increased.
2. DNA testing is available for the most common forms (SMA-1 to SMA-4, Kennedy disease, and some of the more rare distal SMAs).

Treatment

1. There is no proven medical therapy to improve strength and function in patients with different forms of SMA, and the main treatments are supportive but make a considerable difference in quality of life.
2. Physical and occupational therapies are essential. Contractures develop in weak limbs; stretching exercises, particularly at the heel cords, iliotibial bands, and hips, should be started early.
3. Bracing
   a. The appropriate use of bracing assists children with SMA-2 and SMA-3 in ambulation and delays their dependence on a wheelchair.
   b. Long-leg braces (knee–foot orthosis) may stabilize the knees and prevent the knees from buckling.
   c. There may be some advantage to a lightweight, plastic knee–foot orthosis, but it is difficult to keep the foot straight with such a device, whereas a high-top boot worn with double-upright braces, although more cumbersome, provides excellent stability. The choice depends on

preferences of the patient and physician.

d. Night splints are used to maintain the feet at right angles to the leg to prevent ankle contractures, which will impair ambulation.

4. Surgery

a. Reconstructive surgery of the legs often accompanies bracing to keep the legs extended and prevent contractures.

b. A simple way to maintain function in the legs with contractures in the ankles, iliotibial bands, hip flexors, and knee flexors is to perform percutaneous tenotomies of the Achilles tendons, knee flexors, hip flexors, and iliotibial bands. This procedure often allows a child who is becoming increasingly dependent on a wheelchair to resume walking.

c. Scoliosis may develop, leading to pain, aesthetic damage, and respiratory compromise. Spinal fusion is considered in children who experience discomfort because of greater than 35-degree scoliosis. Forced vital capacity (FVC) should generally be greater than 35% to minimize the risk of surgery.

5. Ventilatory failure

a. Ventilatory muscle weakness may initially be managed by noninvasive methods (i.e., bilevel positive airway pressure [BiPAP]) and cough-assist devices. Consider BiPAP in patients with dyspnea or evidence of nocturnal hypopnea (e.g., frequent nocturnal arousals, morning headaches, excessive daytime sleepiness), particularly if the FVC is less than 50% of predicted.

b. Tracheostomy and mechanical ventilation should be discussed with patient and families and offered if it is their wish.

6. Genetic counseling

a. Parents of children with SMA (SMA-1 to SMA-4) should be counseled that subsequent children have a 25% chance of being affected.

b. Kennedy disease is X-linked recessive; therefore, the next generation of males will not be affected but females will be obligate carriers.

c. Prenatal diagnosis is available for each of the SMA subtypes.

HEREDITARY SPASTIC PARAPLEGIA

Background

1. The hereditary spastic paraplegias (HSP) are a clinically and heterogeneous group of disorders characterized by progressive lower limb spasticity. There are over 50 genes described with distinct subtypes.
2. This group of disorders is subclassified by the pattern of inheritance, age of onset, and the presence of additional neurologic defects.
3. The prevalence of HSP ranges from 2.0 to 4.3/100,000 in different populations.

Pathophysiology

1. HSP may be inherited in an autosomal dominant, autosomal recessive, or X-linked manner (see Table 7-1 in *Neuromuscular Disorders, 2nd Edition* by Amato and Russell).
2. Autosomal dominant inheritance accounts for approximately 70% of pure HSP (without additional neurologic features beyond progressive spasticity). Approximately 12 responsible genes have been reported with 40% caused by mutations in the spastin gene (SPG4) and 10% caused by mutations in the atlastin gene (SPG3A).
3. Approximately 41 responsible genes have been identified for autosomal recessive HSP with 10% related to mutations in the gene encoding for paraplegin (SPG7).
4. X-linked SPG1 is caused by mutations in the gene encoding for the L1 cell adhesion molecule (*L1CAM*). X-linked SGP2 is caused by mutations in the proteolipid protein (*PLP1*) gene. SPG22 is caused by mutations in the *SLC16A2* gene.

Prognosis

The disease is usually only slowly progressive, and life expectancy is not affected in "pure" forms but may be reduced in "complicated" forms.

Diagnosis

Genetic testing is available for many of the HSPs (see http://www.genetests.org for lists of laboratories).

Clinical Features

1. Patients may be classified into "pure HSP," if there is only spasticity and sensory involvement, and "complicated HSP," if there is associated optic atrophy, deafness, extrapyramidal disease, dementia, ataxia, peripheral neuropathy, or amyotrophy.
2. Onset is variable: childhood-to-adult life.
3. There is significant clinical and genetic heterogeneity between and within kinships with HSP.

Laboratory Features

1. Cerebrospinal fluid (CSF) is usually normal, although increased protein is noted in some patients.
2. Magnetic resonance imaging (MRI) scans may demonstrate atrophy of the spinal cord and occasionally, the cerebral cortex.
3. Genetic testing is available for some forms of HSP (see www.genetests.org).

Treatment

1. There are no specific medications to slow the progression of the disease.
2. Treatment is supportive with physical and occupational therapies.
3. Stretching exercises are important to prevent contractures.
4. Braces and/or walkers may be necessary to stabilize the gait.
5. Spasticity
   - **a.** Baclofen 5 mg by mouth (p.o.) three times a day (t.i.d.) to start. May increase up to 80 mg daily (20 mg four times a day [q.i.d.]) as tolerated and as needed.
   - **b.** Tizanidine 2 mg t.i.d. to start. May increase up to 12 mg t.i.d. as tolerated and as needed.
   - **c.** Diazepam 2 mg twice a day (b.i.d.). May increase up to 10 mg q.i.d. as tolerated and as needed.
   - **d.** Implanted pumps that deliver baclofen continuously to the intrathecal space are very effective but may migrate out of their proper location and have risks of infection, bleeding, and root pain.

AMYOTROPHIC LATERAL SCLEROSIS

Background

1. Motor neuron disease, the general term for degeneration of upper motor neuron (UMN) and lower motor neuron (LMN), is often divided into four clinical syndromes that may reflect a spectrum of disease: Each subsyndrome can exist in pure form or progress to encompass features of both UMN and LMN disease and spread from one region of the musculature to adjacent areas.
   - **a.** Progressive muscular atrophy is a degeneration of anterior horn cells without UMN involvement. One limb is typically affected first.
   - **b.** Adult-onset progressive bulbar palsy is the result of degeneration of bulbar nuclei and initially has little or no associated spinal anterior horn cell dysfunction or UMN signs.
   - **c.** Primary lateral sclerosis causes corticospinal tract degeneration, while sparing the LMNs.
   - **d.** Amyotrophic lateral sclerosis (ALS) is the archetype of this class of disease and presents with variable combinations of the preceding abnormalities, that is, both UMN and LMN signs affecting the bulbar and somatic musculature.
2. Progressive muscular atrophy accounts for roughly 10%, primary lateral sclerosis for only 1% to 3%, and progressive bulbar palsy for 1% to 2% of motor neuron disease. ALS is more common, with an incidence of 0.4 to 3.0/100,000 in all parts of the world and prevalence of 4 to 6 cases/100,000 population.

Pathophysiology

1. Most cases of ALS are sporadic, but as many as 5% to 10% are familial amyotrophic lateral sclerosis (FALS). The most common cause for FALS in the United States and Europe is mutations in the *C9ORF72* gene (30% to 40%) followed by mutations in the *SOD1* (15% to 25%), *TARDBP*, and *FUS* gene. There are also other less commonly inherited forms that may have autosomal dominant, autosomal recessive, or X-linked inheritance (see Table 6-2 in *Neuromuscular Disorders, 2nd Edition* by Amato and

Russell).
2. The pathogenic basis of sporadic ALS is not known but theories abound.

Prognosis

1. Sporadic ALS and FALS are clinically and pathologically similar.
2. The course of ALS is relentless with a linear decline in strength with time. The median survival of the conventional type of disease is approximately 3 years but depends on adequacy of respiratory and nutritional support.

Diagnosis

Clinical Features

1. Many patients exhibit only LMN signs or purely UMN signs early in the course of the disease.
2. In the limbs, muscle weakness and atrophy usually begin asymmetrically and distally and then spread within the neuraxis to involve contiguous groups of motor neurons.
3. Bulbar involvement manifests initially as dysphagia or dysarthria that may have lingual, buccal, and spastic components.
4. The El Escorial criteria for the diagnosis of ALS were developed in 1994 and later revised ("revised" El Escorial criteria) in 1998. While they have been proposed for research, they have also been used as clinical guidelines:
   a. "Clinically definite ALS" requires the presence of UMN and LMN signs in the bulbar region as well as at least two of the three other spinal regions (cervical, thoracic, and lumbosacral).
   b. "Clinically probable ALS" is defined by the presence of UMN and LMN signs in at least two regions (some UMN signs must be rostral to the LMN deficits).
   c. "Clinically possible ALS" requires UMN and LMN signs in only one region, UMN signs alone in two or more regions, or LMN signs rostral to the UMN signs.
   d. Electrophysiologic criteria for definite LMN degeneration require (1) the presence of fibrillation potentials; (2) large-amplitude, long-duration MUAPs; and (3) reduced recruitment.

e. Fulfilling the El Escorial criteria for definite or even probable ALS can be difficult even in patients with advanced disease.
f. There should be an absence of electrophysiologic, pathologic, and neuroimaging evidence of other disease processes that could explain the observed clinical and electrophysiologic findings

5. The Awaji-Shima Consensus Recommendations in 2008 proposed that evidence of LMN degeneration could be derived from either the clinical exam or needle EMG; two muscles supplied by two different nerve roots and nerves in an extremity, or single muscle in the bulbar or thoracic region. They also proposed for fasciculation potentials to be able to substitute for the presence of fibrillation potentials; however, only in the presence of other abnormalities.

Electrodiagnostic Features

1. Sensory NCS are normal.
2. Motor NCS may be normal or demonstrate reduced amplitudes secondary to atrophy. Distal latencies and conduction velocities are normal or reveal only slight slowing proportional to the degree of axonal loss.
3. No evidence of conduction block or other features of primary demyelination.
4. EMG demonstrates active denervation in the form of fibrillation potentials and positive sharp waves as noted earlier. The earliest abnormality is fasciculation potentials because of motor unit hyperexcitability/instability that occur prior to motor unit degeneration.

Treatment

1. Riluzole
   a. Two randomized, controlled trials demonstrated that riluzole 50 mg p.o. b.i.d. extends tracheostomy-free survival by 2 to 3 months. Unfortunately, the studies did not find that riluzole improves muscular strength or quality of life.
   b. Riluzole is thought to act by inhibiting the release of glutamate at presynaptic terminals.
   c. Side effects include nausea, abdominal discomfort, and hepatotoxicity.
   d. Hepatic function needs to be checked every month for 3 months and then every 3 months while on riluzole. Hepatotoxicity is reversible once

riluzole is discontinued.

2. Supportive care
   - **a.** Despite that the lack of effective therapy to halt or reverse the progression of the disease, there are many therapeutic measures that improve the quality of life in patients with ALS and its variants.
   - **b.** Physical, occupational, nutritional, and respiratory therapy and psychological support are essential. Patients are typically seen in clinic at least every 3 months by coordinated groups of therapists.
   - **c.** Evaluation by psychiatry, gastroenterology, pulmonary medicine, and social work is needed at appropriate junctures.
   - **d.** The neurologist is appropriately responsible for coordinating care and discussing end of life issues.

3. Physical therapy
   - **a.** Stretching exercises, passive and active, to prevent contractures.
   - **b.** Assess gait and needs (i.e., cane, walker, wheelchair).

4. Occupational therapy
   - **a.** Patients should be evaluated for adaptive devices (e.g., ball-bearing feeders) that may improve function.
   - **b.** The patient's home should be evaluated for equipment needs.

5. Dysarthria
   - **a.** Patients should be evaluated by a speech therapist.
   - **b.** Techniques may be given to help patient with articulation.
   - **c.** Patients may benefit from various speech augmentation devices and switch- or light-guided scanning computerized devices.

6. Dysphagia
   - **a.** Because of the associated swallowing difficulties occurring with bulbar weakness, nutrition becomes impaired.
   - **b.** High-calorie and protein-concentrated supplementation should be added to diet.
   - **c.** When dysphagia is severe, a feeding tube is recommended. Some studies have demonstrated that nutrition by percutaneous endoscopic gastrostomy (PEG) or gastrojejunostomy improves quality of life and survival by a few months.
     - **1)** Ideally, feeding tube placement should be done before FVC falls

below 50% to reduce the risks of the surgical procedure.

2) Feeding tube placement does not prevent aspiration.

7. Salivation

a. Drooling and hypersalivation can be a problem secondary to swallowing difficulties.

b. Tricyclic antidepressants (TCAs) (e.g., amitriptyline 10 to 100 mg p.o. at bedtime [qhs]) have anticholinergic properties that can reduce secretions. In addition, patients not uncommonly have a reactive depression that may be helped by the addition of an antidepressant.

c. Scopolamine patches are useful if saliva is pooling and causing aspiration.

d. Other medications that can be used include

1) Glycopyrrolate 1 to 2 mg p.o. b.i.d. to t.i.d.

2) Benztropine 0.5 to 2.0 mg every day (qd)

3) Trihexyphenidyl hydrochloride 1 mg qd to 5 mg t.i.d.

4) Atropine 2.5 mg qd to 5 mg t.i.d.

e. Botulinum toxin injection into the salivary glands is beneficial in patients with refractory hypersalivation, but caution is advised because this may lead to increased pharyngeal weakness.

f. Radiation therapy

1) In patients refractory to other measures, external beam radiation therapy to the caudal parotids and submandibular glands has proven effective.

2) Both short-term and long-term side effects have been reported (including dry mouth, mucositis, taste change, and skin reaction).

8. Thick mucus is reported by some patients, particularly when using the earlier medications to treat hypersalivation. Effective treatments include

a. β-Blockers such as propranolol and metoprolol may help.

b. Acetylcysteine 400 to 600 mg p.o. qd in one to three divided doses or as a nebulizer treatment (3 to 5 mL of 20% solution every 3 to 5 hours).

9. Spasticity

a. Baclofen 5 mg p.o. t.i.d. to start. May increase up to 80 mg qd (20 mg q.i.d.) as tolerated and as needed.

b. Tizanidine 2 mg t.i.d. to start. May increase up to 12 mg t.i.d. as tolerated and as needed.

c. Diazepam 2 mg b.i.d. May increase up to 10 mg q.i.d. as tolerated and as needed.

d. An implanted intrathecal baclofen pump may be beneficial if oral medications are not adequate.

). Pseudobulbar affect

a. A combination of dextromethorphan (20 mg) and quinidine sulfate (10 mg) has been shown to be effective in a randomized trial. Side effects include dizziness, nausea, and somnolence but can be lessened by starting at 1 tablet qhs for 7 days followed by twice-a-day dosing.

b. Antidepressant medications, such as selective serotonin reuptake inhibitors and TCAs, can be used particularly in patients with underlying depression.

l. Constipation

a. Constipation may result from weakness of the pelvic and abdominal muscles, diminished physical activity, anticholinergic and antispasticity medications, and opioids.

b. Management includes increasing dietary fiber and fluid intake, adding bulk-forming laxatives, and using suppositories or enemas as needed.

!. Ventilatory failure

a. Most patients with ALS die as a result of respiratory failure; therefore, it is important to assess for symptoms or signs of ventilatory impairment during each clinic visit.

b. Patients with forced vital capacities below 50% or those with symptomatic respiratory dysfunction are offered noninvasive ventilator support, usually BiPAP and at first, nocturnally.

c. Inspiratory and expiratory pressures are titrated to symptom relief and patient tolerability.

d. Our experience has been that only a few patients desire tracheostomy and mechanical ventilation because it prolongs care and is expensive and can be burdensome to the family. However, this is a decision that must be made by the patient. Tracheostomy needs to be offered to patients along with realistic counseling in regard to what this entails to the patient and the family.

e. Intermittent dyspnea and the anxiety that accompanies it may be treated with lorazepam 0.5 to 2 mg sublingually, opiates (e.g., morphine 5 mg), or

midazolam 5 to 10 mg intravenous (IV) (slowly) for severe dyspnea.

f. Constant dyspnea can be managed with morphine starting at 2.5 mg every 4 hours (q4h) or continuous morphine infusion plus diazepam, lorazepam, or midazolam for associated anxiety.

g. Thorazine 25 mg every 4 to 12 hours rectally or 12.5 mg every 4 to 12 hours IV may alleviate terminal restlessness.

3. Pain

a. Pain occurs in at least 50% of patients because of muscle cramps, spasticity, limited range of motion and contractures related to weakness, and skin pressure secondary to limited movement.

b. Careful positioning and repositioning of the patient, massage, physical therapy to help prevent contractures, antispasticity medications, antidepressants, nonsteroidal anti-inflammatory medications, and opioids may be used to treat pain.

4. Psychosocial issues

a. Depression is not uncommon for patients and family members.

b. Patients and family members may benefit from local support groups.

c. Antidepressant medications may need to be used.

ACUTE POLIOMYELITIS

Background

1. Poliomyelitis is rare in developed nations because of routine use of the polio vaccine; however, not everyone has been vaccinated, thereby limiting "herd immunity."
2. A poliomyelitis-like illness occurs with other viruses (e.g., Coxsackievirus, West Nile virus).
3. Rare cases are caused by transmission of virus from inoculated child to nonimmunized adults via feces.

Pathophysiology

1. The virus gains access to the host usually through oral or respiratory route. The virus proliferates, and viremia ensues.

2. The virus is taken up into the peripheral nervous system (PNS) via binding to receptors and the distal motor nerve terminals.
3. Subsequent transport to the anterior horn cell in the spine occurs with inflammatory destruction of motor neurons in the spinal cord and brainstem.

Prognosis

Most infected individuals recover but to a variable degree. Late in life, some patients develop weakness and achiness in muscles that were previously affected (postpolio syndrome).

Diagnosis

Clinical Features

1. Most people (98%), especially children, experience a minor nonspecific systemic illness for 1 to 4 days: sore throat, vomiting, abdominal pain, low-grade fever, easy fatigue, and minor headache.
2. The core neurologic illness is a febrile meningitis.
3. A small proportion (2%) subsequently develop neck and back stiffness, fasciculations, and asymmetric or focal weakness involving the extremities or bulbar musculature.
4. Following the initial illness and paralytic phase, recovery of function to varying degrees occurs over the ensuing 4 to 8 years.

Laboratory Features

1. CSF examination usually reveals increased protein and pleocytosis initially consisting of both polymorphonuclear leukocytes and lymphocytes and then later predominantly lymphocytes. The cell count is usually less than 100 cells/mm^3.
2. Diagnosis may be confirmed by culture of the offending virus, although the sensitivity is low. Also acute and convalescent antibody titers can be obtained.

Electrophysiologic Findings

1. Sensory NCS are normal.

2. CMAP amplitudes may be reduced in patients with profound muscle atrophy.
3. The motor conduction velocities and distal latencies are normal or slightly abnormal in those individuals consistent with the degree of large-fiber loss.
4. EMG demonstrates reduced recruitment of MUAP early with positive sharp waves and fibrillation potentials within 2 to 3 weeks following the onset of paralysis.

Treatment

1. There is no specific treatment other than supportive care.
2. Respiratory status needs to be monitored closely and patient mechanically ventilated if necessary.
3. Nutritional support should be given if patient is unable to eat on his or her own.
4. Physical and occupation therapy are essential to improve function.
5. An antiepileptic drug (AED) (e.g., gabapentin) or antidepressant medication can be used to treat associated pain that frequently accompanies the acute illness.

POSTPOLIOMYELITIS (POSTPOLIO) SYNDROME

Background

As many as 25% to 60% of patients with a history of paralytic poliomyelitis develop new neuromuscular symptoms 20 or 30 years after the initial acute attack.

Pathophysiology

It is thought that motor neurons unaffected by the poliomyelitis sprout to reinnervate previously denervated muscle fibers. These motor units that are increased in size may be under increased stress compared with normal motor units, leading to gradual degeneration over time in some.

Prognosis

The course and the symptoms are highly variable, but as a rule, muscle weakness is slowly progressive, if at all.

Diagnosis

Clinical Features

1. Patients with postpolio syndrome complain of progressive fatigue (80% to 90%), multiple joint pains (70% to 87%), and muscle pain (70% to 85%).
2. Fifty percent to 80% of patients also develop progressive loss of strength and muscle atrophy. This progressive weakness usually involves previously affected muscles, but muscles thought to be clinically spared at the time of the acute infection may at times become affected.
3. Muscle cramps and fasciculations are also common.

Laboratory Features

1. Unlike acute poliomyelitis, the CSF does not demonstrate pleocytosis or viral particles.
2. Serum CK levels may be mildly elevated.

Electrophysiologic Findings

1. Sensory NCS are normal.
2. CMAP amplitudes may be reduced in patients with profound muscle atrophy.
3. The motor conduction velocities and distal latencies are normal or only slightly abnormal proportionate to the degree of large-fiber loss.
4. EMG demonstrates active denervation in the form of positive sharp waves and fibrillation potentials, fasciculation potentials, and reduced recruitment of long-duration, large-amplitude, polyphasic, and unstable MUAPs.

Treatment

1. There are no specific therapies for postpolio syndrome.
2. Treatment is supportive similar to that for other motor neuron disorders.
3. Physical and occupational therapies can be beneficial.
4. Double-blind, placebo-controlled trials demonstrated no benefit with either

pyridostigmine or modafinil in reducing fatigue.

5. Muscle pain may ease with TCA medications.
6. Severe dysphagia, dysarthria, and respiratory weakness are treated as discussed in the section on amyotrophic lateral sclerosis (ALS).

STIFF PERSON/STIFF LIMB SYNDROME

Background

1. Moersch and Woltman were the first to describe 14 patients with the disorder, which they termed "stiff man" syndrome.
2. Because the disorder is more common in women than in men, stiff person syndrome (SPS) became a preferable name for the disorder.
3. Some authorities have clinically subdivided SPS into three types:
   a. Progressive encephalomyelitis with rigidity
   b. Typical SPS
   c. Stiff limb syndrome
4. There is an increased incidence of insulin-dependent diabetes mellitus (IDDM) and various autoimmune disorders.
5. There are reports of SPS associated with Hodgkin lymphoma, small cell carcinoma of the lung, and cancers of the colon and breast.
6. SPS also can occur in patients with myasthenia gravis or thymoma.

Pathophysiology

SPS is an autoimmune disorder caused by antibodies directed against glutamic acid decarboxylase (GAD) and amphiphysin.

Prognosis

Patients develop progressive stiffness and rigidity of the trunk and spine. Immunomodulating therapies may modulate the course of illness, but most remain with significant and progressive disability.

Diagnosis

Clinical Features

1. Progressive encephalomyelitis with rigidity is a rapidly progressive disorder associated with generalized stiffness, encephalopathy, myoclonus, and respiratory distress that is usually fatal within 6 to 16 weeks.
2. Typical SPS
   - **a.** Characterized by muscular rigidity and episodic spasms involving truncal and limb muscles in the second to sixth decades of life. The limb-girdle area is usually affected first.
   - **b.** Typical involuntary large truncal spasms are elicited by engaging the muscles in use for walking and by loud noises or other forms of startle, but intense attacks of contractions can occur without these stimuli.
   - **c.** The stiffness and muscle spasms usually lead to gait impairment with occasional falls.
   - **d.** Patients may complain of dyspnea secondary to chest restriction because of stiffness in the thoracic muscles.
   - **e.** Paroxysmal autonomic dysfunction characterized by transient hyperpyrexia, diaphoresis, tachypnea, tachycardia, hypertension, pupillary dilation, and occasional sudden death may accompany the attacks of muscle spasm.
   - **f.** Approximately 10% of patients have generalized seizures or myoclonus.
   - **g.** Physical examination often shows exaggerated lumbar lordosis and paraspinal muscle hypertrophy secondary to continuous muscle contraction.
3. Stiff limb syndrome is characterized by asymmetric focal rigidity and spasms in the distal extremities or face.

Laboratory Features

1. Autoantibodies directed against the 65-kDa GAD are evident in 60% of primary autoimmune cases of SPS and sometimes become apparent only after repeated tests over months or years.
2. Antibodies directed against a 128-kDa presynaptic protein, amphiphysin, present in some patients with presumed paraneoplastic SPS.
3. The CSF is often abnormal in patients with SPS demonstrating increased immunoglobulin G (IgG) synthesis, oligoclonal bands, and anti-GAD antibodies.

4. Other autoantibodies and laboratory abnormalities are associated with concomitant autoimmune disorders (e.g., Hashimoto thyroiditis, pernicious anemia, hypoparathyroidism, adrenal failure, myasthenia gravis, systemic lupus erythematosus [SLE], and rheumatoid arthritis).
5. Serum CK levels may be slightly elevated.

Electrophysiologic Findings

1. Sensory and motor conduction studies are normal.
2. EMG demonstrates normal-appearing MUAPs but firing continuously.

Treatment

1. Symptomatic therapies
   - **a.** We usually initiate symptomatic treatment with diazepam 2 mg b.i.d. working up to a dosage of 5 to 20 mg t.i.d. to q.i.d. These patients tolerate, and can benefit from, large doses of diazepam if introduced slowly.
   - **b.** Another option is oral baclofen 5 mg t.i.d., which is increased up to 20 mg q.i.d.
   - **c.** Intrathecal baclofen 300 to 800 μg/d may be tried if other agents are not tolerated or are unsuccessful.
   - **d.** Other symptomatic agents with purported benefit include clonazepam, dantrolene, methocarbamol, valproate, vigabatrin, gabapentin, and botulinum toxin injection.
2. Various forms of immunotherapy may be tried to treat the underlying autoimmune basis and have been found to be beneficial in small trials.
   - **a.** We usually give a treatment trial of intravenous immunoglobulin (IVIG) 2 g/kg monthly for 3 months and, if this is effective, subsequently spread out the dosing interval or reduce the dosage tailored to patient responsiveness.
   - **b.** Plasma exchange (PE) and IVIG are useful in reducing spasms and the frequency of attacks, but they must be repeated at several weekly or monthly intervals and thus are not curative.
   - **c.** A trial of prednisone 0.75 to 1.5 mg/kg/d for 2 weeks and then 0.75 to 1.5 mg/kg every other day (q.o.d.) for 2 to 4 months is tried if IVIG is ineffective. If prednisone is beneficial, we taper the prednisone to the lowest dose that controls the symptoms. We do not use prednisone in

patients with diabetes mellitus (DM).

d. Other immunotherapies (e.g., rituximab, azathioprine, mycophenolate mofetil; Table 10-1) may be tried.

Table 10-1 Immunosuppressive and Immunomodulatory Therapies Commonly Used in Neuromuscular Disorders

Therapy	Route	Dose	Side Effects	Monitor
Prednisone	p.o.	0.75–1.5 mg/kg up to 100 mg/d for 2–4 wk and then 100 mg every other day; single morning dose	Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, cataracts, gastric irritation, osteoporosis, infection, aseptic femoral necrosis	Weight, blood pressure, serum gluco and potassiu cataract formation, DEXA bone scan
Methylprednisolone	IV	1 g in 100 mL/normal saline over 1–2 h daily or every other day for three to six doses	Arrhythmia, flushing, dysgeusia, anxiety, insomnia, fluid and weight gain, hyperglycemia, hypokalemia, infection	Heart rate, bloc pressure, serum gluco and potassiu DEXA
Azathioprine	p.o.	2–3 mg/kg/d single morning dose	Flulike illness, hepatotoxicity, pancreatitis, leukopenia, macrocytosis, neoplasia, infection, teratogenicity	CBC, liver enzymes
Methotrexate	p.o.	7.5–25 mg/wk; single or divided doses; 1–2 d/wk dosing	Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leukopenia, alopecia, gastric irritation,	Liver enzymes CBC; CXR baseline and annual

			stomatitis, teratogenicity	
	s.c.	20–50 mg weekly; 1 d/wk dosing	Same as p.o.	Same as p.o.
Cyclophosphamide	p.o.	1.5–2 mg/kg/d; single morning dose	Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity	CBC, urinalysis
	IV	0.5–1 g/m^2 x 6–12 mo	Same as p.o. (although more severe)	CBC, urinalysis
Cyclosporine	p.o.	4–6 mg/kg/d split into two daily doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure cyclosporine level, creatinine/BU liver enzyme
Tacrolimus	p.o.	0.1–0.2 mg/kg/d in two divided doses	Nephrotoxicity, hypertension, infection, hepatotoxicity, hirsutism, tremor, gum hyperplasia, teratogenicity	Blood pressure tacrolimus level, creatinine/BU liver enzyme
Mycophenolate mofetil	p.o.	Adults (1 g b.i.d. to 1.5 g b.i.d.) Children (600 mg/m^2/dose b. i.d. [no more than 1 g/d in patients with renal failure])	Bone marrow suppression, hypertension, tremor, diarrhea, nausea, vomiting, headache, sinusitis, confusion, amblyopia, cough, teratogenicity, infection, neoplasia	CBC

Intravenous immunoglobulin (IVIG)	IV	2 g/kg over 2–5 d and then q 4–8 wk as needed	Hypotension, arrhythmia, diaphoresis, flushing, nephrotoxicity, headache, aseptic meningitis, anaphylaxis, stroke	Heart rate, bloc pressure, creatinine/BU
Rituximab	IV	375 mg/m^2 weekly x 4 wk or 750 mg/m^2 (up to 1 g)x 2 wk	Infusion-related symptom complex (e.g., hypotension, rash, chills, urticaria, angioedema, bronchospasm), asthenia, headaches, nausea, vomiting, dizziness, infection	Periodic blood counts, avoi live vaccines

p.o., by mouth; DEXA, dual-energy x-ray absorptiometry; IV, intravenous; CBC, complete blood count; CXR, chest x-ray; s.c., subcutaneous; BUN, blood urea nitrogen; b.i.d., twice a day.

Modified from Amato AA, Russell J. *Neuromuscular Disorders*. 2nd ed. New York, NY: McGraw-Hill; 2016, with permission.

ISAACS SYNDROME (SYNDROME OF CONTINUOUS MUSCLE FIBER ACTIVITY)

Background

1. The disorder is caused by hyperexcitability of the motor nerves, resulting in continuous activation of muscle fibers.
2. Most patients develop this disease sporadically; however, several families with apparent autosomal dominant inheritance have been reported. Isaacs syndrome may occur in association with other autoimmune disorders (e.g., SLE, systemic sclerosis, celiac disease).
3. Paraneoplastic neuromyotonia has been reported with lung carcinoma,

plasmacytoma, and Hodgkin lymphoma.
4. Isaacs syndrome may occur in patients with myasthenia gravis or thymoma.
5. Generalized myokymia or neuromyotonia may complicate hereditary motor and sensory neuropathies (e.g., Charcot–Marie–Tooth [CMT] disease), chronic inflammatory demyelinating polyneuropathy (CIDP), and autosomal dominant episodic ataxia.

Pathophysiology

Isaacs syndrome is an autoimmune disease caused by autoantibodies directed against voltage-gated potassium channels (VGKCs) located on peripheral nerves.

Prognosis

Most patients respond well to treatment.

Diagnosis

Clinical Features

1. Isaacs syndrome usually occurs in adults but has been observed in the newborn.
2. Patients manifest with diffuse muscle stiffness, widespread muscle twitching (myokymia), cramps, increased sweating, and occasionally central nervous system (CNS) symptoms (e.g., confusion, hallucinations, insomnia).
3. The myokymia is present continuously even during sleep.
4. The muscle stiffness worsens with voluntary activity of the affected body segment.
5. Patients may experience difficulty relaxing muscles following maximal contraction (i.e., pseudomyotonia).
6. Some patients experience numbness, paresthesias, and weakness.

Laboratory Features

1. Antibodies directed against VGKC are detectable in the serum and CSF.
2. Patients may have other laboratory features associated with concomitant autoimmune diseases.

3. CSF may demonstrate increased protein, increased immunoglobulins, and oligoclonal bands.

Electrophysiologic Findings

1. After-discharges may be evident following standard motor conduction studies.
2. EMG reveals continuous firing of MUAPs.
3. The most common abnormal discharges are combinations of fasciculation potentials, doublets, triplets, multiplets, complex repetitive discharges, and myokymic discharges.

Treatment

1. Various modes of immunomodulation appear to be beneficial in some patients, including plasmapheresis, IVIG, and corticosteroid treatment. We treat patients similar to those with CIDP.
2. Symptomatic treatment with AEDs (e.g., phenytoin, carbamazepine, and gabapentin) may also be useful as well, perhaps by decreasing neuronal excitability by blocking sodium channels.

TETANUS

Background

1. Tetanus is a potentially life-threatening medical condition arising from the in vivo production of a neurotoxin from the bacterium *Clostridium tetani*.
2. *C. tetani* produces tetanospasmin.
3. It is estimated that more than 1 million people per year in the world demonstrate signs of clinical intoxication secondary to infections with *C. tetani*.

Pathophysiology

1. The bacteria or their spores gain access to the patient typically through a minor wound.
2. In the CNS, tetanus toxin lyses the SNARE proteins necessary for the

release of inhibitory neurotransmitters (glycine and γ-aminobutyric acid [GABA]).

3. The result is hyperexcitability of motor neurons, leading to continuous motor unit firing, opisthotonus, and hyperreflexia.
4. A form related to oral ingestion of the toxin by infants is known.

Prognosis

1. The annual mortality rate caused by this organism is variable, depending on the sophistication of health care delivery and immunizations.
2. In the United States, the mortality caused by tetanus intoxication is less than 0.1/100,000.
3. The high number of worldwide deaths from neonatal tetanus (787,000 newborn deaths globally in 1988, based on the World Health Organization [WHO]) led to placing its elimination as a goal in the late 1980s. The most recent WHO estimates from 2013 reported 49,000 newborn deaths from neonatal tetanus, showing a 94% reduction from the earlier number.

Diagnosis

1. The clinical presentation of tetanus is subdivided into four major categories:
   a. Local
   b. Cephalic
   c. Generalized
   d. Neonatal
2. Most patients initially complain of a feeling of increased "tightness" of the muscles adjacent to the wound in the affected extremity. There may be local pain.
3. Both the pain and muscle stiffness can persist for months and remain localized with an eventual spontaneous dissipation.
4. Some patients develop trismus (difficulty opening the mouth secondary to masseter muscle contraction).
5. Progression would lead to generalized tetanus with tonic contraction of either entire limbs or the whole body, secondary to relatively mild noxious stimuli. The generalized whole-body muscle contraction, opisthotonus, consists of extreme spine extension, flexion and adduction of the arms, fist

clenching, facial grimacing, and extension of the lower extremities. This generalized contraction may impair breathing.

5. Neonatal tetanus is usually the result of an infected umbilical stump.
   a. Several hours to days of feeding difficulty (poor suck), general irritability, and possibly less than normal mouth opening or generalized "stiffness."
   b. Infants born to immunized mothers rarely acquire tetanus as the immunity is passively transferred from mother to infant.
   c. Once the massive whole-body contractions start, there is little doubt as to the diagnosis.

Treatment

1. Patients with suspected tetanus intoxication should be hospitalized and evaluated for existent or impending airway compromise.
2. Human tetanus immunoglobulin should be administered as well as adsorbed tetanus toxoid at a different site.
3. The antibiotic of choice is metronidazole (500 mg IV every 6 hours for 7 to 10 days).
4. If airway compromise is noted, there is a good chance that this situation will persist for some time and a tracheotomy should be considered.
5. Benzodiazepines should be administered in large dosages intravenously to control muscle contractions. If this is ineffective, therapeutic neuromuscular blockade is warranted in addition to the benzodiazepines to maintain somnolence.
6. If autonomic symptoms or signs develop, these should be treated immediately with appropriate medications.
7. Physical and occupational therapies are usually needed during the recovery period to regain strength, endurance, and function.

GUILLAIN–BARRé SYNDROME AND RELATED ACUTE POLYNEUROPATHIES

Background

1. There are three major subtypes of Guillain–Barré syndrome (GBS): acute

inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor and sensory axonal neuropathy (AMSAN), and acute motor axonal neuropathy (AMAN).

2. The Miller Fisher syndrome (MFS) (ophthalmoplegia, ataxia, and areflexia) may share similar pathogenesis and can be considered a variant of GBS.
3. Two-thirds of cases follow an infectious process by several days or weeks. There may be serologic evidence of recent infection with *Campylobacter jejuni* (32%), cytomegalovirus (CMV) (13%), Epstein–Barr virus (EBV) (10%), and *Mycoplasma pneumoniae* (5%). Many other cases follow a mundane febrile illness or immunization and about one-third have no evident precedent.

Pathophysiology

1. GBS and its variants have an immune basis.
2. The proposed mechanism is through molecular similarity between myelin epitopes and glycolipids expressed on *Campylobacter*, *Mycoplasma*, and other infectious agents, which precede attacks of GBS (molecular mimicry). Antibodies directed against these infectious agents cross-react with specific antigens on Schwann cells or the axolemma. Binding of these antibodies to target antigens on the peripheral nerve may lead to conduction block before there is structural nerve damage.
3. A similar immunologic mechanism probably occurs in those few cases that follow immunization.
4. In AIDP, inflammatory demyelination ensues and in AMSAN and AMAN axonal degeneration occurs.

Prognosis

1. Progression is usually over 2 to 4 weeks. At least 50% of patients reach a nadir by 2 weeks, 80% by 3 weeks, and 90% by 4 weeks.
2. Longer progression of symptoms and signs, particularly if over 8 weeks, is more consistent with CIDP. Subacute progression over 4 to 8 weeks falls between typical AIDP and CIDP. The subacute disease is usually self-limited as in AIDP but responds to corticosteroids as in CIDP.
3. Respiratory failure develops in approximately 30% of patients. Weakness of

neck flexion and shoulder abduction correlate with diaphragmatic failure to some extent.

4. Following the disease nadir, a plateau phase of several days to weeks usually occurs. Subsequently, most patients gradually recover satisfactory function over several months. However, only about 15% of patients are without any residual deficits 1 to 2 years after disease onset, and 5% to 10% of patients remain with persistent and variably disabling motor or sensory symptoms.
5. The mortality rate is less than 5% with patients dying as a result of ventilatory failure or respiratory distress syndrome, aspiration pneumonia, pulmonary embolism, cardiac arrhythmias, and sepsis related to secondarily acquired infections.
6. Risk factors for a poorer prognosis (slower and incomplete recovery) are age greater than 50 to 60 years, abrupt onset of profound weakness, the need for mechanical ventilation, and distal CMAP amplitudes less than 10% to 20% of normal.

Diagnosis

Clinical Features

1. Most patients initially have weakness, numbness, and tingling in the distal parts of the lower limbs that ascends to the proximal legs, arms, and face. Occasionally, symptoms begin in the face or arms and descend to involve the legs.
2. Weakness is symmetric affecting proximal and distal muscles.
3. Large-fiber sensory modalities (touch, vibration, and position sense) are more severely affected than small-fiber functions (pain and temperature perception).
4. Patients with AMAN have no sensory signs or symptoms.
5. Muscle stretch reflexes are reduced or absent.
6. Autonomic instability is common with hypotension or hypertension and occasionally cardiac arrhythmias.

Laboratory Features

1. Elevated CSF protein levels accompanied by no or a few mononuclear cells

are evident in over 80% of patients after 2 weeks. Within the first week of symptoms, CSF protein levels are normal in approximately one-third of patients.

2. In patients with CSF pleocytosis of more than 10 lymphocytes/mm^3 (particularly with cell counts greater than 50/mm^3), GBS-like neuropathies from Lyme disease, recent HIV infection, CNS lymphoma/leukemia, neurosarcoidosis, and poliomyelitis need to be considered.
3. Elevated liver function tests (LFTs) are evident in many patients. In such cases, it is appropriate to evaluate the patient for viral hepatitis (A, B, and C), EBV, and CMV infections as triggers for the GBS.
4. Antiganglioside antibodies, particularly anti-GM1 antibodies, may be found. Anti-GM1 antibodies are associated with *C. jejuni* infection but are not specific or prognostic, and there is no clinical need to order antibody tests.

Electrodiagnostic Features

1. In AIDP, the NCS demonstrate evidence of a multifocal demyelinating process.
   - **a.** Sensory conductions are often absent, but when present, the distal latencies are markedly prolonged, conduction velocities are very slow, and amplitudes may be reduced. Of note, sural SNAPs may be normal when median, ulnar, and radial SNAPs are abnormal as AIDP is not a length-dependent neuropathy.
   - **b.** Motor conduction studies are most important for diagnosis. Distal latencies are prolonged and conduction velocities are very slow. The distal amplitudes may be normal or reduced secondary to distal conduction block. Conduction block or temporal dispersion may be apparent on proximal stimulation.
   - **c.** F waves and H reflexes may be delayed or absent.
   - **d.** Prolonged distal motor latencies and prolonged or absent F waves are often the earliest abnormal features. Early abnormalities of the distal CMAP amplitude and latency, and of the F waves, reflect the early predilection for involvement of the distal motor nerve terminals and proximal spinal roots in AIDP, respectively.
   - **e.** Distal CMAP amplitudes less than 10% to 20% of normal are associated with a poorer prognosis.

2. In AMSAN, the NCS demonstrate features of a primary axonopathy.
   a. Sensory NCS are absent or show reduced amplitudes with normal distal latencies and conduction velocities.
   b. Motor NCS likewise show absent or reduced amplitudes with normal distal latencies and conduction velocities.
3. In AMAN, the NCS are similar to those in AMSAN except that sensory conductions are normal.

Treatment

1. There have been no treatment trials devoted solely to AMAN or AMSAN. Nevertheless, treatments used for AIDP are given to all patients with GBS-related neuropathies with any substantial disability.
2. Treatment is generally instituted when the patient is no longer able to walk; however, those who are still able to walk but continue to deteriorate because of illness are also treated. Treatment should begin as soon as possible, preferably within the first 7 to 10 days of symptoms.
3. PE and IVIG have been demonstrated in prospective controlled trials to be equally effective in the treatment of GBS.
   a. The total PE is 200 to 250 mL/kg of patient body weight over 10 to 14 days. The removed plasma is generally replaced with albumin.
   b. Thus, a 70-kg patient would receive 14,000 to 17,500 mL (14 to 17.5 L) total exchange, which can be accomplished by four to six alternate-day exchanges of 2 to 4 L each.
4. IVIG has replaced PE in many centers because it is easier to administer than PE, at least as effective, and more widely available. The dose of IVIG is 2.0 g/kg body weight infused over 5 days.
5. There is no added benefit of IVIG following PE. Repeated courses of IVIG are sometimes used in patients who are not improving, but there is limited evidence for this approach.
6. The mean time to improvement of one clinical grade in the various controlled, randomized PE and IVIG studies ranged from 6 days to as long as 27 days. Thus, one may not see dramatic improvement in strength in patients during the PE or IVIG treatments. There is no evidence that PE beyond 250 mL/kg or IVIG greater than 2 g/kg is of any added benefit.

7. As many as 10% of patients treated with either PE or IVIG develop a relapse following initial improvement. In patients who suffer such relapses, we give additional courses of PE or IVIG.
8. Respiratory care
   a. Monitor FVC and negative inspiratory force (NIF) for signs of respiratory distress. FVC and NIF will decline prior to development of hypoxia and arterial blood gas.
   b. Consider elective intubation once the FVC declines to less than 15 mL/kg or NIF to less than −20 to −30 cm H_2O.
9. Physical therapy
   a. Careful positioning of patients is important to prevent bed sores and nerve compression.
   b. Range-of-motion exercises are started early to prevent contractures.
   c. As patient improves, exercises to improve strength, function, and gait are started.
10. Supportive care
   a. Deep venous thrombosis prophylaxis with pneumonic devices and heparin 5,000 units subcutaneously b.i.d.
   b. Reactive depression is common in patients with severe weakness. Psychiatry consult can be beneficial.
11. Neuropathic pain control is important (see section on Neuropathy Treatment section).
12. The issue of allowing immunizations for patients who have had GBS is not settled. In cases that have followed an immunization, repeat exposure is not endorsed. For most others, necessary vaccinations including those for influenza and pneumonia are appropriate after weighing the possible small risk of recurrence of GBS.

MILLER FISHER SYNDROME (MFS)

Background

1. In 1956, C. Miller Fisher reported three patients with ataxia, areflexia, and ophthalmoplegia. He related the syndrome to GBS.

2. There is a 2:1 male predominance with a mean age of onset in the early 40s.
3. An antecedent infection occurs in over two-thirds of cases, the most common being *Haemophilus influenzae* and *C. jejuni*.

Pathophysiology

1. Perhaps through molecular mimicry, autoantibodies directed against these infectious agents cross-react with neuronal epitopes.
2. Anti-GQ1b antibodies can be detected in most patients with MFS.
3. GQ1b is a ganglioside concentrated on oculomotor neurons, sensory ganglia, and cerebellar neurons.

Prognosis

1. Clinical return of function usually begins within about 2 weeks.
2. Full recovery of function is typically seen within 3 to 5 months.

Diagnosis

Clinical Features

1. Diplopia is the most common initial complaint (39%); ataxia is evident in 21% at the onset.
2. Ophthalmoparesis can develop asymmetrically but often progresses to complete ophthalmoplegia. Ptosis usually accompanies the ophthalmoparesis, but pupillary involvement is less common.
3. Other cranial nerves can also become involved. Facial weakness is evident in 57%, dysphagia in 40%, and dysarthria in 13% of patients.
4. Some patients describe paresthesias of the distal limbs and less frequently, the face.
5. Areflexia is evident on examination in more than 82% of patients.
6. Mild proximal limb weakness can be demonstrated in the course of the illness in approximately one-third of cases. Some patients progress to develop more severe generalized weakness similar to typical GBS.

Laboratory Features

1. Most patients with MFS have an elevated CSF protein without significant

pleocytosis, but normal CSF protein does not exclude the diagnosis.
2. Anti-GQ1b are an almost uniform finding, but the diagnosis can be established on clinical grounds without using the test.

Electrophysiologic Findings

1. The most prominent electrophysiologic abnormality in MFS is reduced amplitudes of SNAPs alone or out of proportion to prolongation of distal latencies or slowing of sensory conduction velocities.
2. CMAPs in the arms and legs are usually normal.
3. In contrast to limb CMAPs, mild-to-moderate reduction of facial CMAPs can be demonstrated in over 50% of patients with MFS.
4. Blink reflex may be abnormal if there is facial nerve involvement. Reduced facial CMAPs coincide with the loss or mild delay of R1 and R2 responses on blink reflex testing.

Treatment

1. There are no controlled treatment trials of patients with MFS.
2. However, we treat patients with either IVIG 2 g/kg over 5 days or PE 250 mL/kg over 2 weeks, similar to GBS. Whether mild cases require treatment, particularly if walking is preserved, is uncertain.

IDIOPATHIC AUTONOMIC NEUROPATHY AND PURE PANDYSAUTONOMIA

Background

1. In many cases, this probably represents a postinfectious variant of GBS.
2. There is heterogeneity in the onset, the type of autonomic deficits, the presence or absence of somatic involvement, and the degree of recovery.
3. Approximately 20% of patients have selective cholinergic dysfunction, and 80% have various degrees of widespread sympathetic and parasympathetic dysfunction.

Pathophysiology

1. The disorder is suspected to be the result of an autoimmune attack directed against peripheral autonomic fibers or the ganglia.
2. Patients may have antibodies directed against calcium channels or acetylcholine receptors located in presynaptic autonomic nerve terminals.

Prognosis

1. Most patients have a monophasic course with progression followed by a plateau and slow recovery or a stable deficit.
2. Although some patients exhibit a complete recovery, it tends to be incomplete in most.

Diagnosis

Clinical Features

1. The most common symptom is orthostatic dizziness or light-headedness, occurring in about 80% of patients.
2. Gastrointestinal involvement as indicated by complaints of nausea, vomiting, diarrhea, constipation, ileus, or postprandial bloating is present in over 70% of patients.
3. Thermoregulatory impairment with heat intolerance and poor sweating is also present in most patients.
4. Blurred vision, dry eyes and mouth, urinary retention or incontinence, and impotence also are often present.
5. As many as 30% of patients also describe numbness, tingling, and painful dysesthesia of their hands and feet.
6. Muscle strength is normal.

Laboratory Features

1. The CSF often reveals slightly elevated protein without pleocytosis.
2. Antiganglionic acetylcholine receptor antibodies are reported to be present in half of the patients with autoimmune autonomic ganglionopathy.
3. Supine plasma norepinephrine levels are normal, but standing levels are significantly reduced when compared to normal controls.

Autonomic Testing

1. Cardiovascular studies reveal orthostatic hypotension and reduced variability of the heart rate to deep breathing in over 60% of patients.
2. An abnormal response to Valsalva maneuver can be demonstrated in over 40% of patients.
3. Summated quantitative sudomotor axon reflex test (QSART) scores are abnormal in 85% of patients. Most patients have abnormal thermoregulatory sweat tests with areas of anhidrosis in 12% to 97% of the body.
4. Gastrointestinal studies can demonstrate hypomotility anywhere from the esophagus to the rectum.

Electrophysiologic Findings

1. Routine motor and sensory NCS and EMG are normal.
2. Quantitative sensory testing may reveal abnormalities in thermal thresholds.
3. Sympathetic skin response may be absent.

Treatment

1. Conclusions regarding the efficacy of immunotherapy are limited because of the retrospective and uncontrolled nature of most reports. Trials of PE, prednisone, IVIG, and other immunosuppressive agents have been tried with variable success.
2. We generally recommend a trial of IVIG 2 g/kg over 2 to 5 days.
3. The most important aspect of management is supportive therapy for orthostatic hypotension and bowel and bladder symptoms.
   - **a.** Fludrocortisone is effective at increasing plasma volume. Fludrocortisone is administered only in the morning or in the morning and at lunch to avoid nocturnal hypertension. Initiate treatment at 0.1 mg/d and increase by 0.1 mg every 3 to 4 days until the blood pressure is corrected.
   - **b.** Midodrine, a peripheral α_1-adrenergic agonist, is also effective and can be used in combination with fludrocortisone. Midodrine is started at 2.5 mg/d and can be gradually increased to 40 mg/d in divided doses (every 2 to 4 hours) as necessary.
   - **c.** Gastrointestinal hypomotility can be treated with metoclopramide, cisapride, or erythromycin.

d. Bulking agents, laxatives, and enemas may be needed in patients with constipation.
e. Urology should be consulted in patients with neurogenic bladders. Patients may require cholinergic agonists (e.g., bethanechol), intermittent self-catheterization, or other modes of therapy.

CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

Background

1. CIDP is an immune-mediated neuropathy characterized by a relapsing or progressive course.
2. CIDP most commonly presents in adults with a peak incidence at about 40 to 60 years of age, and there is a slightly increased prevalence in men.
3. The relapsing form has an earlier age of onset, usually in the 20s, compared to the more chronic progressive form of the disease.
4. Relapses have been associated with pregnancy.
5. The association of CIDP with infections has not been studied as extensively as in AIDP; however, an infection has been reported to precede only 20% of CIDP relapses or exacerbations.

Pathophysiology

The pathogenic basis of CIDP is autoimmune.

Prognosis

1. Approximately 90% of patients improve with therapy; however, at least 50% have a subsequent relapse within the next 4 years, and less than 30% achieve remission off medication.
2. Patients treated early are more likely to respond, underscoring the need for early diagnosis and treatment.
3. Progressive course, CNS involvement, and particularly axonal loss have been associated with a poorer long-term prognosis.

Diagnosis

Clinical Features

1. Most patients present with relapsing or progressive, symmetric proximal and distal weakness of the arms and legs.
2. Although over 80% have both motor and sensory involvement, a few patients may have pure motor (10%) or pure sensory (5% to 10%) symptoms and signs.
3. Almost all patients with CIDP have areflexia or hyporeflexia.
4. Cranial nerve involvement can occasionally occur but is usually mild and not the presenting feature in CIDP.

Laboratory Features

1. Elevated CSF protein (more than 45 mg/dL) is found in 80% to 95% of patients.
2. CSF cell count is usually normal, although up to 10% of patients have more than 5 lymphocytes/mm^3.
3. Elevated CSF cell counts should lead to the consideration of HIV infection, Lyme disease, neurosarcoidosis, and lymphomatous or leukemic infiltration of nerve roots.
4. As many as 25% of patients with CIDP or a CIDP-like neuropathy have an IgA, IgG, or IgM monoclonal gammopathy. A small number have one of the connective tissue diseases such as SLE.
5. MRI with gadolinium may reveal hypertrophy and enhancement of the nerve roots and peripheral nerves.

Electrophysiologic Findings

1. Various research criteria have been used to define demyelination on NCS. American Academy of Neurology (AAN) criteria include a combination of slowing of motor nerve conduction velocity to less than 80% of the lower limit of normal (LLN) (<70%, if amplitude <80% LLN), prolonged distal motor latencies to >125% of the upper limit of normal (ULN) (>150% if amplitude <80% LLN), prolonged F wave latencies to >125% ULN (>150% if amplitude <80% LLN), conduction block, and temporal dispersion.
2. As many as 40% of patients with CIDP do not fulfill the rigid research

criteria for demyelination and yet are responsive to immunotherapy. Treatment is not withheld in such patients if the diagnosis is considered likely on the basis of symmetric proximal and distal weakness in the arms and legs, diminished reflexes, and elevated CSF protein with appropriate nerve conduction findings.

Histopathology

1. Nerve biopsies may reveal evidence of segmental demyelination and remyelination, endoneurial and perineurial edema, mononuclear inflammatory cell infiltrate in the epineurium, perineurium, or endoneurium that is often perivascular.
2. Nerve biopsies, however, can reveal mainly axonal degeneration or may be completely normal.
3. Nerve biopsy is not often performed and is only necessary if patients do not have characteristic clinical and electrophysiologic features.

Treatment

Various immunotherapies are used (see Table 10-1), albeit many have not been studied in a rigorous fashion. Randomized control trials have demonstrated efficacy of corticosteroids, PE, and IVIG in the treatment of CIDP. Patients may respond to one mode of treatment when other approaches have failed or the disease has become refractory. In most instances, repeated treatments over the years are required.

1. IVIG
   - **a.** Several double-blind, placebo-controlled studies have demonstrated that IVIG is efficacious in CIDP, and it has become the treatment of choice by many clinicians.
   - **b.** An observer-blinded, randomized trial of PE compared with IVIG found no difference in efficacy.
   - **c.** The dosage and interval between IVIG treatments needs to be individualized.
   - **d.** We begin IVIG treatment with a total dose of 2 g/kg over 3 to 5 days and subsequently repeat IVIG 2 g/kg over 2 to 5 days every month for 2 more months.
   - **e.** We then try to reduce the total dose or increase dosing interval, depending

on the response. Some patients may only need IVIG 1 g/kg every 2 to 3 months, whereas others may need infusions every several weeks.

f. Serum IgA level may be assayed in patients prior to administering IVIG. Patients who are IgA-deficient may develop anaphylactic reactions to IVIG, if containing IgA.

g. IVIG should be used cautiously in patients with diabetes and avoided in those with renal insufficiency, as it has been associated with renal failure secondary to acute tubular necrosis.

h. Many patients develop headaches (up to 50%), diffuse myalgias, fever, blood pressure fluctuations, and flulike symptoms. These side effects can be treated with prophylactic administration of hydrocortisone 100 mg IV, loratadine (Claritin) 10 mg p.o. or diphenhydramine (Benadryl) 25 to 50 mg p.o., and acetaminophen (Tylenol) 650 mg p.o. 30 minutes prior to each IVIG infusion. Also, lowering the rate of infusion and keeping the patient hydrated should lessen side effects during treatment.

i. A few patients actually develop aseptic meningitis. There are rare thrombotic complications (e.g., stroke and myocardial infarction), perhaps related to hyperviscosity.

j. Mild neutropenia is common, but this is rarely clinically significant.

2. Corticosteroids

a. Corticosteroids are very effective in CIDP but have been used less since IVIG was introduced. When used, we usually initiate treatment with prednisone 0.75 to 1.5 mg/kg (up to 100 mg) daily for 2 to 4 weeks then switch to alternate-day treatment (e.g., 100 mg q.o.d.).

b. Patients with diabetes may not be able to be treated with alternate-day prednisone secondary to wide fluctuations in blood glucose. In such cases, we treat with equivalent dose of daily prednisone (i.e., 50 mg/d).

c. Patients are maintained on this dose of prednisone until their strength is normalized or there is a clear plateau in clinical improvement, which may occur by 6 months.

d. Subsequently, the dose of prednisone is slowly decreased by 5 to 10 mg every 2 to 3 weeks until they are on 20 mg q.o.d. At that point, we taper the prednisone no faster than about 2.5 mg every 2 to 3 weeks.

e. There are significant side effects related to long-term corticosteroid treatment including osteoporosis, glucose intolerance, hypertension,

cataract formation, aseptic necrosis of the hip, weight gain, hypokalemia, and type 2 muscle fiber atrophy.

f. Obtain baseline bone density studies and repeat the study every 6 months while patients are receiving prednisone.

g. Start calcium (1,000 to 1,500 mg/d) and vitamin D (400 to 800 IU/d) for osteoporosis prophylaxis. Stress the importance of smoking cessation and avoidance of excessive alcohol intake.

h. Bisphosphonates, including alendronate, risedronate, and zoledronic acid, are effective in the prevention and treatment of glucocorticoid-induced osteoporosis. Although the assessment of bone density using reduced dual-energy x-ray absorptiometry (DEXA) scans is important for determining risk, other factors are also important. The American College of Rheumatology 2010 guidelines recommend the use of the FRAX score (http://www.shef.ac.uk/FRAX/) or patients' overall clinical risk profiles for calculating risk and most appropriate therapy (see bibliography).

i. Obtain baseline and periodic fasting blood glucose and serum electrolytes. Patients need to be instructed on keeping a low-sodium, low-carbohydrate diet to avoid excessive weight gain, hypertension, and hyperglycemia.

j. We recommend weight-bearing exercise in order to reduce these side effects.

k. To prevent pneumocystis infection, some authorities advocate starting prophylactic trimethoprim-sulfamethoxazole.

3. PE

a. Two prospective, randomized, double-blinded, placebo-controlled trials using sham PE demonstrated its efficacy.

b. Response to treatment is transient, usually lasting only a few weeks. Thus, chronic intermittent PE or the addition of immunosuppressive agents is required.

c. We use PE, usually in combination with prednisone, in patients with severe generalized weakness because the response to PE may be quicker than that of using prednisone alone.

d. Approximately 200 to 250 mL/kg body weight is exchanged over five to six treatments during a 2-week period. Some patients will require more exchanges for maximum improvement to occur. Fibrinogen levels may be

checked prior to each exchange to be certain that a bleeding diathesis has not occurred from removal of clotting factors.

e. Exchanges can be scheduled every 1 to 2 weeks and the duration between exchanges is gradually increased, sometimes with coadministration of low-dose prednisone.

f. We use PE alone in patients for whom we wish to avoid long-term prednisone (e.g., patients with poorly controlled DM or HIV infection) or in whom IVIG is contraindicated (e.g., patients with renal insufficiency).

g. We also use a trial course of PE in patients who do not fulfill all the criteria for CIDP or those who have an underlying condition making the diagnosis difficult (e.g., patients with diabetes and superimposed CIDP-like neuropathy). Because the response to PE is generally faster than the response to prednisone, one can often determine earlier whether such patients could have an immune-responsive neuropathy.

4. Azathioprine

a. We usually do not treat with azathioprine alone, but it is an option in patients who cannot be given prednisone, PE, or IVIG.

b. Azathioprine in combination with prednisone can be used in patients who are resistant to prednisone taper.

c. Begin azathioprine at a dose of 50 mg/d and gradually increase by 50 mg every week to a total dose of 2 to 3 mg/kg/d.

d. Approximately 12% of patients receiving azathioprine develop a "flulike" syndrome with fever, abdominal pain, nausea, and vomiting, requiring discontinuation of the drug.

e. Other side effects include bone marrow suppression, hepatotoxicity, and risk of infection and future malignancy.

f. Monitor complete blood counts (CBCs) and LFTs every 2 weeks while adjusting the dose of azathioprine and then every 3 months once the dose is stable.

5. Mycophenolate mofetil

a. Small anecdotal reports suggest that some patients may benefit from mycophenolate mofetil.

b. We start at 1 g p.o. b.i.d. The dose can be increased by 500 mg per month up to 1.5 g p.o. b.i.d.

c. Monitor CBC.

5. Methotrexate
   a. Small studies have suggested that methotrexate may be effective in CIDP. However, a double-blind, placebo-controlled trial of patients also receiving IVIG or prednisone did not demonstrate an added benefit.
   b. For dosing recommendations, see Table 10-1.

7. Rituximab
   a. Rituximab is a monoclonal antibody directed against CD20 cell marker and will deplete B cells for 6 months to a year or more. As B cells are precursors to plasma cells, antibody production drops over time as well.
   b. A few small reports have suggested that rituximab may be effective in patients with CIDP or demyelinating neuropathies associated with anti-myelin-associated glycoprotein (MAG) antibodies, although results have been mixed for the latter.
   c. The dose of rituximab is 750 mg/m^2 (up to 1 g) IV that is then repeated in 2 weeks. This course is generally repeated every 6 to 12 months.
   d. The main side effects are infusion reactions. Because rituximab depletes B cells, there is increased risk of infection. There have been a few reports of progressive multifocal leukoencephalopathy in patients with SLE.

8. Cyclophosphamide
   a. Both oral (50 to 150 mg/d) and monthly pulses of IV cyclophosphamide (up to 1 g/m^2) have been reported to be beneficial in some patients but are associated with significant side effects. The dose should be adjusted based on degree of post-infusion neutropenia.
      1) Sodium 2-mercaptoethane sulfonate (mesna) is usually given during therapy (depending on the route and dose being given) to reduce the incidence of bladder toxicity.
      2) Ondansetron 8 mg p.o. prior to cyclophosphamide infusion and 8 hours later is used to diminish nausea prior to infusion.
      3) Patients should be vigorously hydrated to minimize bladder toxicity.
   b. The major side effects including hemorrhagic cystitis, bone marrow suppression, increased risk of infection and future malignancy, teratogenicity, alopecia, nausea, and vomiting have limited its use.
   c. It is important to frequently monitor CBCs and urinalysis in patients treated with cyclophosphamide.

9. Cyclosporine

a. Several retrospective reports suggest that cyclosporine can be effective in some patients with CIDP, even in those refractory to other modes of therapy.
b. We administer cyclosporine at a dose of 4 to 6 mg/kg orally per day, initially aiming for a trough level between 150 and 200 mg/dL.
c. The major side effects of cyclosporine include nephrotoxicity, hypertension, tremor, gingival hyperplasia, hirsutism, and increased risk of infection and future malignancies—mainly skin cancer and lymphoma.
d. Electrolytes and renal function need to be monitored monthly while adjusting the dose and then every 3 months.

). Tacrolimus may be beneficial in some patients (see Table 10-1 for dosing details).
l. Supportive care consists mainly of physical and occupational therapies to improve strength, gait, and function and assess need for orthotic devices (e.g., ankle braces).

MULTIFOCAL MOTOR NEUROPATHY

Background

l. Multifocal motor neuropathy (MMN) is a peripheral nerve motor disorder commonly misdiagnosed as ALS. In MMN, weakness is in the distribution of individual peripheral nerves, not the motor neurons as it is in ALS.
2. The incidence of MMN is much lower than that for ALS. Most large neuromuscular centers diagnose one case of MMN for every 50 cases of ALS.
3. There is a male predominance with a male-to-female ratio of approximately 3:1.
4. The age of onset of symptoms is usually early in the fifth decade of life, ranging from the second to eighth decades of life.

Pathophysiology

l. MMN is a distinct entity from CIDP because it has a relatively uniform presentation with special laboratory features, histopathology, and response

to treatment.
2. The disparity between pure motor nerve involvement, in contrast to spared sensory nerves, suggests that an autoimmune attack is directed against an antigen on the motor nerve.
3. The pathogenic role of antiganglioside antibodies, found in a large number of cases, is not known.
4. An immune attack directed against an ion channel could account for conduction block of neural impulses, and secondary inflammatory attack may result in demyelination.

Prognosis

1. Approximately two-thirds of patients improve with IVIG or cyclophosphamide.
2. Patients with long-standing disease with atrophy of muscles are less likely to respond.

Diagnosis

Clinical Features

1. Asymmetric weakness and atrophy are the presenting and ongoing features, typically in the distribution of individual peripheral nerves, usually beginning in the arms.
2. There is little or no atrophy in weak muscle groups early in the course of the illness; however, decreased muscle bulk develops over time because of secondary axonal degeneration.
3. Sensory examination should be normal.
4. Deep tendon reflexes are variable in that unaffected regions can be normal, whereas weak and atrophic muscles usually have depressed or absent reflexes.

Laboratory Features

1. In contrast to CIDP and multifocal acquired demyelinating sensory and motor (MADSAM) (see further on), CSF protein is usually normal in MMN.
2. In various studies, 22% to 84% of patients with MMN have detectable IgM

antibodies directed against not only gangliosides, mainly GM1, but also asialo-GM1 and GM2. The role of these antibodies in pathogenesis is not clear.

3. When present in high titers, the antibodies appear to be specific for MMN, but the sensitivity of the test is low. The most sensitive and specific test is the NCS, and the antiganglioside antibody test in a patient who has clinical electrophysiologic abnormalities consistent with MMN has limited additional value.

Electrophysiologic Findings

1. There is often evidence of conduction block in multiple upper and lower limb nerves. The location of conduction block is not at the common nerve entrapment sites, but instead, it is typically in the mid-forearm or leg, upper arm, across the brachial plexus, or nerve root region.
2. Other features of demyelination (i.e., prolonged distal latencies, temporal dispersion, slow conduction velocities, and prolonged or absent F waves) may be present on motor NCS. In fact, conduction block need not be present if other features of demyelination are present.
3. The sensory NCS are normal.
4. EMG reveals reduced recruitment in weak muscles. When secondary loss of axons has occurred as the illness progresses, positive sharp waves and fibrillation potentials are commonly detected in degrees commensurate with the amount of nerve injury and clinical wasting.

Treatment

1. IVIG is the main treatment.
   - **a.** IVIG is initially given in a dose of 2 g/kg over 2 to 5 days with subsequent maintenance courses as necessary, similar to the management of CIDP.
   - **b.** Not all patients with MMN respond to IVIG. Some series have reported that a later age of onset and the presence of significant muscle atrophy are associated with less response to treatment.
   - **c.** We give three courses of monthly IVIG before concluding a patient has failed this treatment.
2. In patients who fail IVIG, rituximab may be considered as outlined in the earlier section on CIDP.

3. If the aforementioned treatments fail or are contraindicated (IgA deficiency, previous allergic reaction to IVIG, renal insufficiency, severe cardio- or cerebrovascular disease), IV cyclophosphamide is considered.
   a. Cyclophosphamide was the first immunosuppressive agent demonstrated to be effective in MMN, with over 70% of patients clinically improved.
   b. The initial dosage of cyclophosphamide is 0.5 g/m^2 IV/mo.
   c. If no improvement is noted after 3 months, we increase the dose to 0.75 g/m^2 IV/mo.
   d. If there is still no improvement after 3 months, we increase the dose to 1.0 g/m^2 IV/mo.
   e. If there is no improvement after 3 more months, we discontinue the cyclophosphamide. If there has been clear improvement, we continue monthly infusions for 6 months.
   f. Risks of cyclophosphamide include alopecia, nausea and vomiting, hemorrhagic cystitis, and significant bone marrow suppression.
   g. Sodium 2-mercaptoethane sulfonate (mesna) may be given to reduce the incidence of bladder toxicity and ondansetron 8 mg p.o. prior to cyclophosphamide infusion and 8 hours later is used to diminish nausea.
   h. Patients should be vigorously hydrated to minimize bladder toxicity.
4. In contrast to CIDP and MADSAM neuropathy, few patients (<3% of reported cases) with MMN improve with high doses of corticosteroids, PE, or other immunosuppressive agents.

MULTIFOCAL ACQUIRED DEMYELINATING SENSORY AND MOTOR NEUROPATHY

Background

1. There have been several series of patients who have the characteristics of MMN clinically, electrophysiologically, and histologically but who have subjective and objective sensory abnormalities.
2. The terms “Lewis–Sumner syndrome” and “multifocal acquired demyelinating sensory and motor” (MADSAM) neuropathy have been used to describe this probable variant of CIDP.

Pathophysiology

1. The pathogenic basis for MADSAM neuropathy is not known, but, as mentioned, it is generally classified in the spectrum of CIDP and likely has a similar pathogenesis.
2. MADSAM neuropathy and CIDP have similar CSF and sensory nerve biopsy findings as well as response to corticosteroids.

Prognosis

Similar to CIDP, most patients improve with immunotherapy.

Diagnosis

Clinical Features

1. Motor and sensory loss conforms to a discrete peripheral nerve distribution rather than a generalized stocking or glove pattern. Some patients describe pain and paresthesias.
2. Distal upper extremities are more commonly involved than the distal lower extremities. Cranial neuropathies can rarely occur.
3. There is a 2:1 male predominance. The average age of onset is in the early 50s (range, 14–77 years). Onset is usually insidious and slowly progressive.
4. Reflexes may be normal or decreased.

Laboratory Features

1. CSF protein is elevated in 60% to 82% of patients.
2. Unlike MMN, GM1 antibodies are usually absent.
3. In patients with demyelination localized to the cervical roots or brachial plexus, MRI scans have revealed enlarged nerves that enhance in some, but not all, cases.

Histopathology

1. Sensory nerve biopsies demonstrate many thinly myelinated, large-diameter fibers and scattered demyelinated fibers.
2. Subperineurial and endoneurial edema and mild onion bulb formations may also be appreciated similar to CIDP.

Electrophysiologic Findings

1. As with CIDP and MMN, NCS in MADSAM neuropathy demonstrate conduction blocks, temporal dispersion, prolonged distal latencies, prolonged F waves, and slow conduction velocities in one or more motor nerves.
2. In contrast to MMN, the sensory studies are also abnormal. SNAPs are usually absent or small in amplitude, similar to those seen in patients with generalized CIDP.

Treatment

1. Most patients with MADSAM neuropathy improve with IVIG treatment.
2. We initiate treatment with IVIG 2 g/kg over 2 to 5 days and repeat every month for 3 months and then individualize subsequent doses and treatment intervals as described in the CIDP section.
3. If there is no satisfactory response to IVIG, we start prednisone 0.75 to 1.5 mg/kg/d p.o. as discussed in the CIDP section.
4. In contrast to MMN, but similar to CIDP, most patients with MADSAM neuropathy have also demonstrated improvement with steroid treatment.
5. This illustrates the importance of distinguishing MADSAM from MMN in which cyclophosphamide represents the only other medication reported to be beneficial besides IVIG.

VASCULITIC NEUROPATHIES

Background

1. Vasculitis is a histologic diagnosis requiring the finding of transmural inflammation and necrosis of blood vessel walls.
2. Vasculitic disorders can be classified on the basis of caliber of vessel involved (i.e., small, medium, or large), whether the vasculitis is primary (e.g., polyarteritis nodosa [PAN], Churg–Strauss syndrome [CSS], or granulomatosis with angiitis [GAN]) or secondary to a systemic disorder (connective tissue diseases, infection, drug reactions, malignancy), or by systemic vasculitis or vasculitis isolated to the PNS.

3. PAN is the most common of the necrotizing vasculitides with an incidence ranging from 2 to 9 per million.
   a. The onset is usually between 40 and 60 years of age.
   b. PAN is a systemic disorder involving small- and medium-caliber arteries in multiple organs.
   c. Vasculitis of the gastrointestinal tract can manifest as abdominal pain, bleeding, or mesenteric infarction.
   d. Ischemia of the kidneys can lead to renal failure.
   e. Orchitis can also be a feature of PAN.
   f. Weight loss, fever, and loss of appetite are also usually noted.

4. CSS manifests similarly to PAN.
   a. The incidence is roughly one-third that of PAN, but the frequency of PNS and CNS involvement in cases of CSS is similar to PAN.
   b. In contrast to PAN, patients with CSS usually present with respiratory involvement, typically allergic rhinitis, nasal polyposis, and sinusitis followed by asthma.
   c. In CSS, asthma begins later in life, in contrast to common asthma, which usually develops before the age of 35 years.
   d. Pulmonary infiltrates are present in nearly half the patients, usually in association with asthma and hypereosinophilia.
   e. Symptoms and signs of systemic vasculitis occur on an average of 3 years after the onset of asthma.
   f. Rather than an ischemic nephropathy as evident in PAN, up to half of patients with CSS develop a necrotizing glomerulonephritis.

5. GAN is a rare disorder (previously referred to as Wegener granulomatosis).
   a. The early symptoms of respiratory disease (nasal discharge, cough, hemoptysis, and dyspnea) and facial pain can help distinguish this from other vasculitic disorders.
   b. Vasculitis affects medium and small blood vessels. Granulomatous infiltration of the upper and lower respiratory tract and necrotizing glomerulonephritis are also seen.
   c. About 30% to 50% of patients may have nervous system lesions, although only 15% to 20% of patients have peripheral neuropathy. Either a mononeuropathy multiplex or generalized symmetric pattern of involvement can occur.

d. Cranial neuropathies, particularly the second, sixth, and seventh nerves, are involved in approximately 10% of cases as a result of contiguous extension of nasal or paranasal granulomas rather than vasculitis.

5. Microscopic polyangiitis (MPA)
   a. The clinical symptoms of MPA are similar to those of PAN, except that the lungs are often involved.
   b. MPA is about one-third as common as PAN and has an average age of onset of 50 years.
   c. Polyneuropathy complicates MPA in 14% to 36% of cases.
   d. Impaired renal function as illustrated by increased blood urea nitrogen (BUN) and creatinine levels and hematuria is evident in most patients.

Pathophysiology

The pathogenic basis of vasculitis is cytotoxic- or complement-mediated destruction of blood vessels (depending on the specific type of vasculitis) with resultant focal infarction of peripheral nerves.

Prognosis

1. Since the use of corticosteroids to treat systemic vasculitis began in the 1950s, the 5-year survival rate has increased from 10% to 55%.
2. The addition of cyclophosphamide to corticosteroids further increased the 5-year survival rate to over 80%.
3. Nonsystemic vasculitis carries a better prognosis and often responds to treatment with prednisone alone.

Diagnosis

Clinical Features

1. Motor and sensory fibers are affected, resulting in numbness, pain, and weakness.
2. Three patterns of peripheral nerve involvement can be appreciated:
   a. Multiple mononeuropathies, usually painful.
   b. Overlapping mononeuropathy multiplex.
   c. Generalized symmetric polyneuropathy.

d. The mononeuropathy multiplex pattern (simple and overlap forms) are the most common, found in 60% to 70% of cases at the time of diagnosis, whereas a generalized polyneuropathy is evident in approximately 30% to 40% of patients.

Electrophysiologic Findings

1. Motor and sensory nerve conduction demonstrates unobtainable potentials or reduced amplitudes with relatively normal distal latencies and conduction velocities consistent with axonal degeneration.
2. EMG demonstrates evidence of active denervation in affected muscles.
3. There is asymmetric involvement of motor and sensory nerves and EMG abnormalities reflective of the multifocal pathophysiology.

Laboratory Features

1. Erythrocyte sedimentation rate (ESR), C-reactive protein, and rheumatoid factor are elevated in most patients.
2. CSS: Evaluation is remarkable for eosinophilia and antineutrophil cytoplasmic antibodies (ANCAs), primarily myeloperoxidase (MPO) or p-ANCA, because of its perinuclear staining pattern. These p-ANCA antibodies are present in as many as two-thirds of patients.
3. PAN: As many as one-third of cases are associated with hepatitis B antigenemia. In addition, hepatitis C and HIV infection have also been reported with PAN. Abdominal angiograms can reveal a vasculitic aneurysm. Ten percent to 20% have anti-MPO/p-ANCA antibodies.
4. GAN: Evaluation is remarkable for the presence of antineutrophil antibodies directed against proteinase-3 (c-ANCA). The specificity of c-ANCA for GAN is 98%, and the sensitivity is 95%. Granulomatous infiltration of the respiratory tract and necrotizing glomerulonephritis can be seen. The lack of peripheral eosinophilia and eosinophilic infiltrates on biopsy and absence of asthma help distinguish GAN from CSS.
5. MPA: Laboratory evaluation usually demonstrates the presence of p-ANCA, although c-ANCAs can also occasionally be detected.

Histopathology

1. We prefer to biopsy the superficial peroneal nerve, if it is involved, because

the peroneus brevis muscle can also be biopsied at the same time. The diagnostic yield is increased when nerve and muscle are both biopsied.

2. The definitive histologic diagnosis of vasculitis requires transmural inflammatory cell infiltration and necrosis of the vessel wall.

Treatment

1. The mainstay of initial treatment for systemic vasculitis is a combination of corticosteroids and cyclophosphamide.
2. Although hypersensitivity vasculitis and some isolated PNS vasculitis can be treated with prednisone, its combination with cyclophosphamide has found to be more effective.
3. Initiate corticosteroid treatment.
   - **a.** In severe vasculitis, start with pulsed methylprednisolone (1 g IV qd for 3 days) and then switch to oral prednisone 1.5 mg/kg/d (up to 100 mg/d) as a single dose in the morning (in patients with less severe vasculitis treatment can be started with oral therapy).
   - **b.** After 2 to 4 weeks, switch to alternate-day prednisone (i.e., 100 mg q.o.d.).
   - **c.** Concomitantly treat with calcium and vitamin D supplementation as well as bisphosphonates to prevent and treat steroid-induced osteoporosis, as discussed in the section on CIDP.
4. Cyclophosphamide is started the same time as the corticosteroids and can be given orally or in IV pulses.
   - **a.** Oral cyclophosphamide at a dose of 1.0 to 2.0 mg/kg per day is a more potent suppressor of the immune system, but it is associated with more adverse side effects (e.g., hemorrhagic cystitis) than IV pulses.
   - **b.** We prefer monthly IV pulses of cyclophosphamide at a dose of 500 to 1,000 mg/m^2 of body surface area. Sodium 2-mercaptoethane sulfonate (mesna) can be given to reduce the incidence of bladder toxicity, as well as antiemetics (such as ondansetron 8 mg p.o. prior to cyclophosphamide infusion and 8 hours later) to diminish nausea. Patients should be vigorously hydrated to minimize bladder toxicity.
   - **c.** Following IV pulses of cyclophosphamide, the leukocyte count drops with a nadir between 7 and 18 days, during which time the risk of infection is greatest.

d. Check CBCs and urinalysis prior to each treatment. Urinalysis is obtained every 3 to 6 months after treatment because of the risk of future bladder cancer.

e. If patients do not respond to pulsed cyclophosphamide, oral dosing should be tried prior to concluding the patient failed cyclophosphamide treatment.

5. Continue high-dose corticosteroids and cyclophosphamide treatment until the patient begins to improve or the deficits stabilize, which is usually within 3 to 6 months.
6. Subsequently discontinue pulse cyclophosphamide and replace with azathioprine or methotrexate (see Table 10-1). Then gradually taper the prednisone by 5 mg every 2 to 3 weeks down to 20 mg q.o.d. and then by 2.5 mg every 2 to 3 weeks.
7. Patients with CSS often require continued low doses of prednisone secondary to their associated asthma. Relapses are uncommon in PAN, MPA, and isolated PNS vasculitis but occur in as many as 50% of cases of GAN. Such patients may require lifelong immunosuppressive therapy.
8. Rituximab 375 mg/m^2/wk for 4 weeks may be used to induce remission in "ANCA-associated" vasculitis (GAN, CSS, and MPA). Two randomized trials have shown that the combination of rituximab with corticosteroid is not inferior to the combination of cyclophosphamide and corticosteroid and increasingly being considered as the treatment of choice in this group.
9. Other immunosuppressive agents may be used for the treatment of vasculitis, but experience with their use is less well documented:

a. Methotrexate, up to 25 mg/wk, combined with corticosteroids, may be used to induce remission in GAN, in patients without life-threatening disease, or in those who cannot tolerate cyclophosphamide.

b. Mycophenolate mofetil (1,000 to 1,500 mg p.o. b.i.d.) is less effective than azathioprine to maintain remission but can be used in those who cannot tolerate methotrexate and azathioprine or who have had a relapse on them.

c. Azathioprine, cyclosporine, tacrolimus, and IVIG have been tried in refractory cases with variable success.

10. Patients with hepatitis B– or hepatitis C–related vasculitis (PAN or mixed cryoglobulinemia) require antiviral therapy.

a. Conventional treatment with high-dose corticosteroids and

cyclophosphamide may allow the virus to persist and replicate, thus increasing the risk of liver failure.

b. We use corticosteroids only during the first few weeks of treatment to manage life-threatening manifestations of systemic vasculitis. Afterward, the corticosteroids are discontinued.

c. PE and antiviral agents are used to suppress the virus and control the course of the neurologic illness.

d. Two studies comparing treatment with antivirals (peginterferon-α/riboflavin) alone or in combination with rituximab, in patients with hepatitis C mixed cryoglobulinemia, suggested a better response in the latter group.

NEUROPATHY ASSOCIATED WITH SARCOIDOSIS

Background

1. Sarcoidosis is a multisystem granulomatous disorder affecting primarily not only the lungs and lymph nodes but also liver, spleen, mucous membranes, parotid glands, muscle, CNS, and PNS.
2. Women are affected more commonly than men.
3. The PNS or CNS is involved in about 5% of patients with sarcoidosis.
4. Nervous system involvement without systemic disease is rare.

Pathophysiology

1. Sarcoidosis is an autoimmune disorder, although the etiology and pathogenesis are not known. A connection to tuberculosis has been repeatedly proposed but not proven.
2. Peripheral neuropathy may result from direct compression by granulomas, ischemia, a combination of these, or other ill-defined factors.

Prognosis

1. Patients with neurosarcoidosis, particularly of the cranial nerves, may

respond well to corticosteroid treatment.
2. If patients are resistant to corticosteroids, other immunosuppressive agents can be tried.
3. Polyneuropathy/polyradiculoneuropathy-related neurosarcoidosis may be refractory to treatment.

Diagnosis

Clinical Features

1. Nonspecific constitutional symptoms of fever, weight loss, and fatigue are usually the presenting complaints.
2. Palpable peripheral lymph nodes may be noted.
3. A common finding on presentation is acute granulomatous uveitis, which can progress to visual impairment. Erythema nodosum and hypercalcemia may be present.
4. Patients may present with multiple cranial nerve involvement. The most common cranial nerve involved is the seventh, which can be affected bilaterally. The second and eighth cranial nerves are also frequently affected.
5. Multiple peripheral mononeuropathies, plexopathy, and polyradiculoneuropathy may occur. With generalized root involvement, patients may present with signs and symptoms quite similar to AIDP or CIDP.
6. The most common involvement of the PNS is a subclinical mononeuropathy multiplex, which can be demonstrated by electrodiagnostic evaluation. Less commonly, patients present with symptoms and signs suggestive of a slowly progressive primarily sensory, motor, or sensorimotor peripheral neuropathy.
7. Hilar adenopathy is found on chest radiographs and CT.

Histopathology

1. The major histopathologic finding is noncaseating granulomas in various tissues.
2. When the peripheral nerves are affected, nerve biopsy can reveal profuse infiltration of the nerve by multiple sarcoid granulomas affecting all regions

of the supporting neural structures (endoneurium, perineurium, and epineurium) associated with lymphocytic angiitis.

Electrophysiologic Findings

1. The most common finding is an absence or reduction in SNAP amplitudes and, less frequently, CMAP amplitudes in a mononeuropathy multiplex pattern.
2. A few patients have more profound slowing indicating demyelinating as opposed to axonal component of nerve damage.

Treatment

1. We initiate treatment with prednisone 1–1.5 mg/kg/d p.o. and adjust the dose as described in the treatment section on CIDP.
2. Second-line agents in patients unresponsive or refractory to steroids are azathioprine (2 to 3 mg/kg/d), methotrexate (7.5 to 35 mg/wk), cyclosporine (3 to 6 mg/kg/d), and cyclophosphamide (1 to 2 mg/kg/d) as described in the section on CIDP.

NEUROPATHY ASSOCIATED WITH LEPROSY

Background

1. The acid–fast bacteria *Mycobacterium leprae* causes leprosy.
2. Commonly encountered in Southeast Asia, Africa, South America, and Europe, it is also endemic in certain areas of the United States of America (i.e., Hawaii, Texas).
3. Three primary clinical manifestations of the disease are recognized: tuberculoid, lepromatous, and borderline leprosy.
4. The host's immunologic status determines which form develops.

Pathophysiology

1. The clinical and pathologic spectrum of the disease is dependent on the host's immune response to *M. leprae* and reflects the relative balance between T helper cell type 1 (T_H1; helper) and type 2 (T_H2) (suppressor)

cells.

2. Tuberculoid leprosy and lepromatous leprosy represent the two extremes of disease manifestation.
3. The tuberculoid form defines one end of the spectrum, in which the T_H1 cells predominate. The T_H1 cells produce interleukin (IL)-2 and γ-interferon, which in turn lead to activation of macrophages.
4. On the other extreme, the lepromatous form is dominated by T_H2 cells, which produce IL-4, IL-5, and IL-10, thereby downregulating cell-mediated immunity and inhibiting macrophages.
5. The borderline subtypes exhibit immune responses spanning the spectrum between tuberculoid and lepromatous forms.

Prognosis

The neuropathy is very responsive to antibiotics.

Diagnosis

Clinical Features

1. In tuberculoid (paucibacillary) leprosy, the cell-mediated immune response is intact leading to focal, circumscribed inflammatory lesions involving the skin or nerves.
   - **a.** The skin lesions appear as well-defined, scattered hypopigmented patches and plaques with central anesthesia and raised, erythematous borders.
   - **b.** The organism has a predilection for the cooler regions of the body (e.g., face, limbs) rather than warmer regions such as the groin or axilla.
   - **c.** The more superficial nerves in the vicinity of the skin lesions may also be affected.
   - **d.** There is a predilection for involvement of specific nerve trunks; the ulnar nerve at the medial epicondyle, the median nerve at the distal forearm, the peroneal nerve at the fibular head, the sural nerve, the greater auricular nerve, and the superficial radial nerve at the wrist.
   - **e.** The most common neurologic manifestation of tuberculoid leprosy is mononeuropathy or mononeuropathy multiplex.
2. In lepromatous (multibacillary) leprosy, cell-mediated immunity is impaired

resulting in an extensive infiltration of the bacilli process, anesthesia, and anhidrosis.

   a. Clinical manifestations tend to be more severe in the lepromatous subtype, but, as in the tuberculoid form, cooler regions of the body are more susceptible.
   b. The organisms multiply virtually unchecked and hematogenously disseminate, producing confluent and symmetric areas of rash.
   c. A slowly progressive symmetric sensorimotor polyneuropathy develops over time.
   d. As with the tuberculoid subtype, nerve trunks can be affected with time leading to superimposed mononeuropathies.

3. Patients with borderline leprosy have the highest incidence of neurologic complications.
   a. These patients can show clinical and histologic features of both the lepromatous and the tuberculoid forms of leprosy.
   b. Patients can develop generalized symmetric sensorimotor polyneuropathies, mononeuropathies, and mononeuropathy multiplex, including multiple mononeuropathies in atypical locations, such as the brachial plexus.

4. Rarely, patients with leprosy present with isolated peripheral neuropathy without skin lesions.
   a. Lepromatous neuropathy should be suspected in individuals without skin lesions who live in endemic areas.
   b. Virtually all the cases of pure neuritic leprosy have the tuberculoid or borderline tuberculoid subtypes of the disease.

Electrophysiologic Studies

EMG and NCS are consistent with multiple axonal mononeuropathies.

Histopathology

Diagnosis of leprosy can be confirmed with a skin or nerve biopsy.

Treatment

1. Multidrug therapy is presently the mainstay of treatment.

2. The choice of medication and treatment duration depend on the type of leprosy. Based on WHO recommendations for adults:
   a. Tuberculoid (paucibacillary) leprosy is treated with dapsone 100 mg p.o. daily and rifampin 600 mg p.o. per month. The treatment duration is 6 months.
   b. Lepromatous (multibacillary) leprosy is also treated with dapsone 100 mg p.o. daily and rifampin 600 mg p.o. per month, with the addition of clofazimine 300 mg p.o. per month and 50 mg p.o. daily. The treatment duration is 1 to 2 years or until the skin smear is zero.
   c. Paucibacillary leprosy with single skin lesion is treated with a single dose of p.o. rifampin 600 mg, ofloxacin 400 mg, and minocycline 100 mg. Proven relapses are treated with multidrug regimen.
3. The patients should be instructed regarding the side effects of these medications. Rifampin may cause reddish discoloration of the urine for a few hours. Clofazimine may cause brownish-black discoloration of the skin that will resolve after stopping therapy. Dapsone may cause and allergic reaction with skin rashes and dermatitis and should also not be given to patients with sulfa allergy.
4. A potential complication of therapy, particularly in borderline leprosy, is the "reversal reaction."
   a. Can occur at any time during treatment of the disease because of a shift to the tuberculoid end of the spectrum with an increase in cellular immunity.
   b. This may cause new granuloma formation with exacerbation of the skin lesions and neuropathy.
   c. High-dose prednisone (50 mg/d) appears to blunt this adverse reaction and may even be used prophylactically in high-risk patients at treatment onset.
5. Another reaction to treatment may be erythema nodosum leprosum (ENL), which occurs during the treatment of patients with lepromatous leprosy.
   a. ENL is associated with the appearance of multiple erythematous, sometimes painful, subcutaneous nodules; exacerbation of the neuropathy can also occur.
   b. It is because of the slow degradation of antigens (bacterial debris) resulting in antigen–antibody complex and complement deposition in affected tissue.

c. Can be treated with prednisone (50 mg/d), clofazimine, or thalidomide.

6. Prevention of leprosy is the ultimate goal and involves multiple strategies, starting with the prompt diagnosis and treatment of suspected cases, often with brief hospitalizations to ensure understanding and compliance with multidrug regimens.
7. Various vaccinations are available in endemic areas, including Bacillus Calmette–Guérin (BCG), killed leprae, and chemically modified organism.

NEUROPATHY ASSOCIATED WITH LYME DISEASE

Background

1. *Borrelia burgdorferi*, a spirochete transmitted by ticks.
2. It is transmitted by the deer tick, *Ixodes dammini*.
3. A spirochete acquired by a tick by feeding on an infected host animal, which then transmits the spirochete to its next host when feeding.
4. Approximately 12 to 24 hours of tick attachment are required to accomplish this secondary host infection.

Pathophysiology

1. The pathogenic mechanism for the Lyme neuropathy is unknown.
2. The neuropathy may be the result of an indirect immunologic response or some form of immune vasculopathy.

Prognosis

Patients improve with appropriate antibiotic treatment.

Diagnosis

Clinical Features

1. Three stages of the systemic disease are recognized:

a. Early infection (erythema migrans of the skin: localized)
b. Disseminated infection
c. Late-stage infection

2. Within 1 month following a bite from an infected tick, an expanding erythematous circular region surrounding the original tick bite is noted. However, erythema migrans is not noticed by all patients.
3. With respect to the PNS manifestations, the findings can vary depending on the stage of the disease.
4. In stage 2 disease, cranial mononeuropathies can be documented. Facial nerve palsy is the most common and is bilateral in about 50% of cases.
5. Asymmetric polyradiculoneuropathies, plexopathies, or multiple mononeuropathies can occur. Aseptic meningitis is fairly common.
6. Rarely, the patients may be mistaken to have AIDP.
7. In stage 3, a distal symmetric sensorimotor polyneuropathy can occur.

Laboratory Features

1. Antibodies directed against the spirochete can be measured using immunofluorescent or enzyme-linked immunosorbent assay (ELISA). False-positive reactions are not uncommon.
2. Western blot analysis is useful to confirm a positive ELISA.

Electrophysiologic Findings

NCS reveal reduced CMAP and SNAP amplitudes and denervation changes on EMG in the distribution of affected nerves.

Treatment

1. Adults with isolated facial nerve palsies secondary to Lyme disease, similar to those with erythema migrans, are usually treated with doxycycline 100 mg p.o. b.i.d. for 2 to 3 weeks. Amoxicillin 500 mg p.o. t.i.d. or azithromycin 500 mg daily could be used instead.
2. Children younger than 4 years with facial palsies can be treated with amoxicillin 20 to 40 mg/kg/d in four divided doses for 2 to 4 weeks. If allergic to penicillin, children can be treated with erythromycin 30 mg/kg/d in four divided doses for 2 to 4 weeks.
3. Adult patients with other types of peripheral neuropathy are treated with IV

ceftriaxone 2 g IV daily for 2 to 4 weeks or IV penicillin 20 million U/d for 10 to 14 days. Adults who are allergic to penicillin can receive doxycycline 100 to 200 mg p.o. b.i.d. instead.

4. Children with Lyme neuropathy (other than facial nerve palsy) can receive IV penicillin G 250,000 U/kg/d in divided doses or ceftriaxone 50 to 80 mg/kg/d IV for 2 to 4 weeks.

HIV-ASSOCIATED DISTAL SYMMETRIC POLYNEUROPATHY

Background

A distal symmetric polyneuropathy (DSP) is usually seen in patients with AIDS.

Pathophysiology

1. Vitamin B_{12} deficiency has been noted in some series, but other studies have suggested that vitamin metabolism does not play a role in the neurologic complications of HIV.
2. Nerve biopsies may demonstrate perivascular inflammation (mainly macrophages and T cells) suggesting a possible immune-mediated basis.

Prognosis

The neuropathy is poorly responsive to treatment.

Diagnosis

Clinical Features

1. Patients complain of numbness and painful paresthesias of the hands and feet.
2. Some are asymptomatic but are found to have diminished sensation to all modalities and reduced reflexes on examination.

Electrophysiologic Findings

The electrodiagnostic medicine examination reveals evidence of a symmetric, axonal, sensory polyneuropathy greater than motor polyneuropathy.

Treatment

1. Antiretroviral agents have no demonstrable effect on the course of DSP.
2. Treatment is largely symptomatic pain relief (Table 10-2).

Table 10-2 Treatment of Painful Sensory Neuropathies

Therapy	Route	Dose	Side Effects
First line			
Pregabalin	p.o.	50–200 mg t.i.d. (taper slowly)	Cognitive changes, sedation, edema
Gabapentin	p.o.	300–1,200 mg t.i.d. (taper slowly)	Cognitive changes, sedation, edema
Serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine)	p.o.	Duloxetine 30–120 mg daily Venlafaxine 37.5–225 mg daily	Cognitive changes, sedation
Tricyclic antidepressants (e.g., amitriptyline, nortriptyline)	p.o.	10–100 mg qhs	Cognitive changes, sedation, dry eyes and mouth, urinary retention, constipation, QT prolongation
Second line			
Tramadol	p.o.	50–100 mg q.i.d.	Cognitive changes, sedation, GI upset, addiction, seizure
Opioids (oxycodone, morphine)	p.o.	10–120 mg daily	Cognitive changes, sedation, GI upset, addiction
Dextromethorphan	p.o.	400 mg daily	Drowsiness, dizziness, nausea, vomiting

Other agents			
Lidocaine 2.5%/prilocaine 2.5% cream	Apply cutaneously	q.i.d.	Local irritation
Lidoderm 5% patch	Apply to painful area	Up to 3 patches daily for 12 h at a time	Local irritation
Capsaicin 0.025–0.075% cream	Apply cutaneously	q.i.d.	Painful burning skin

p.o., by mouth; t.i.d., three times daily; qhs, at night; q.i.d., four times daily; GI, gastrointestinal.

Modified from Amato AA, Russell J. *Neuromuscular Disorders*. 2nd ed. New York, NY: McGraw-Hill; 2016, with permission.

HIV-ASSOCIATED POLYRADICULONEUROPATHY

Background

1. Patients with advanced AIDS can develop acute, progressive polyradiculopathy, plexopathy, or multiple mononeuropathies secondary to CMV infection.
2. Typical GBS (polyradiculoneuropathy) may occur soon after seroconversion, and typical CIDP may develop at any stage.

Pathophysiology

The basis is believed to be secondary to infection and secondary inflammation of neurons, in the case of CMV-related nerve damage, and altered immunomodulation, in the case of GBS and CIDP.

Prognosis

The prognosis in most patients with CMV infection is poor, with most reported patients with this complication dying within several weeks or months.

Diagnosis

Clinical Features

1. CMV-infected patients have severe numbness, pain, and weakness in the legs, which is usually asymmetric.
2. They also note a reduction in perineal sensation with painful paresthesias. Incontinence of urine and stool is common.
3. Occasionally, the upper limbs and cranial nerves become involved.
4. Patients may have evidence of CMV infection in other parts of the body (i.e., CMV retinitis).
5. The patients with GBS and CIDP demonstrate typical clinical findings of these disorders.

Laboratory Features

1. With CMV, CSF reveals an increased protein, neutrophilic pleocytosis, and decreased glucose. CMV may be cultured from the CSF, blood, and urine.
2. CSF in patient with GBS and CIDP will show lymphocytic pleocytosis in addition to elevated albumin, thus differentiating them from the idiopathic forms.

Electrophysiologic Findings

1. In the case of CMV, EMG and NCS demonstrate evidence of an axonal, multifocal polyradiculoneuropathy.
2. Electrodiagnostic findings

Treatment

1. In the case of CMV, a trial of ganciclovir or foscarnet is warranted, although prognosis is still poor.
2. GBS and CIDP are best treated with IVIG and PE. Prednisone can be used in CIDP, but it would be best to avoid steroids and other second-line immunosuppressive agents because of implications of long-term immunosuppression in patients with HIV.
3. Pain should be managed similarly to other painful neuropathies (see Table 10-2).

HERPES VARICELLA ZOSTER–RELATED NEUROPATHY

Background

1. Herpes varicella zoster (HVZ) infection can result from reactivation of latent virus, or from a primary infection.
2. Primary acquired HVZ infection is frequently associated with severe disseminated zoster in the immunocompromised patients.
3. The incidence of HVZ infection is approximately 480 persons per 100,000.
4. The peak age of developing the disease is between 55 and 75 years of age.

Pathophysiology

1. Following initial infection, the HVZ migrates to the sensory ganglia.
2. With reactivation, the virus replicates and travels down the sensory nerves and results in the typical skin lesions of shingles.
3. Motor paresis is postulated to develop by the virus causing local neuritis in the spinal nerve and subsequently gaining access to the motor axons.

Prognosis

Roughly 25% of affected patients have a substantial residual pain that is referred to as postherpetic neuralgia.

Diagnosis

1. Two-thirds of infections are manifested by dermal zoster (shingles).
2. Pain and paresthesias in a dermatome distribution may precede the vesicular rash by a week or more.
3. Five percent to 30% of patients with typical cutaneous herpes zoster develop weakness affecting the myotomal muscles that correspond to the dermatomal distribution of the eruption.

Treatment

1. Vaccination using a live-attenuated varicella zoster virus vaccine is

effective for prevention against herpes zoster and resulting postherpetic neuralgia. It is approved by the U.S. Food and Drug Administration (FDA) for individuals aged 50 years or older.

2. IV acyclovir can be lifesaving in immunocompromised patients with severe infections.
3. The treatment of postherpetic neuralgia is symptomatic (see Table 10-2).
4. Neurontin, pregabalin, and carbamazepine have been noted to be effective in postherpetic neuralgia.
5. Placebo-controlled studies have demonstrated that TCAs initiated early in the course of the rash reduce the incidence postherpetic pain.
6. Lidoderm 5% patches can be applied over the painful sites. Up to three patches can be used per day.
7. A salve of aspirin mixed in cold cream (or better, if available, chloroform) when applied to the affected area reduces pain.

DIABETIC DISTAL SYMMETRIC SENSORY AND SENSORIMOTOR POLYNEUROPATHY

Background

1. The most common form of diabetic neuropathy is a distal symmetric sensory polyneuropathy (DSPN).
2. The risk of developing peripheral neuropathy correlates with the duration of DM, the adequacy of control of hyperglycemia, and the presence of retinopathy and nephropathy.

Pathophysiology

1. The pathogenic basis for DSPN is unknown and controversial.
2. The major theories involve a metabolic process, ischemic damage, or an immunologic disorder.

Prognosis

The neuropathy is slowly progressive but can stabilize or improve with tight

control of diabetes.

Diagnosis

Clinical Features

1. This is a length-dependent neuropathy, which manifests clinically with sensory loss beginning in the toes and gradual progression to involve the legs.
2. The sensory symptoms can progress to affect the hands, again beginning with the fingers and move proximally to result in the commonly referred to "glove and stocking" distribution.
3. When severe, there may be sensory loss over the abdominal region progressing from the midline laterally toward, but not typically affecting, the back.
4. Patients often complain of tingling, lancinating pains, burning, and a deep aching.
5. Although there may be mild atrophy and weakness of foot intrinsic muscles and ankle dorsiflexors, significant weakness is uncommon and seen in advanced cases.
6. Patients with DSPN can also develop symptoms and signs of an autonomic neuropathy.

Electrophysiologic Findings

EMG and NCS demonstrate evidence of a length-dependent, generalized, symmetric, and sensory neuropathy greater than motor polyneuropathy that is primarily axonal in nature.

Treatment

1. Several studies have demonstrated that tight control of glucose may reduce the risk of developing neuropathy or improve the underlying neuropathy.
2. Pancreatic transplantation also results in stabilization or slight improvement.
3. A variety of medications have been used to treat painful symptoms associated with DSPN, including AEDs, antidepressants, sodium channel blockers, and other analgesics with variable success. Our approach to

treating diabetic neuropathic pain is similar to that of any form of painful sensory neuropathies (see Table 10-2).

4. Topical therapy with Lidoderm 5% patch to the feet can be tried first if pain is limited to the feet.
5. Gabapentin, starting at a dosage of 300 to 400 mg t.i.d. and gradually increased as tolerated and necessary up to 1,200 mg t.i.d., can be then used. Other antiepileptics can be tried in lieu of gabapentin, including pregabalin, phenytoin, carbamazepine, and topiramate.
6. If gabapentin and Lidoderm patches are insufficient to control the pain, antidepressant such as nortriptyline and amitriptyline can be used. The dosage is 10 to 25 mg qhs, increased by 25 mg every 3 to 4 weeks up to 100 mg qhs or as tolerated. Duloxetine 60 mg daily is an alternative.
7. Tramadol 50 mg q.i.d. can be given to patients refractory to an AED in combination with a TCA and Lidoderm patches. Fentanyl patches are a reasonable but an extreme resort.
8. We have not found capsaicin cream to be particularly useful, but it could be tried.
9. Treatment of autonomic neuropathy is symptomatic.
   a. Orthostatic hypotension can be treated with fludrocortisone (starting at 0.1 mg b.i.d. given in the morning and early afternoon) or midodrine (10 mg t.i.d.).
   b. Nonsteroidal anti-inflammatory agents may also be of benefit.
   c. Metoclopramide is used to treat diabetic gastroparesis.
   d. Clonidine may help treat persistent diarrhea.
   e. Sildenafil and related drugs are popular in treatment of impotence.
   f. The patient with orthostatic hypotension should be advised to sleep with the entire bed tilted upward 20 to 40 degrees at the head.
10. There should be a focus on foot care, prevention of ulcerations, abrasions, and nail problems.

DIABETIC LUMBOSACRAL RADICULOPLEXUS NEUROPATHY

Background

1. Also known as diabetic amyotrophy, Bruns–Garland syndrome, diabetic lumbosacral radiculoplexus neuropathy, and proximal diabetic neuropathy.
2. This is more commonly affects older patients with DM type II, but it can affect type I diabetics. In approximately one-third of patients, the polyradiculoneuropathy is the presenting manifestation of DM.

Pathophysiology

An immune-mediated microangiopathy has been speculated but not proven.

Prognosis

1. Although the onset is typically unilateral, it is not uncommon for the contralateral leg to become affected several weeks or months later. Rarely, it begins in both legs at the same time.
2. The radiculoplexus neuropathy progresses gradually or in a stepwise fashion, usually over several weeks or months, but cases of worsening over 18 months have been documented.

Diagnosis

Clinical Features

1. The symptoms usually begin unilaterally with severe pain in the low back, hip, and thigh.
2. Within a few days or weeks, atrophy and weakness of proximal and distal muscles in the affected leg are apparent. About half of the patients complain of numbness and paresthesia. The knee jerk is almost always lost on the affected side.
3. The polyradiculoneuropathy is often heralded by severe weight loss.
4. Thoracic mono- or polyradiculopathy and cervical polyradiculoneuropathy may also occur.

Laboratory Features

1. CSF protein concentration is usually mildly elevated, whereas cell count is

normal.
2. ESR may be increased.
3. MRI scans of the lumbosacral roots and plexus can reveal enhancement.

Electrophysiologic Findings

1. In patients with underlying DSPN, electrophysiologic features of a generalized axonal sensorimotor polyneuropathy as described earlier are evident.
2. The NCS and EMG of diabetic amyotrophy reflect multifocal axonal damage to the roots and plexus.
3. Needle EMG demonstrates positive sharp waves and fibrillation potentials in proximal and distal muscles in the affected limbs and in paraspinal muscles. Recruitment of MUAPs is reduced in weak muscle groups. As reinnervation occurs over time, large-amplitude, long-duration, polyphasic MUAPs can be appreciated.

Treatment

1. Small retrospective studies have reported that IVIG, prednisone, and other forms of immunosuppressive therapy are effective in treating patients with diabetic amyotrophy.
2. We generally avoid treating with IVIG, given the increased risk of renal failure because of acute tubular necrosis in diabetics.
3. We have seen that short courses of corticosteroids can help ease the pain associated with the severe polyradiculoneuropathy. This may allow the patients to undergo physical therapy.
   a. We start prednisone 50 mg/d for 1 week and then taper by 10 mg/wk.
   b. This should be done in conjunction with the patient's primary care provider as the glucose needs to be monitored closely and insulin/oral hypoglycemic agents adjusted during this short course of prednisone therapy.

CRITICAL ILLNESS POLYNEUROPATHY

Background

1. As opposed to AIDP and myasthenia gravis, which are the most common neuromuscular causes for admission to an intensive care unit (ICU), weakness that develops in critically ill patients in the ICU setting is caused by critical illness polyneuropathy, critical illness myopathy, or much less commonly, prolonged neuromuscular blockade.
2. In our experience, critical illness myopathy is much more common than critical illness neuropathy.

Pathophysiology

The pathogenic basis of critical illness polyneuropathy is not clear. Episodes of sepsis predispose to its development. Circulating cytokines have been implicated.

Prognosis

In patients who survive the underlying sepsis and multiorgan failure, muscle strength recovers slowly over several months.

Diagnosis

Clinical Features

1. The peripheral neuropathy is often first suspected when the patient is unable to be weaned from a ventilator.
2. It is often difficult to ascertain the degree of sensory loss and modalities if the patient's mental status is altered. Nevertheless, generalized weakness of the limb muscles can be appreciated.
3. Deep tendon reflexes are absent or reduced.

Laboratory Features

1. CSF protein is usually normal or only mildly elevated, unlike AIDP and CIDP in which there is an increased protein concentration.
2. Serum CK levels are normal.

Electrophysiologic Features

1. Motor and sensory nerve NCS are remarkable for reduced or absent potentials.
2. EMG reveals profuse positive sharp waves and fibrillation potentials and decreased recruitment of MUAPs. It is not unusual in patients with severe weakness to be unable to recruit MUAPs.

Treatment

1. There is no specific therapy for critical illness neuropathy other than supportive care and treatment of the underlying sepsis and organ failure.
2. Physical and occupational therapies are essential to prevent contractures and build strength and endurance as the patient recovers.

PARANEOPLASTIC SENSORY NEURONOPATHY/GANGLIONOPATHY

Background

1. This is a subacute neuropathy that develops in the context of systemic cancer. Small cell lung carcinoma is the most common associated malignancy, but cases of carcinoma of the esophagus, breast, ovaries, and kidney and lymphoma have also been reported.
2. The disorder is rare, and most commonly affects women in late-middle life with a mean age of onset of 59 years.
3. Neuropathy often coexists with other paraneoplastic syndromes including cerebellar degeneration and limbic (medial temporal lobe) encephalitis.

Pathophysiology

Antigenic similarity between proteins in the tumor cells and the neurons may lead to an immune response directed against both tumor and neuronal cells or the cells may elaborate an antineural antibody.

Prognosis

The neuropathy generally does not improve with treatment of the tumor or with

immunosuppressive and immunomodulatory therapies.

Diagnosis

Clinical Features

1. The predominant symptoms are the subacute onset of numbness, dysesthesia, and paresthesia beginning distally and then spreading proximally.
2. These symptoms begin in the arms in over 60% and asymmetric in approximately 40% of cases.
3. The onset can be more acute or more insidiously progressive over months.
4. Alterations in mental status, autonomic dysfunction, and cranial nerve abnormalities occur in about two-thirds of patients as a result of a superimposed paraneoplastic encephalomyelitis.
5. While most cases of sensory neuronopathy have only sensory abnormalities, mild weakness may occasionally be evident.
6. The symptoms of the neuropathy may precede those of the cancer by several months or years. Discovery of a sensory neuronopathy should lead to an aggressive evaluation for an underlying malignancy. We obtain a chest computed tomography (CT) scan, mammogram, pelvic CT or ultrasound, and antineuronal nuclear antibodies (anti-Hu).

Laboratory Features

1. CSF may be normal or may demonstrate mild lymphocytic pleocytosis and slightly elevated protein.
2. Type 1 antineuronal nuclear antibody (ANNA-1), also known as “anti-Hu,” can be demonstrated in serum and CSF in patients with small cell carcinoma of the lung complicated by paraneoplastic sensory or sensorimotor polyneuropathy, encephalitis, and cerebellar degeneration.
3. We advise obtaining periodic chest radiograph or chest CT or MRI (e.g., every 6 months) in patients who initially have no identifiable cancer but have a sensory neuronopathy with a positive ANNA-1.

Electrophysiologic Findings

1. NCS reveal low-amplitude or absent SNAPs with normal CMAPs.
2. There may be abnormal SNAPs in the hands when SNAPs are normal in the

legs. This feature is suggestive of a ganglionopathy as opposed to the much more common length-dependent axonopathies in which the sural SNAPs are affected earlier and more severely than the upper limb SNAPs.

Treatment

1. Treatment of the underlying cancer may prolong survival but generally does not affect the course of the underlying neuronopathy. However, there are rare cases of remission following treatment of the tumor.
2. Immunosuppressive and immunomodulatory therapies with prednisone, PE, and IVIG are typically not effective, but there have been infrequent exceptions in patients treated early.
3. Supportive care with treatment of associated neuropathic pain (see Table 10-2).
4. Physical and occupational therapies are helpful.

NEUROPATHY ASSOCIATED WITH POEMS SYNDROME

Background

1. POEMS is a special paraproteinemic neuropathy (P ∇ polyneuropathy, O ∇ organomegaly, E ∇ endocrinopathy, M ∇ monoclonal gammopathy, S ∇ skin changes) that has also been termed "Crow–Fukase syndrome."
2. Patients may display all or none of these features.
3. Most patients have osteosclerotic myeloma, but POEMS can also be seen with Castleman disease, extramedullary plasmacytoma, or a solitary lytic plasmacytoma.

Pathophysiology

The pathogenesis of POEMS syndrome is not clear but likely autoimmune in nature. Increased circulating vascular endothelial growth factor (VEGF) is evident and may be responsible, with various cytokines secreted by the tumor, for leaky capillaries and the organomegaly and skin changes.

Prognosis

1. The neuropathy improves in almost 50% of cases treated with radiation of the bone lesion(s), prednisone, with or without some other form of chemotherapy (such as melphalan).
2. The neuropathy and plasmacytoma usually recur, even in patients with an initial positive response to treatment.
3. Autologous peripheral blood stem cell transplantation (Auto-PBSCT) may be required.

Diagnosis

Clinical Features

1. The neuropathy manifests as tingling, numbness, and weakness of the distal lower limbs that gradually progress proximally in the lower limbs into the upper limbs similar to CIDP.
2. The peripheral neuropathy is usually present for several years prior to establishing the correct diagnosis.

Laboratory Features

1. Most patients have an IgG or IgA-λ chain monoclonal gammopathy.
2. In up to 20% of patients, the monoclonal protein is demonstrated in the urine but not in serum.
3. CSF protein levels are often elevated similar to CIDP.

Radiographic Studies

1. Skeletal survey reveals sclerotic (two-thirds of cases) or mixed sclerotic and lytic bony lesions (one-third of cases), usually in the vertebral bodies, pelvis, or ribs. Bone scan is not adequate to detect these lesions.
2. In 50% of cases, these skeletal lesions, which represent focal plasmacytomas, are multiple.

Electrophysiologic Findings

1. NCS are suggestive of a demyelinating or mixed-axonal and demyelinating sensorimotor peripheral neuropathy similar to CIDP.

2. Needle EMG can demonstrate fibrillation potentials and positive sharp waves with reduced recruitment of MUAPs of long duration and increased amplitude.

Treatment

1. The neuropathy is often refractory to usual treatment given to patients with idiopathic CIDP that POEMS can mimic.
2. The neuropathy may respond to radiation or a surgical excision of an isolated plasmacytoma or to chemotherapy (such as melphalan).
3. A study of Auto-PBSCT in nine patients with POEMS syndrome showed benefit.

NEUROPATHY ASSOCIATED WITH PRIMARY AMYLOIDOSIS

Background

1. Amyloidosis is a relatively nonspecific term to designate heterogeneous disorders that share the unified theme of amyloid deposition in different tissues.
2. Classification of amyloidosis is based on the hereditary or acquired nature of the disease and the identification of the major protein constituent of the accumulating amyloid.
3. Familial amyloidosis is caused by mutations in the genes for transthyretin (TTR), apolipoprotein A-1, or gelsolin. These will be discussed in the section on Charcot–Marie–Tooth Disease.
4. Secondary amyloidosis (AA) is seen in patients with rheumatoid arthritis and other chronic inflammatory diseases and is associated with the accumulation of protein A. Peripheral neuropathy is uncommon.
5. Primary amyloidosis or amyloid light-chain (AL) amyloidosis is the designation given when the amyloid is composed of light chains derived from the systemic circulation. Primary amyloidosis can cause neuropathy and occurs in the setting of multiple myeloma, Waldenström macroglobulinemia, lymphoma, other plasmacytomas or lymphoproliferative

disorders, or without any other identifiable disease.

Pathophysiology

Light chain deposit has either a toxic or mechanical effect on nerve fibers.

Prognosis

The prognosis of patients with AL amyloidosis is poor with a median survival of 2 years. Death is generally secondary to progressive congestive heart failure or renal failure.

Diagnosis

Clinical Features

1. AL amyloidosis is a systemic disorder that typically affects men past the sixth decade of life.
2. Peripheral neuropathy occurs in up to 30% of patients with AL amyloidosis and is the presenting manifestation in one-sixth of cases.
3. Initially, small-fiber modalities are affected, resulting in painful dysesthesia along with diminished pain and temperature sensation.
4. The neuropathy is slowly progressive and eventually symmetric weakness develops, beginning in the distal lower limbs along with large-fiber, discriminatory sensory loss.
5. Most patients develop autonomic involvement with postural hypertension, syncope, impotence, gastrointestinal disturbance, impaired sweating, and loss of bladder control.
6. Carpal tunnel syndrome (CTS) occurs in 25% of patients and may be a presenting manifestation.

Laboratory Features

1. Amyloid deposits are composed of the complete or variable portion of the monoclonal light chain.
2. Lambda (λ) is more common than kappa (κ) light chains (2:1) in AL amyloidosis (in contrast to monoclonal gammopathy of uncertain significance [MGUS] paraproteinemia).

Histopathology

1. Nerve biopsies may reveal amyloid deposition in either a globular or diffuse pattern, infiltrating the epineurial and endoneurial connected tissue and in blood vessel walls.
2. Congo red or metachromatic staining confirms deposits as amyloid.
3. Immunohistochemistry is used to demonstrate that the amyloid deposits are secondary to light chain accumulation as opposed to TTR (familial amyloid polyneuropathy [FAP]).

Electrophysiologic Findings

1. NCS may be normal early on secondary to a propensity to damage small fibers initially.
2. Median neuropathy at the wrist (CTS) is also a common finding.
3. With time, an axonal or mixed-axonal demyelinating sensory greater than motor neuropathy picture develops.

Treatment

1. Chemotherapy with melphalan, prednisone, and colchicine that reduce the concentration of monoclonal proteins has generally been unsatisfactory.
2. Autologous stem cell transplantation may be of benefit in some patients with AL amyloidosis.
3. Supportive care is important (e.g., physical and occupational therapies).
4. Treat autonomic dysfunction as per section on Idiopathic Autonomic Neuropathy and Pure Pandysautonomia.
5. Neuropathic pain can be treated with a variety of medications (see Table 10-2).

NEUROPATHY ASSOCIATED WITH MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE

Background

1. MGUS refers to monoclonal gammopathies occurring in the absence of malignancy including multiple myeloma, other plasmacytomas, and lymphoma. The abnormal serum protein has been called a paraprotein or "M-spike."
2. One of the aforementioned hematopoietic neoplasms may subsequently develop in up to one-third of patients over the years.
3. MGUS neuropathy is heterogeneous in regard to clinical, laboratory, and electrophysiologic features.
4. The neuropathies can be either demyelinating or axonal. Neuropathies associated with an IgM monoclonal protein are typically demyelinating, while IgG and IgA monoclonal gammopathies can be axonal or demyelinating in nature.

Pathophysiology

1. The demyelinating neuropathies are likely immunologic in nature.
2. The relationship of the paraprotein to the axonal neuropathies is less clear. The monoclonal proteins in such cases are not necessarily pathogenic, thus explaining the lack of efficacy of treatments dedicated to lowering the concentration of the monoclonal protein.

Prognosis

1. Demyelinating neuropathies associated with IgM monoclonal gammopathy (often antibodies directed against MAG are usually associated with distal sensory loss and minimal weakness. This so-called distal acquired demyelinating neuropathy is generally relatively refractory to immunosuppressive and immunomodulating therapies.
2. Demyelinating neuropathies associated with IgG or IgA monoclonal gammopathies are indistinguishable from CIDP and are similarly responsive to immunosuppressive and immunomodulatory therapies.
3. Axonal neuropathies with IgM, IgG, or IgA monoclonal gammopathies are typically not responsive to immunotherapy.

Diagnosis

Clinical Features

1. Patients with demyelinating disease can present with symmetric proximal and distal weakness consistent with idiopathic CIDP, or distal sensory loss and minimal weakness as described earlier.
2. Patients with an axonal neuropathy present with distal sensory more than motor loss in a length-dependent fashion.

Laboratory Features

1. At least 50% of the patients with IgM-MGUS neuropathy have antibodies directed against MAG.
2. Elevated CSF protein levels, with normal cell count, are common in patients with the demyelinating form.

Electrophysiologic Findings

1. Depend on the type of neuropathy as described earlier.

Treatment

1. Patients with MGUS neuropathy who fulfill clinical and electrophysiologic criteria for CIDP should be treated with immunotherapy as recommended in the section on CIDP (see Table 10-1).
2. Patients with IgM-MGUS/MAG demyelinating neuropathy and predominantly sensory symptoms are relatively refractory to treatment. We generally do not treat these patients with immunosuppressive agents, IVIG, or PE. The response to rituximab has been inconclusive, but some patients have shown a limited response. A double-blind, placebo-controlled study, however, failed to demonstrate definitive efficacy.

NEUROPATHY FROM LEAD INTOXICATION

Background

1. Lead neuropathy is increasingly rare.
2. Mainly seen in children who consume lead-based paints in older buildings and in industrial workers dealing with metals, batteries, or paints containing

lead products.

Pathophysiology

It is unclear whether the primary target of the toxic insult is the anterior horn cell or more distally the motor nerves.

Prognosis

Progressive disorder if untreated.

Diagnosis

Clinical Features

1. Patients may note the insidious and progressive onset of upper limb weakness. Classically, there is noticeably motor involvement of the radial nerve with a wrist/finger extensor weakness. When the lower limbs are involved, an asymmetric foot drop is frequent.
2. There are few or no sensory complaints and sensory examination for all modalities is usually found to be well preserved.

Laboratory Features

1. Elevated serum coproporphyrin level, basophilic stippling of erythrocytes, and reduced hemoglobin content suggesting a microcytic/hypochromic anemia.
2. A 24-hour urine collection reveals elevated levels of lead excretion.

Electrophysiologic Findings

Motor and sensory NCS and EMG are consistent with an axonal, motor neuropathy greater than sensory neuropathy.

Treatment

1. The most important treatment is removing the source of the exposure.
2. Chelation therapy could be considered depending on the level of toxicity. Agents include calcium disodium ethylenediaminetetraacetate (EDTA),

British anti-Lewisite (BAL), dimercaptosuccinic acid (DMSA), and penicillamine, with variable efficacy.

NEUROPATHY FROM THALLIUM INTOXICATION

Background

Thallium is available as a rodenticide and occasionally may be recognized in persons who are victims of homicide attempts by poisoning.

Pathogenesis

It is not known whether the primary insult is on the neuronal cell body or the axons.

Prognosis

A lethal dose of thallium in humans is rather variable but averages about 1 g or 8 to 15 mg/kg, and death can result in less than 48 hours following a particularly large dose.

Diagnosis

Clinical Features

1. Patients usually present with burning pain and paresthesias in the feet bilaterally, abdominal pain, and vomiting.
2. With severe intoxication, proximal weakness and involvement of the cranial nerves can occur. Some patients require mechanical ventilation caused by respiratory muscle involvement.
3. The hallmark of thallium poisoning is alopecia; however, this may not be evident until the third or fourth week after exposure and can be mild in some patients.

Laboratory Features

1. Serum and urine levels of thallium are increased.
2. Routine laboratory testing can reveal anemia, azotemia, and liver function abnormalities.
3. CSF protein levels are elevated.

Electrophysiologic Findings

EMG and NCS are consistent with a severe axonal sensorimotor polyneuropathy.

Treatment

1. In acute intoxication, potassium ferric ferrocyanide (Prussian blue) may be effective in preventing absorption of thallium from the gut. However, it is not clear if the medication is effective once thallium has been absorbed.
2. Unfortunately, chelating agents have not been found to be particularly useful.
3. Maintaining adequate diuresis will help in eliminating thallium from the body without increasing tissue availability from the serum.

NEUROPATHY FROM ARSENIC INTOXICATION

Background

Arsenic is another heavy metal that can cause a toxic sensorimotor polyneuropathy. The neuropathy begins 5 to 10 days after ingestion of arsenic and progresses for several weeks.

Pathophysiology

The pathogenic basis of arsenic toxicity is not known.

Prognosis

If the dosage ingested is large enough, rapid progression to death secondary to vascular collapse may ensue.

Diagnosis

Clinical Features

1. Abrupt onset of abdominal discomfort, nausea, vomiting, pain, and diarrhea followed within several days by the development of a burning sensation in the feet and hands.
2. Soon thereafter, progressive loss of muscle strength distally develops.
3. With severe intoxication, weakness progresses to proximal muscles and the cranial nerves. Some patients may require mechanical ventilation.
4. Symptoms and signs can mimic GBS.
5. Mees lines, which are transverse lines at the base of the fingernails and toenails, may become evident by 1 or 2 months.

Laboratory Features

1. Clearance from blood is rapid; therefore, serum concentration of arsenic is not diagnostically helpful.
2. Arsenic levels are increased in the urine, hair, or fingernails of affected patients.
3. Similar to lead intoxication, basophilic stippling of erythrocytes as well as aplastic anemia with pancytopenia can occasionally be observed.
4. Increased CSF protein levels without pleocytosis as seen in AIDP can be demonstrated as well.

Electrophysiologic Findings

EMG and NCS are consistent with a severe axonal sensorimotor polyneuropathy.

Treatment

1. Chelation therapy with BAL has yielded inconsistent results in small retrospective studies, and given the low beneficial effect, it is generally not recommended.
2. Treatment is mainly supportive.

NEUROPATHY ASSOCIATED WITH VITAMIN B_{12} DEFICIENCY

Background

1. Vitamin B_{12}–deficient states can occur as a result of dietary deficiency (vegetarian diet), lack of intrinsic factor (pernicious anemia with autoimmune destruction of parietal cells, or gastrectomy), malabsorption syndromes (sprue or lower ileum resection), genetic defects in methionine synthetase, and bacteria (blind-loop syndrome) or parasites (tapeworm).
2. Cobalamin is necessary for demethylation of methyltetrahydrofolate.
3. Tetrahydrofolate, in turn, is important in the production of folate coenzymes, which are required for DNA synthesis.

Pathophysiology

1. The pathogenic mechanism for the neuropathy associated with cobalamin deficiency is not fully known.
2. The neuropathy may result from the earlier noted impairment in DNA synthesis or secondary to some other biochemical defect.

Prognosis

Although the neuropathy may, or may not, improve, further deterioration is prevented by treatment with vitamin B_{12}.

Diagnosis

Clinical Features

1. Patients present with numbness in the distal lower extremities.
2. Numbness may begin in the hands and mimic CTS, but this is secondary to the myelopathy associated with vitamin B_{12} deficiency and not the neuropathy.
3. The combination of hyporeflexia at the ankles, hyperreflexia elsewhere and extensor plantar responses, in the presence of numb extremities and gait instability should make one suspicious for vitamin B_{12} deficiency.

Laboratory Features

1. Serum vitamin B_{12} levels are decreased or in the low normal range.

2. In patients with vitamin B_{12} levels in the low normal range but with symptoms and signs suggestive of cobalamin deficiency, it is useful to determine serum or urine levels of methylmalonic acid and homocysteine. These metabolites are increased in patients with cobalamin deficiency and can precede the reduction in serum vitamin B_{12} concentrations.
3. A CBC and blood smear can reveal the classic finding of megaloblastic anemia; however, the neurologic complications of cobalamin deficiency can be evident before hematologic abnormalities.
4. Patients with an autoimmune basis for their vitamin B_{12} deficiency (pernicious anemia) may have autoantibodies directed against gastric parietal cells.

Electrophysiologic Findings

1. EMG and NCS reveal features of an axonal sensory greater than motor polyneuropathy.
2. Somatosensory evoked potentials and magnetic stimulation demonstrate slowing of central conduction.

Treatment

Cobalamin deficiency is treated with intramuscular (IM) injections of vitamin B_{12} 1 g daily for 5 days and then 1 g IM every month. Oral treatment has also been shown to be effective.

NEUROPATHY ASSOCIATED WITH COPPER DEFICIENCY

Background

Copper deficiency can cause a myeloneuropathy that is indistinguishable from the subacute combined degeneration of vitamin B_{12} deficiency.

Pathophysiology

1. Copper is absorbed in the stomach and proximal jejunum, and thus,

deficiency may arise as a complication of gastric surgery.

2. Excess zinc intake can cause copper deficiency because zinc upregulates enterocyte production of metallothionein, which results in decreased absorption of copper.
   a. Denture adhesives are a major source of zinc and probably the cause of copper deficiency. Cold medicines and over-the-counter zinc supplements are other sources.
   b. Other potential causes of copper deficiency include malnutrition, prematurity, total parenteral nutrition, and ingestion of copper chelating agents.

Prognosis

1. Hematologic features usually completely normalize with copper replacement therapy.
2. The degree of clinical improvement in the myeloneuropathy is more variable, and residual deficits are common.

Diagnosis

Clinical Features

1. Copper deficiency is associated with an unusual myeloneuropathy, neutropenia, and sometimes pancytopenia.
2. Most patients manifest with numbness and tingling in the legs, weakness, spasticity, and gait difficulties that closely simulate the subacute combined degeneration of vitamin B_{12} deficiency.

Laboratory Features

1. In addition to low serum copper, ceruloplasmin level may be low and the zinc level may be elevated.
2. Patients may also have pancytopenia.
3. Spine MRI may demonstrate abnormal T2-weighted signal in the dorsal columns.

Electrophysiologic Findings

1. NCS reveal features of an axonal sensorimotor polyneuropathy.
2. Somatosensory evoked potentials demonstrate impaired conduction in the central pathways.

Treatment

1. Zinc intoxication, if present, should be resolved. Although this may restore copper levels back to normal, it is usually a very slow process.
2. Replacement usually requires oral copper sulfate or gluconate (2 mg one to three times daily) or, if oral replacement is inadequate, IV copper sulfate or copper chloride (2 mg daily for 3 to 5 days followed by weekly infusions for 1 to 2 months until levels normalize).
3. Depending on the etiology, continuing on 2 mg/d oral copper may be needed to maintain normal serum levels.
4. Periodic assessment of serum copper is essential to determine adequacy of replacement.

NEUROPATHY ASSOCIATED WITH VITAMIN E DEFICIENCY

Background

Three major conditions are associated with vitamin E deficiency:

1. Deficient fat absorption (e.g., cystic fibrosis, chronic cholestasis, short-bowel syndrome, and intestinal lymphangiectasia)
2. Deficient fat transport (abetalipoproteinemia, hypobetalipoproteinemia, normotriglyceridemic abetalipoproteinemia, and chylomicron retention disease)
3. Genetically based abnormality of vitamin E metabolism

Pathophysiology

1. The pathogenic basis for the neuropathy is unknown.
2. Vitamin E has antioxidant properties and may serve to modulate glutamate excitotoxicity.

3. The dorsal root ganglia and posterior column nuclei have the lowest concentrations of vitamin E in the nervous system.
4. Low concentrations of vitamin E may leave these neurons particularly vulnerable to deficiency of the vitamin and its possible neuroprotective effects.

Prognosis

Early recognition is imperative because treatment can arrest and sometimes reverse the neurologic symptoms.

Diagnosis

Clinical Features

1. Patients present with numbness, incoordination, and gait instability.
2. Physical examination reveals loss of vibratory perception, proprioception, a positive Romberg test, and ataxia. Muscle stretch reflexes are reduced.
3. Ocular examination reveals ophthalmoplegia and retinopathy in patients with significant disease.

Laboratory Features

Serum vitamin E level is reduced.

Electrophysiologic Findings

1. Sensory NCS reveal reduced amplitudes or are absent.
2. Somatosensory evoked potentials demonstrate normal peripheral nerve potentials with marked slowing and attenuation of central responses documenting slowing of central conduction with loss of posterior column fibers.
3. Motor conduction studies are normal.

Treatment

1. Treatment can be done with 800 to 1,200 mg of α-tocopherol per day, but patients with abetalipoproteinemia may need as much as 5,000 to 7,000 mg/d.

2. Patients with malabsorption syndromes may require water-miscible vitamin E preparations or IM injections of vitamin E.

CHRONIC CRYPTOGENIC (IDIOPATHIC) SENSORY OR SENSORIMOTOR POLYNEUROPATHY

Background

1. Chronic acquired sensory or sensory motor polyneuropathies occur in approximately 3% of middle-aged to older adults.
2. Despite extensive evaluation, the cause of as many as 50% of polyneuropathies cannot be determined, and these are categorized as chronic cryptogenic sensory (idiopathic) polyneuropathy (CSPN).

Pathophysiology

The pathogenic basis is, by definition, not known.

Prognosis

1. Sensory symptoms begin in the toes, slowly progress up the legs, and eventually reach the distal upper limbs.
2. In about 50% of patients, sensory symptoms are confined to the lower limbs.
3. The average time to involvement of the upper limbs is about 5 years.
4. Mild distal weakness and atrophy involving foot intrinsic muscles may develop overtime.
5. The ankle muscle stretch reflex is usually absent unless they have pure small fiber sensory polyneuropathy.

Diagnosis

Clinical Features

1. Most patients present with sensory symptoms between the ages of 45 and 70

years.

2. Patients often complain of numbness, tingling, or pain (e.g., sharp stabbing paresthesias, burning, or deep aching sensation) in the feet.

Laboratory Features

1. The diagnosis of chronic idiopathic polyneuropathy is one of exclusion.
2. Laboratory testing for fasting blood sugar; hemoglobin A1c; antinuclear antibody (ANA); ESR; serum and urine protein electrophoresis/immunofixation; serum free light chains; vitamin B_{12} level; and thyroid, liver, and renal functions should all be normal.

Electrophysiologic Findings

1. Sensory NCS demonstrate either absent or reduced amplitudes, particularly of the sural SNAPs.
2. Motor conduction tests demonstrate reduced amplitudes of peroneal and posterior tibial nerves in about 60%.
3. EMG may reveal positive sharp waves, fibrillation potentials, and reduced recruitment in distal lower limb muscles.
4. Within this category, there are patients that appear to have pure small-fiber sensory neuropathies.
   a. By definition, these patients have normal nerve conduction.
   b. Skin biopsies can be performed to measure the density of intraepidermal nerve fibers.

Treatment

1. There is no treatment for slowing the progression or reversing the "numbness" or lack of sensation.
2. Treatment of the painful paresthesias and burning sensation associated with chronic idiopathic sensory neuropathy is similar to the treatment of neuropathic pain regardless of etiology (e.g., painful sensory neuropathies related to DM, HIV infection, herpes zoster infection) (see Table 10-2).

ENTRAPMENT/COMPRESSION

NEUROPATHIES

Background

1. The most common entrapment neuropathies in the arms involve the median nerve at the wrist (CTS) and ulnar neuropathies at the elbow and lesser extent at the wrist.
2. In the legs, peroneal (fibular) neuropathy across the fibular head is the most common.

Pathophysiology

Compression of these nerves initially leads to focal demyelination with focal slowing and block of conduction. If compression is severe and prolonged, secondary axonal loss ensues.

Prognosis

Most patients improve with surgery if conservative treatment fails.

Diagnosis

1. Patients describe numbness, paresthesias, and weakness in the distribution of affected nerves.
2. NCS are used to demonstrate focal slowing and/or conduction block across area of compression.
3. Ultrasound can be used to demonstrate focal swelling of nerves at sites of compression, as well as showing other anatomical details that may useful in diagnosis (e.g., the presence of cysts or anatomical variations).

Treatment

1. CTS
   - **a.** Conservative therapy with neutral angle wrist splints, a nonsteroidal medication (e.g., ibuprofen 200 to 800 mg t.i.d. to q.i.d.) is initiated in patients with suspected CTS.
   - **b.** If no relief with conservative management, we refer patients to a hand surgeon.

2. Ulnar neuropathy at the elbow
   a. Instruct patients on not leaning on elbow.
   b. Elbow pad to buffer the ulnar nerve against compression.
   c. If no improvement with conservative management, we refer for surgery.
3. Ulnar neuropathy at the wrist
   a. It is important to image the hand with ultrasound or MRI to look for structural abnormalities (e.g., ganglion cysts) that might be compressing the nerve.
   b. If such abnormalities are evident, surgery is recommended; otherwise, management is supportive with physical and occupational therapies.
4. Peroneal (fibular) neuropathy at the fibular head
   a. Cause is usually external compression (e.g., crossing legs or cysts) rather than entrapment.
   b. One could consider imaging of the peroneal nerve with MRI or ultrasound if a source for external compression is not clear (e.g., habitual leg crossing).
   c. Treatment is conservative, such as avoiding leg crossing, physical therapy, ankle–foot orthosis for foot drop, unless there are abnormalities that require surgical intervention.

CHARCOT–MARIE–TOOTH DISEASE

Background

The various categories of CMT are subclassified according to the nature of the pathology (e.g., demyelinating or axonal), mode of inheritance (autosomal dominant, autosomal recessive, or X-linked), age of onset (e.g., infancy or childhood/adulthood), and the specific mutated gene (see Table 11-1 in *Neuromuscular Disorders, 2nd Edition* by Amato and Russell).

Pathophysiology

Mutations have been identified in various genes in the different forms of CMT, with new mutations being identified at a fast pace. Recent information can be found at http://www.molgen.ua.ac.be/CMTMutations and clinical laboratories

for genetic testing can be found at http://www.genetests.org

Prognosis

There is a broad spectrum of severity, even within the specific subtypes of CMT.

Diagnosis

1. CMT1
   - **a.** Includes autosomal dominant and demyelinating CMTs.
   - **b.** Most common form of hereditary neuropathy. CMT1A (*PMP22* duplication) is the most common form of CMT1, representing 70% of the cases, followed by CMT1B (*MPZ* mutation) that represents 20%. The remaining 10% belongs to one of the other subtypes (CMT1C-G).
   - **c.** Usually manifests in the first to third decades, with atrophy and weakness of the peroneal muscle groups resulting in progressive foot drop. Atrophy and weakness of the hand intrinsic muscles follows.
   - **d.** Most patients have pes cavus or equinovarus and hammertoes.
   - **e.** Electrophysiologic findings
     - **1)** The sensory NCS in both the upper and the lower limbs are usually markedly abnormal in most patients with CMT1.
     - **2)** Motor NCS reveal markedly prolonged distal latencies and slow conduction velocities, usually in the range of 20 to 25 m/s. Unlike acquired demyelinating neuropathies (AIDP/GBS and CIDP), conduction block and temporal dispersion are not seen.
   - **f.** Genetic testing is available for the most common subtypes.

2. CMT2
   - **a.** Includes autosomal dominant and axonal CMTs.
   - **b.** Half as common as CMT1 with CMT2A2 (*MFN2* mutation) being the most common subtype, comprising one-third of CMT2 cases.
   - **c.** The peak age of symptom onset in CMT2 is usually in the second decade, with some patients becoming symptomatic only in their seventh decade.
   - **d.** Clinical features are very similar to those of CMT1. CMT2C is associated with vocal cord paralysis and diaphragmatic weakness and may present in infancy or early childhood.

e. Electrophysiologic findings
   1) The electrodiagnostic findings in the various subtypes of CMT2 are quite distinct from those in CMT1.
   2) Sensory and motor NCS reveal reduced SNAP and CMAP amplitudes in both the upper and the lower limbs.
   3) Distal latencies are either normal or only mildly prolonged and conduction velocities are also normal or only mildly slow.

f. Commercial genetic testing is available for only some types of CMT2.

3. CMT3 (Dejerine–Sottas disease, congenital hypomyelinating neuropathy)

a. CMT3 has been removed from recent classifications of CMT, with Dejerine–Sottas disease remaining as a clinical syndrome, given it is a severe presentation of CMT with mutation of genes classified under CMT1 (*PMP22*, *MPZ*, and *ERG2*).

b. Manifests as generalized weakness and hypotonia at birth.

c. Respiratory distress and swallowing difficulties are not uncommon, and unfortunately, the course is usually terminal in days to a few months.

d. In less severe cases, infants appear normal at birth, but motor milestones are delayed. Some children achieve independent ambulation, although it may take several years.

e. Electrophysiologic findings
   1) The characteristic nerve conduction findings in Dejerine–Sottas are the profound demyelinating features.
   2) SNAPs are usually unobtainable.
   3) Motor nerve conduction velocities are markedly slow (typically 5 to 10 m/s or less); distal latencies are very prolonged with only moderately reduced amplitudes.

4. CMT4

a. Includes autosomal recessive demyelinating and axonal CMTs. Some authorities, however, classify autosomal recessive axonal CMTs as AR-CMT2.

b. May resemble CMT1 clinically and electrophysiologically.

c. Onset can be in infancy or early adulthood.

d. Nerve biopsies reveal severe hypomyelination.

e. Electrophysiologic findings
   1) SNAPs are generally unobtainable.

2) CMAPs are usually reduced in amplitude.
3) Motor NCS are slow, ranging from less than 10 to 30 m/s.

f. Genetic testing is available for some types of CMT4.

5. X-linked Charcot–Marie–Tooth disease (CMTX)

a. CMTX is an X-linked dominant disorder that has clinical features similar to CMT1 except that the neuropathy is much more severe in men than in women.

b. CMTX comprises approximately 12% of the overall CMT cases.

c. Onset in men usually occurs in the first two decades of life. In contrast to men, obligate women carriers are frequently asymptomatic.

d. Electrophysiologic findings

1) NCS abnormalities are consistent with demyelination and axonal degeneration and are much more prominent in men compared to women.
2) SNAPs are reduced in amplitude or absent in most patients. When obtainable, the distal latencies and conduction velocities of the SNAPs are slow.
3) Motor nerve conductions reveal normal or moderately reduced amplitudes.
4) Distal motor latencies are prolonged in men more than women.
5) In men, motor conduction velocities are in the range of 30 m/s, whereas in women, they are slightly faster, in the range of 35 to 45 m/s.

e. Genetic testing is available to screen for mutations in the connexin 32 gene.

Treatment

1. There are no specific medical therapies available to reverse or slow the progression of the various forms of CMT.

2. Primary treatment is supportive.

3. Physical and occupational therapies are essential to prevent contractures and optimize the patient's functional capabilities.

4. Some patients with foot drop will benefit from bracing (e.g., ankle–foot orthosis for foot drop). Bracing of the hands and fingers at night, although cumbersome, may help prevent claw deformities of the fingers.

5. Other orthotic devices may be useful to help with distal hand intrinsic weakness.
6. Genetic counseling is imperative for the patient and other family members.

HEREDITARY SENSORY AND AUTONOMIC NEUROPATHIES

Background

There is a group of rare disorders described as hereditary sensory and autonomic neuropathies (HSANs). Unlike CMTs, in which motor findings are most prominent, loss of sensory and autonomic function predominate in HSANs. There are classified into seven main types and can be inherited in an autosomal dominant or recessive pattern (see Table 11-3 in *Neuromuscular Disorders, 2nd Edition* by Amato and Russell).

Pathophysiology

Mutations have been identified in various genes for the different subtypes of HSAN. HSAN1 is the most common subtype (*SPTLC1* mutation).

Prognosis

These disorders are progressive, but the morbidity and mortality are variable in the different subtypes.

Diagnosis

Genetic testing is available for some HSANs.

Treatment

1. There are no specific medical therapies available.
2. Treatment is primarily supportive.
3. Prevention of mutilating skin lesions with instruction to patients and families regarding the risk of trauma caused by insensitivity of pain.
4. Appropriate antibiotics to treat skin ulcerations and osteomyelitis bone

lesions.

5. Physical and occupational therapy.

FAMILIAL AMYLOID POLYNEUROPATHIES

Background

There are several forms of FAP.

Pathophysiology

Mutations in the genes for *TTR*, apolipoprotein A1, or gelsolin are responsible for the various forms of FAP. Mutations in *TTR* are the most common cause.

Prognosis

Most patients die by the age of 50 years from systemic complications, although some patients do not manifest symptoms until late in life.

Diagnosis

1. TTR-associated FAP.
   - **a.** Characterized by the development of a generalized or multifocal sensorimotor polyneuropathy.
   - **b.** Superimposed CTS is common and may be presenting feature.
   - **c.** Patients usually develop numbness in the distal lower limbs in the third decade of life. Pain and temperature sensation are the most common modalities affected. Patients often describe stabbing, lancinating pains in the feet.
   - **d.** Autonomic dysfunction can be quite severe, resulting in impotence, postural hypotension, constipation, or persistent diarrhea.
   - **e.** Later in the course of the illness, distal limb atrophy and weakness can be appreciated.
   - **f.** Occasionally, cranial neuropathies develop.
   - **g.** Vitreous opacities may also be apparent.
2. Apolipoprotein A1-associated FAP

   a. Patients develop numbness and painful dysesthesia in the lower limbs in the fourth decade of life. Muscle weakness and atrophy is also seen.
   b. Symptoms progress to the distal upper limbs and more proximally.
   c. Autonomic neuropathy is not severe, but some patients develop diarrhea, constipation, and gastroparesis.

3. Gelsolin-associated FAP
   a. Characterized by the combination of lattice corneal dystrophy and multiple cranial neuropathies (e.g., facial palsies and bulbar weakness).
   b. Onset of symptoms is usually in the third decade of life.
   c. Over time, a mild generalized sensorimotor polyneuropathy develops.

4. Electrophysiologic studies reveal abnormalities consistent with a generalized or multifocal, axonal sensorimotor polyneuropathy.
5. Diagnosis of FAP can be made on genetic testing or by detection of amyloid deposition in abdominal fat pad, rectal, or nerve biopsies.

Treatment

1. Because the liver produces 90% of the body's TTR, liver transplantation has been used to treat FAP related to *TTR* mutations. Serum TTR levels decrease after transplantation, and improvement in clinical and neurophysiologic features has been reported. However, abnormal TTR can continue to be synthesized in the CNS (by the choroid plexus) and within the eyes and potentially result in progressive deficits from local accumulation in these areas.
2. Tafamidis and diflunisal are TTR stabilizers that appear to prevent TTR tetramer dissociation. Diflunisal is commercially available, and a dose of 250 mg p.o. b.i.d. has been reported to reduce the rate of progression in TTR-FAP. Tafamidis 20 mg daily is available in Europe but is not yet FDA-approved.
3. There are no other specific medical or surgical therapies for the other FAPs.
4. Treatment is largely supportive.
5. Neuropathic pain can be treated with a variety of medications (see Table 10-2).
6. Autonomic symptoms also may be partially responsive to therapy (see section on Idiopathic Autonomic Neuropathy and Pure Pandysautonomia).

FABRY DISEASE

Background

Fabry disease (angiokeratoma corporis diffusum) is an X-linked disorder that usually manifests in males in childhood or adolescence. Recent studies have indicated a high prevalence of disabling clinical symptoms in heterozygous female patients.

Pathophysiology

The disorder is caused by mutations in the α-galactosidase gene located on chromosome Xq21–22.

Prognosis

The course of the disease is slowly progressive. The major manifestation of the disorder is premature atherosclerosis leading to hypertension, renal failure, cardiac disease, stroke, and death by the fifth decade of life.

Diagnosis

Clinical Features

1. Patients present with burning or stabbing pain in the hands and feet.
2. Characteristic skin lesions (angiokeratomas), which appear as a reddish purple maculopapular rash around the umbilicus, scrotum, inguinal, and perineum can be seen. In addition, punctate red angiectasias are present in the nail beds, oral mucosa, and conjunctiva.
3. Occasionally, women carriers develop a mild painful sensory neuropathy.
4. Some men and women having a cardiac variant develop a severe dilated cardiomyopathy.

Laboratory Features

A decrease in α-galactosidase activity can be demonstrated in leukocytes and cultured fibroblasts.

Electrophysiologic Findings

As this disorder affects mainly small myelinated and unmyelinated nerve fibers, NCS and needle EMG are typically normal.

Treatment

1. Treatment of systemic manifestations (e.g., hypertension, cardiac disease, renal insufficiency, and stroke).
2. Treat neuropathic pain (see Table 10-2).
3. Enzyme replacement therapy (ERT) with recombinant α-galactosidase (Fabrazyme) 1 mg/kg IV infusion every 2 weeks has been proven to be beneficial in regard to the nephropathy. ERT has been associated with a reduction in neuropathic pain and an improvement of some neurophysiologic data but does not completely normalize the function of the PNS.

REFSUM DISEASE

Background

1. Refsum disease is a peroxisomal disorder of lipid metabolism in which phytanic acid fails to undergo α-oxidation.
2. The disease can manifest in infancy to early adulthood.
3. A tetrad of symptoms form the cardinal clinical features of the disorder:
   - **a.** Peripheral neuropathy
   - **b.** Retinitis pigmentosa (often the earliest symptom that manifests as night blindness)
   - **c.** Evidence of cerebellar dysfunction
   - **d.** Elevated protein content in the CSF

Pathophysiology

1. This disease is inherited in an autosomal recessive manner and appears to be genetically heterogenic.
2. Refsum disease with childhood or early adulthood onset has been linked to mutations in the phytanoyl-CoA α-hydroxylase gene. Phytanic acid

accumulates in various organs including the CNS and PNS, leading to neuronal degeneration.

3. Mutations in various genes encoding for peroxins (proteins involved in the peroxisomal transport/import, biogenesis, and proliferation) are suspected to be alternative causes of Refsum disease, especially in the infantile type.

Prognosis

It is important to diagnose Refsum syndrome early because it is potentially treatable.

Diagnosis

Clinical Features

1. Infantile Refsum disease falls within the clinical spectrum of Zellweger syndrome and neonatal adrenoleukodystrophy (ALD), albeit much milder in severity.
2. Typical Refsum disease is associated with sensorineural hearing loss, cardiac conduction abnormalities, neuropathy, and dermal alterations (ichthyosis) that usually manifest in most patients by the end of the second decade.
3. Distal lower limb muscle wasting and weakness (e.g., bilateral foot drop) are evident early. The relentless nature of the disease results in muscle weakness progressing proximally to involve both the lower and the upper limbs.
4. Some patients may complain of paresthesias and spontaneous pain sensations in the limbs.
5. The neuropathy can have a fluctuating course.

Laboratory Features

Serum phytanic acid levels are increased.

Electrophysiologic Findings

Motor and sensory NCS may demonstrate features suggestive of a primary demyelinating or axonal, generalized sensorimotor polyneuropathy.

Treatment

Elimination of phytanic precursors (phytols: fish oils, dairy products, and ruminant fats) from the diet may help patients with respect to reducing the clinical complications of the disease.

PORPHYRIC NEUROPATHIES

Background

1. The porphyrias are a group of inherited disorders caused by defects in heme biosynthesis. There are three major forms of porphyria that are associated with neuropathy: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), and variegate porphyria (VP).
2. Regardless of the type of porphyria inherited, the acute neurologic manifestations are quite similar and can affect the CNS and PNS.
3. Patients with HCP and VP can exhibit photosensitive skin lesions, which are not seen in AIP.
4. Attacks of porphyria can be precipitated by certain drugs, hormonal changes (e.g., pregnancy, luteal phase of the menstrual cycle), and dietary restrictions.
5. Any drug that is metabolized by the cytochrome P450 system in the liver can induce an attack of porphyria.

Pathophysiology

The porphyrias are inherited in an autosomal dominant fashion. AIP is associated with porphobilinogen deaminase deficiency, HCP is caused by defects in coproporphyrin oxidase, and VP is associated with protoporphyrinogen oxidase deficiency.

Prognosis

The neuropathy improves with treatment.

Diagnosis

Clinical Features

1. Patients experiencing an attack of porphyria often complain of acute abdominal pain that can mimic a surgical abdomen.
2. Soon thereafter is the development of agitation and restlessness that can progress to overt hallucinations and seizures.
3. Within 48 to 72 hours, the onset of lower limb and back pain followed by motor weakness resembling GBS occurs.
4. Patients may complain of numbness and paresthesias, although sensory loss can be hard to determine given the patients' mental state.
5. The deep tendon reflexes are variably diminished.
6. Autonomic dysfunction manifested by signs of sympathetic overactivity (e.g., pupillary dilatation, tachycardia, and hypertension) is common.

Laboratory Features

1. The CSF protein can be normal or mildly elevated.
2. The urine may be brown secondary to the high concentration of porphyrin metabolites.
3. The diagnosis is made by evaluating the urine or stool for the accumulating intermediary precursors of heme (i.e., δ-aminolevulinic acid, porphobilinogen, uroporphobilinogen, coproporphyrinogen, and protoporphyrinogen). The specific lowered enzyme activities can also be measured in erythrocytes and leukocytes.
4. Genetic screening for AIP is commercially available.

Electrophysiologic Findings

1. Motor NCS reveal decreased amplitudes with normal or only mildly reduced nerve conduction velocities and normal and occasional mild prolongation of the distal motor latencies.
2. Sensory NCS usually demonstrate preservation of SNAP conduction velocities and distal sensory latencies. A reduction in SNAP amplitudes can be seen in some patients, but this is not as common as the finding of reduced CMAP amplitudes.
3. EMG during the acute stage of weakness demonstrates primarily a reduced recruitment. Over the course of the next 4 to 6 weeks, in those patients with significant clinical weakness, fibrillation potentials and positive sharp

waves can be observed in the affected muscles.

Treatment

1. The primary treatment is prevention by awareness of drugs that can precipitate the acute porphyric attack in patients with known porphyria.
2. Once an attack occurs, hematin and glucose should be administered to prevent the accumulation of heme precursors.
3. Autonomic symptoms are treated as discussed in the section on Idiopathic Autonomic Neuropathy and Pure Pandysautonomia.
4. Supportive therapy as discussed in the section on Guillain–Barré Syndrome.

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11 Chronic Pain

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BACKGROUND

Definitions

1. *Pain* is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
2. *Chronic pain* is pain that persists beyond the normal time of healing, typically 3 to 6 months.
3. *Allodynia* is pain caused by a stimulus that does not normally provoke pain.
4. *Analgesia* is absence of pain to a normally painful stimulus.
5. *Paresthesia* is an abnormal sensation, whether spontaneous or evoked.
6. *Hyperalgesia* is increased pain from a stimulus that normally provokes pain.
7. *Primary hyperalgesia* is increased pain in the area of tissue injury, typically caused by peripheral sensitization.
8. *Secondary hyperalgesia* is increased pain beyond the anatomical area of injury, typically caused by central sensitization.
9. *Temporal summation* is an increasing pain sensation from a repetitive, equal stimulus, typically caused by central sensitization.
10. *Peripheral sensitization* is a decreased pain threshold and increased responsiveness of (peripheral) nociceptors and results in primary hyperalgesia.
11. *Central sensitization* is an increased responsiveness of nociceptive neurons in the central nervous system (CNS) to their normal or subthreshold afferent input and results in secondary hyperalgesia.
12. *Nociceptors* are high-threshold primary sensory neurons, which run in thinly myelinated A-δ and unmyelinated C-fiber. Transducing ion channels enable them to sense mechanical, temperature, and chemical stimuli.

Epidemiology

1. Pain affects more Americans than diabetes, heart disease, and cancer combined, and chronic pain is estimated to afflict about 30% of the adult population in the United States.
2. Pain is the most common reason Americans access the health care system and is the most common cause of long-term disability and a major contributor to health care cost.
3. The most common pain conditions are chronic low back pain, neck pain, and headaches, followed by large joint pain (hip, knee, shoulder) and to a lesser degree hand/wrist and ankle/foot pain as well as abdominal pain.
4. Most chronic pain conditions are more common in females.
5. Prevalence of headaches peaks around age 30 years, whereas most other chronic pain conditions have increased prevalence with age mostly because of arthritic conditions.
6. At least 50% of patients with cancer have chronic pain as a prominent symptom of their disease, and these numbers increase for certain cancer types/locations (e.g., head/neck cancer) and for advanced stages, in which pain control often becomes the focus of clinical management.

Classification

1. Pain can be classified according to its anatomical location, pathologic state, or underlying cellular mechanism.
   - **a.** In clinical practice, there is a strong emphasis on anatomical location (e.g., low back pain caused by facet joint disease, disc disease, muscle spasms) especially among surgical and interventional specialties.
   - **b.** Identifying distinct pathologic pain states can be challenging, because they often coexist, for example, herniated disc causing changes in mechanical joint pressure (nociceptive pain), an inflammatory response in the surrounding tissue (inflammatory pain) as well as compression/ damage to the nerve root (neuropathic pain).
   - **c.** Cellular mechanisms are currently almost impossible to detect clinically, except in distinct genetic pain conditions and possibly by elaborate quantitative sensory testing (QST).

Anatomical Classification (Exemplified by Pain of Spine

Origin)

1. Facet joint disease: Osteoarthrosis, osteoarthritis (secondary to degenerative changes or underlying rheumatologic disease), facet cyst
2. Disc disease: Degenerative disc disease, disc herniation
3. Bone disease: Caused by fracture or neoplasm
4. Nerve root disease: Compression by herniated disc, bone (bone spur, antero- or retrolisthesis), facet cyst, or muscle spasm (e.g., piriformis syndrome); infiltration by neoplasm; immune-mediated inflammation (e.g., diabetic radiculoplexus neuropathy, chronic inflammatory demyelinating disease [CIDP])
5. Myofascial pain

Pathologic State

1. *Nociceptive pain*: Caused by activation of nociceptors (high-threshold primary sensory neurons) by intense, typically in the case of clinical pain, mechanical stimuli. Examples include
   - **a.** Deep somatic nociceptive pain caused by, e.g., joint capsule stretch, increased mechanical forces on spinal discs because of degenerative destruction of facet joints, nerve impingements.
   - **b.** Superficial somatic nociceptive pain includes skin damage from trauma, chemical and thermal stimuli, and irritation of mucous membranes.
   - **c.** Visceral nociceptive pain is typically poorly localized because of the low nociceptive density and extensive divergence of visceral input within the CNS. It can result from distention or compression of all visceral organs and especially their visceral capsule.
2. *Inflammatory pain*: Caused by activation and sensitization of nociceptors by inflammatory mediators. Clinically, there is often an interplay between mechanical irritation and subsequent inflammation.
   - **a.** Tissue damage or inflammation results in release of inflammatory signaling molecules from local immune cells (e.g., prostaglandins, cytokines). These agents can either directly activate transducing ion channels at nociceptor endings or sensitize them, resulting in a lower activation threshold.
   - **b.** Ongoing inflammation can result in longer lasting changes of trafficking, cell surface expression, and gating properties of these nociceptive ion

channels.

c. Ongoing peripheral inflammation induces changes in the affected spinal segments as well as higher brain areas via systemically acting cytokines such as IL-1β, resulting in anatomically more widespread pain and pain triggered by several different stimuli (mechanical, thermal, etc.).

d. Examples of inflammatory pain include

1) *Osteoarthritis*: Joint degeneration (osteoarthrosis), which can result in an inflammatory immune response, leading to further destruction of the joint and eventually, chronic inflammation. Most common joints affected are knee, hip, facet joints, and hands.

2) *Primary/autoimmune synovitis* as seen in rheumatologic arthritides (e.g., rheumatoid arthritis), where the primary event is an autoimmune inflammation of the synovia, resulting in synovial hyperplasia, joint destruction, and systemic inflammatory symptoms.

3) *Disc herniation*: Release of the immunogenic nucleus and other disc material into close proximity of the nerve root, causing local inflammation of the root and adjacent structures.

4) *Inflammatory diseases* of the visceral organs, for example, cholecystitis, inflammatory bowel disease, tumor infiltration.

5) *Infection* causing secondary, immune-mediated inflammation. In addition, certain gram-negative and gram-positive bacteria can directly activate nociceptive receptors via specific surface antigens.

b. *Neuropathic pain*: Caused by damage to the sensory components of the nervous system, either in the peripheral or central nervous system.

a. *Peripheral neuropathic pain* because of damage of peripheral nerves, plexus, or roots.

1) Systemic diseases, toxicities, or deficiency states cause typically a polyneuropathy or mononeuritis multiplex, whereas a focal process results in a mononeuropathy/radiculopathy.

2) The etiology of neuropathic pain is manyfold: Nerve damage/cut (e.g., postmastectomy pain syndrome, post-inguinal hernia repair pain), mechanical compression (e.g., entrapment neuropathies), ischemia (e.g., because of vasculitis or diabetes), axonal degeneration because of systemic disease (alcohol, diabetes), demyelination (CIDP), postinfectious (postherpetic neuralgia).

3) In many neuropathic pain conditions, there is an element of peripheral

inflammation driving sensitization of the affected nerve/root: Root inflammation from ruptured disc, postsurgical inflammation, mechanical nerve compression, autoimmune inflammation as in CIDP.

4) Neuroma: A tangled mass of regenerating axons embedded within nerve connective tissue, often developing after traumatic nerve severance or amputation (stump neuroma). Because of changes in nociceptive nerve fiber phenotype with upregulation of sodium channels, these nerve bundles show abnormal electrical hyperexcitability and cause spontaneous as well as easily provoked neuropathic pain.

b. *Central neuropathic pain* occurs because of pathology disrupting nociceptive processing anywhere along the CNS. The pathology of the lesion is less important than its anatomical location. Damage to the nerve root entry zone, the spinothalamic tract (STT), or the sensory thalamus by any process can result in central neuropathic pain.

1) Common conditions include ischemic and hemorrhagic stroke, brain or spinal cord tumor or trauma, spinal syringomyelia, demyelination because of multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), etc.

2) For central poststroke pain (CPSP), see page 387.

Pain Mechanisms

1. Nociception

a. Pain-sensing neurons (nociceptors) feature specialized receptors (transducers) at their nerve endings which translate specific stimuli into membrane depolarization. Transducer examples include TRPV1 (heat, capsaicin), TRPM8 (cold), acid-sensing ion channels (ASICs) for free protons, and Piezo2 (mechanical stimulus).

b. Voltage-gated sodium channels (e.g., $Na_{v1.7}$, $Na_{v1.8}$, and $Na_{v1.9}$) can then increase the initial signal, ultimately translating stimulus intensity into action potential frequency. Depending on their activation threshold, these sodium channels can determine the excitability of nociceptors. As an example, a rare $Na_{v1.7}$ mutation can cause either complete inability to sense pain or intense, intermittent pain attacks (erythromelalgia).

2. Pain pathways

a. *A-δ and C-fibers* are the major contributors to physiologic nociception. *A-β fibers* contribute in pathologic states of central sensitization, causing mechanical allodynia.

b. Activation of nociceptors results in the emission of glutamate and peptides at central neurons in the spinal cord dorsal horn (mostly superficial laminae LI and LII with some projections to LV).

c. Modulated afferent information is transmitted via the *anterior and lateral spinothalamic tracts (STTs)* to the *ventral posterior lateral (VPL) subnucleus* of the thalamus, conveying sensations of pain, temperature, and itch from the contralateral side of the body, which ultimately reach the primary *sensory cortex (SM1, SM2)*.

d. *Trigeminothalamic axons* from the spinal nucleus of the trigeminal nerve decussate to the contralateral STT to convey equivalent sensations from the face to the ventral posterior medial (VPM) subnucleus.

e. Other nociceptive projections include collaterals to different *thalamic nuclei*:

1) The posterior ventral medial nucleus (VMpo), which further projects to the posterior insula, where information is integrated with visceral afferent activity (e.g., vagal and gustatory afferents) to influence autonomic responses.

2) The medial dorsal nucleus (MDvc), which relays information to the anterior cingulate cortex and is important for the affective/motivational aspect of pain.

3) The intralaminar thalamic nuclei, which have widespread cortical projections contributing to arousal and attention.

f. *Descending pathways* can modulate incoming afferents at the dorsal horn level and originate in the periaqueductal gray (PEG), the serotoninergic nucleus raphe, and the norepinephrinergic locus coeruleus. They project mainly to superficial spinal laminae (LI and LII) and inhibit via γ-aminobutyric acid (GABA) and glycine-release central projection neurons.

g. Further modulation of incoming signals is mediated by a complex network of inhibitory and excitatory *spinal interneurons*.

3. Peripheral sensitization

a. Decreased threshold and increased responsiveness of nociceptors as a result of posttranslational changes and altered trafficking of transducer

receptors (e.g., TRPV1) and voltage-gated ion channels (e.g., Na_V channels)

b. Typically driven by inflammatory molecules (e.g., bradykinin, histamine, prostaglandins, nerve growth factor) resulting in phosphorylation and therefore sensitization of transducers and sodium channels and, if longer lasting, changes in their expression pattern.

c. Clinically, this results in pain (especially thermal) hypersensitivity confined to the inflamed area (zone of *primary hyperalgesia*).

I. Central sensitization

a. Increased responsiveness of nociceptive neurons in the CNS to their normal or subthreshold afferent input. This occurs in both pain of peripheral and central origin and often coexists with peripheral sensitization.

b. *Activity-dependent mechanisms* (i.e., driven by ongoing peripheral afferent activity) include

1) *Homosynaptic potentiation*: Strengthening of the synapse between the nociceptor and dorsal horn projection neuron. Clinically results in *temporal summation*.

2) *Heterosynaptic potentiation*: Strengthening of synapses between other, non-nociceptive afferents (e.g., Aβ fibers), and dorsal horn projection neurons. Low-threshold Aβ fibers (sensing, e.g., light touch) get to be recruited into the pain pathway, resulting in *mechanical allodynia* as well as pain hypersensitivity outside the primary affected area (zone of *secondary hyperalgesia*).

c. *Spinal disinhibition* of central projection neurons is caused by decreased GABA-ergic and glycinergic tone.

1) Mechanisms include reduced descending inhibitory control, loss of GABA-ergic and glycinergic interneurons through cell death (e.g., after peripheral nerve trauma), reduced GABA levels, and altered properties of $GABA_A$ and glycinergic receptors.

d. *Central inflammation* ensues after peripheral nerve injury and is driven by

1) Neuronally derived mediators activating spinal microglia, which then release molecules causing astrogliosis and invasion of T cells into the spinal cord.

2) Further release of immune mediators from microglia enhances

synaptic neurotransmission by increasing glutamate release as well as AMPA and *N*-methyl-D-aspartate (NMDA) receptor modulation. Astrocytes contribute to increased synaptic glutamate levels by downregulation of spinal astrocyte glutamate transporters.

e. *Brain changes* in chronic pain include (partially reversible) decrease in neocortex gray matter, changes in excitatory and inhibitory transmitters and in functional connectivity of pain-sensing brain areas.

5. The biopsychosocial model

a. The relationship between the nociceptive stimulus ("disease") and the degree of pain reported or pain-related behaviors ("illness") depends on biologic, psychological, and social factors.

b. The level of suffering and the affective and behavioral expression of pain are mediated by cognitive reactions to the nociceptive stimulus and its environmental context (e.g., cancer pain engenders fear and exaggerates the experience of pain).

c. Although the nociceptive component can often not be cured, the affective reaction and behavior can be modulated to reduce disability.

d. Management of chronic pain requires that the treating physician incorporates the multidimensional nature of the pain experience, adjusts treatments, and advises accordingly.

Diagnosis

1. As with any medical specialty, treatment is most impactful if it is geared toward a specific pathology. The goal is to identify a specific anatomical location and/or underlying mechanism of pain generation, which is often difficult and sometimes impossible to do with certainty.

2. Medical diagnosis is hampered by low specificity of subjective symptoms and most physical exam signs, as well as the poor correlation of imaging findings and symptoms. There is no gold standard to diagnose the cause of chronic pain.

3. Along the lines of the biopsychosocial construct, modulating psychological (both affective and cognitive) factors and behaviors can often result in reduced disability and should be evaluated.

4. It is important to adjust patient expectations toward pain reduction/management rather than cure and to define goals more by

functional improvement rather than absolute pain scores. The relentless pursuit of a "definitive" diagnosis is discouraged unless worrisome systemic symptoms or progressive neurologic deficits exist.

Pain Assessment

1. Pain characteristics include
   - **a.** Pain location: focal, radiating, referred, multifocal/whole body
   - **b.** Severity: best to evaluate range (least to worst); several scales can be used:
     - **1)** Numeric rating scale (0 to 10, 0 to 20, or 0 to 100)
     - **2)** Verbal rating scale (e.g., mild, moderate, severe, horrible, excruciating)
     - **3)** Visual analog scale (VAS) (e.g., using drawn faces of pain expression)
   - **c.** Quality of pain (nonspecific, best validated for neuropathic pain)
     - **1)** Characteristics of neuropathic pain (based on pain questionnaires): mechanical and temperature-evoked allodynia, numbness to several modalities, burning/tingling/electric shocklike paresthesias, absence of persistent pain, and presence of intermittent pain attacks
     - **2)** There are no specific symptoms of nociceptive or inflammatory pain.
     - **3)** Typically, several pain states coexist in any given condition.
   - **d.** Temporal profile and frequency: intermittent/ paroxysmal, continuous
   - **e.** Modulating factors: precipitating, aggravating, and relieving pain
   - **f.** Neurologic deficits: changes in tone, involuntary movements or posturing, weakness, paresthesias, numbness, disequilibrium, neuraxial symptoms like bowl and bladder incontinence
   - **g.** Autonomic features: changes in color, temperature, sweating, trophic changes (skin, hair growth, nails)
   - **h.** Symptoms suggestive of more serious systemic pathology: progressive severity/location/neurologic deficit, weight loss, fever, malaise, skin rashes
2. Structured assessments of aforementioned pain characteristics can be done using pain questionnaires: McGill Pain Questionnaire or the Brief Pain Inventory. Correlation to specific pathology or impact on treatment choices is uncertain.
3. Great efforts have been made to identify symptom clusters to identify

subgroups of patients who share common pathology and might respond to a certain treatment. Commonly used and validated pain questionnaires focus on identifying patient with neuropathic pain/neuropathic components and are available in several languages: Douleur Neuropathique 4 (DN4), Neuropathic Pain Questionnaire (NPQ), and painDETECT questionnaire.

Pain-Related Assessment

1. The affective presentation and psychiatric diseases such as anxiety, depression, and posttraumatic stress disorder (PTSD) can play a major role in the patient's disability and should be explored. Useful questionnaires include the Beck Anxiety Inventory, the Beck Depression Inventory, and the Center for Epidemiological Studies-Depression Scale.
2. Behavioral assessment should include evaluation of recent doctor/emergency room visits, pain-specific behaviors (e.g., guarding, moaning), and impairment of activities of daily life and social interactions.
3. The cognitive perception of pain is an important modulator of the pain experience. Beliefs that activity-induced pain causes more damage, that pain controls one's life (helplessness), that a serious illness is the cause of pain, or that pain catastrophizing results in higher disability and should be treated with cognitive behavioral therapy.
4. Psychosocial variables including relationships, work environment, social support, etc., as well as presence of litigation and spiritual attitudes can all influence the patient's pain experience.

Physical Signs in the Examination of the Patient with Chronic Pain

1. A targeted musculoskeletal and neurologic examination should be performed. While many physical exam findings are too unspecific to point toward a specific pain generator, they are most valuable to exclude dangerous conditions.
2. Important physical signs include
   a. *Sensation*: Diminished or absent sensibility to primary sensory modalities, including small fiber (pinprick and temperature) and large fiber (vibration and position sense) modalities, and the anatomical distribution of the deficit: bilateral symmetric versus peripheral nerve

versus dermatomal

b. *Pain*: Increased pain to noxious stimuli in a defined anatomical distribution (e.g., nerve, dermatome, joint) indicates peripheral sensitization and is termed primary hyperalgesia. Pain beyond the anatomical location of a disease process (secondary hyperalgesia) as well as mechanical allodynia and temporal summation (see section on Definitions) indicate central sensitization.

c. *Weakness*: Anatomical distribution of weakness (symmetric vs. peripheral nerve vs. myotomal) and focal/ symmetric loss of reflexes.

d. *Neuraxial symptoms*: Sensory trunk level, increased tone/spasticity (if chronic), Babinski sign, and incontinence

e. *Cranial nerve findings*: Including optic disc visualization (particularly important for head/neck pain)

f. *Autonomic findings*: Vasomotor (swelling, color and temperature changes) and sudomotor (sweating) changes. Particularly important for diagnosing autonomic/small fiber neuropathies and complex regional pain syndrome (CRPS)

g. *Physical maneuvers* (all hampered by lack of gold standard to determine sensitivity and specificity of the maneuver)

1) Straight leg (high sensitivity) and crossed straight leg raise (high specificity) test are indicative of a lumbar radiculopathy or sciatic nerve disease.

2) Spurling test (laterally flexing, rotating, and compressing the patient's head toward the symptomatic side), traction/neck distraction, and the Valsalva maneuver might be suggestive of a cervical radiculopathy (higher specificity), while a negative upper limb traction test might be used to rule it out (higher sensitivity).

3) Musculoskeletal palpation and manipulation of the spine as well as provocative tests for facetogenic and sacroiliac pain show poor diagnostic validity and interobserver reliability.

Special Pain Syndromes

I. Centralized pain

a. *Centralized pain syndrome* is an umbrella term for chronic, often widespread, pain conditions, where there is no noxious stimulus, no detectable inflammation, and no structural damage to the nervous system

or any other tissue. These syndromes likely result from abnormal pain amplification within the CNS (e.g., more pain is felt than expected from any nociceptive input), start typically in adolescence or young adulthood, and manifest by pain experienced in different body regions at different times or simultaneously.

1) *Somatic syndromes*: Fibromyalgia, chronic headache, temporomandibular joint (TMJ) disorder, atypical facial pain, chronic back and neck pain
2) *Visceral syndromes*: Irritable bowel syndrome (IBS), bladder pain syndrome (BPS) (formerly interstitial cystitis), chronic pelvic and abdominal pain, dysmenorrhea
3) *Cognitive syndromes*: Chronic fatigue syndrome, memory and attention disorder
4) *Frequent comorbidities*: Depression, anxiety, sleep disorder, PTSD, obsessive compulsive disorder (OCD), multiple chemical sensitivities/idiopathic environmental intolerances

Fibromyalgia

1. Epidemiology: Prevalence is from 2% to 8% of the population; female-to-male ratio of 2:1, similar to other chronic pain conditions. Fibromyalgia can develop at any age, including in childhood.
2. Diagnosis according to the modified American College of Rheumatology (ACR) 2010 fibromyalgia diagnostic criteria, which requires all of three conditions: (a) Widespread Pain Index ≥7 and Symptom Severity Score ≥5 or Widespread Pain Index between 3 and 6 and Symptom Severity Score ≥9, (b) symptoms have been present at a similar level for at least 3 months, and (c) the patient does not have a disorder that would otherwise sufficiently explain the pain (Fig. 11-1).
3. The physical exam (with exception of diffuse tenderness), lab tests, and imaging are normal and helpful only to exclude other disorders. Establishing the clinical diagnosis can often result in decreased testing/referrals as well as patient relief.
4. Nonpharmacologic treatment
   a. Education about the nature of this condition (e.g., pain does not equal damage) and emphasizing an active role in own care is critical. A suggested website for patients is https://fibroguide.med.umich.edu/

b. Simple interventions such as stress reduction, improved sleep patterns, and increased activity and exercise should be reinforced.

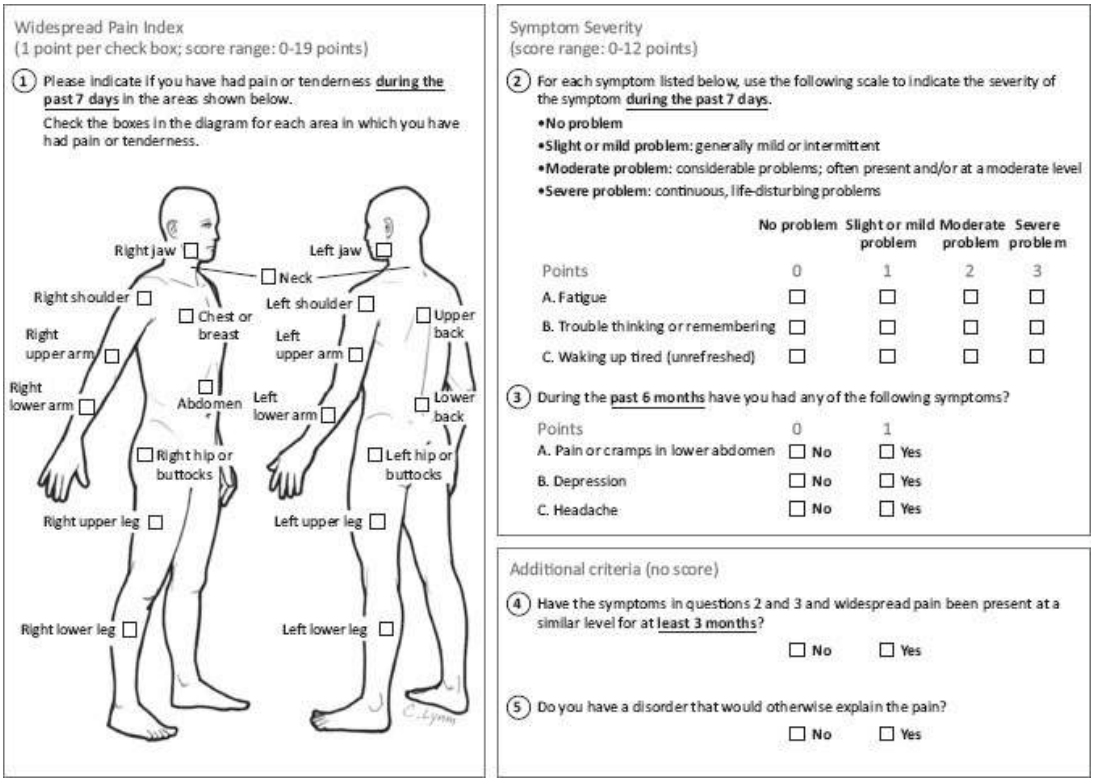

Figure 11-1. A: Widespread Pain Index. Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain? Score will be between 0 and 19. **B:** Symptom Severity Score. Fatigue, waking unrefreshed, and cognitive symptoms. For each of these three symptoms, indicate the level of severity over the past week using the following scale: 0 = No problem; 1 = Slight or mild problems, generally mild or intermittent; 2 = Moderate, considerable problems, often present and/or at a moderate level; 3 = Severe: pervasive, continuous, life-disturbing problems. The Symptom Severity Score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, and cognitive symptoms) plus the sum of the number of the following symptoms occurring during the previous 6 months: headaches, pain or cramps in lower abdomen, and depression (0 to 3). The final score is between 0 and 12.

c. Psychological factors like catastrophizing and fear of movement are treatable by cognitive behavioral therapy.

5. Pharmacologic treatment

a. Should always be used in conjunction with nonpharmacologic strategies

b. Medications with strong evidence include tricyclic antidepressants

(TCAs) (amitriptyline, cyclobenzaprine), gabapentinoids (pregabalin, gabapentin), serotonin norepinephrine reuptake inhibitors (SNRIs) (duloxetine, milnacipran), and γ-hydroxybutyrate.

c. Medications with less evidence include selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, sertraline), low-dose naltrexone, and cannabinoids.

d. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used as adjunct for musculoskeletal pain.

e. The use of opioids is discouraged, as it can increase centralized pain (see section on Opioid-Induced Hyperalgesia).

f. Treatment should consider psychiatric comorbidities: Patients with anxiety and sleep disorder should be preferentially tried on gabapentinoids, while patients with depression might benefit more from SNRIs. All patients should be tried on TCAs.

5. Other therapies

a. There is limited evidence for trigger-point injections, chiropractic manipulation, tai chi, yoga, acupuncture, and myofascial release therapy.

b. Treating with local therapy, despite the central nature of the disease, decreases nociceptive input and might therefore have some benefit.

Somatic Symptom and Related Disorder

1. According to the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*), the category of somatic symptom and related disorders encompasses disorders that are marked by prominent somatic symptoms as well as substantial distress and/or psychosocial impairment. The category includes the following specific disorders:

a. Somatic symptom disorder (SSD)

b. Illness anxiety disorder

c. Conversion disorder (functional neurologic symptom disorder)

d. Psychological factors affecting other medical conditions

e. Factitious disorder

2. *SSD*: A *DSM-5* diagnosis of SSD requires each of the following criteria:

a. One or more somatic symptoms that cause distress or psychosocial impairment

b. Excessive thoughts, feelings, or behaviors associated with the somatic

symptoms, as demonstrated by one or more of the following:

1) Persistent thoughts about the seriousness of the symptoms

2) Persistent, severe anxiety about the symptoms or one's general health

3) The time and energy devoted to the symptoms or health concerns is excessive.

c. Although the specific somatic symptom may change, the disorder is persistent (usually more than 6 months).

d. Of note:

1) SSD is an umbrella term intended to describe most of the patients who had previously held such diagnoses as somatization disorder, pain disorder, and hypochondriasis (all somatoform disorders in *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* [*DSM-IV*]).

2) Diagnosis does not require that the somatic symptoms are medically unexplained. In other words, symptoms may or may not be associated with another medical condition.

3) *DSM-IV* diagnosis of somatization disorder required a specific number of complaints from among four symptom groups. The SSD criteria no longer have such a requirement; however, somatic symptoms must be significantly distressing or disruptive to daily life.

4) *DSM-IV* pain disorder is now classified as SSD with predominant pain.

3. Treatment

a. Pharmacologic treatment of concurrent mental disorders (e.g., depression) may help; however, the primary intervention is psychotherapy, particularly cognitive behavioral therapy.

b. Patients also benefit from having a supportive relationship with a primary care physician, who coordinates all of their health care, offers symptomatic relief, sees them regularly, and protects them from unnecessary tests and procedures.

Complex Regional Pain Syndrome

1. CRPS is a clinical diagnosis, based on the 2010 Budapest Criteria (sensitivity 0.99, specificity 0.68), endorsed by the International Association for the Study of Pain (IASP) and must meet all of the following criteria:

a. Continuing pain, which is disproportionate to any inciting event
b. Must report at least one symptom in three of the four following categories:
  1) Sensory: Reports of hyperesthesia and/or allodynia
  2) Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
  3) Sudomotor/edema: Reports of edema and/or sweating changes and/or sweating asymmetry
  4) Motor/trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
c. Must display at least one sign at time of evaluation in two or more of the following categories:
  1) Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch, temperature sensation, deep somatic pressure, and/or joint movement)
  2) Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
  3) Sudomotor/edema: Evidence of edema, sweating changes, and/or sweating asymmetry
  4) Motor/trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
d. There is no other diagnosis that better explains the signs and symptoms.

2. Of note:
a. An inciting event is not necessary to make the diagnosis.
b. Compared to previous diagnostic criteria, presence of physical signs (rather than symptoms alone) is required for diagnosis and increased specificity from previous 0.41 to 0.68.
c. Symptoms occur distally, affect the extremities, and do not correspond to a nerve or root territory. Typically, isolated joints and the head/face are not involved.
d. Spreading along the ipsilateral side to involve the other extremity is possible; rarely, bilateral extremities are involved.

3. Epidemiology: Much more common in women, average age is 40 years, and it is rare in the elderly and in children.
4. Two types of CRPS: Nerve lesion absence (CRPS I) and presence (CRPS

II)

a. Type I: No nerve lesion; synonyms: sympathetic dystrophy (RSD), Sudeck atrophy, reflex neurovascular dystrophy (RND), algoneurodystrophy

b. Type II: Nerve lesion present; synonym: causalgia

5. Clinical stages (not reliable because of large interindividual variability)

a. Stage I (acute, 0 to 3 months): Pain/sensory abnormalities, edema

b. Stage II (dystrophic, 3 to 9 months): More pain/sensory dysfunction, motor/trophic changes

c. Stage III (atrophic, >9 months): Less pain, increased motor/trophic changes

6. Ancillary diagnostic testing (not required to make diagnosis)

a. Temperature differences of >1°C, measuring of swelling with measure band or water bath, sweat testing

b. Magnetic resonance imaging (MRI) is mostly helpful to exclude alternate diagnosis and can show bone marrow edema of affected limb (not specific).

c. X-ray to compare bone mineralization of the affected and unaffected extremity (on same film) can show patchy areas of deossification (low sensitivity).

d. Three-phase bone scan is a sensitive (0.7) and relatively specific (>0.75) tool for upper extremity CRPS within the first 5 months after onset. Proposed region of interest localization is over the metacarpophalangeal (MCP) joint of the affected hand, and phase 3 is acquired 2 to 3 hours after tracer injection. A positive finding is increased periarticular tracer uptake of the MCP joints of the affected hand. Diagnostic value decreases beyond 5 months after CRPS onset.

7. Nonmedical treatment: Early therapeutic intervention is essential to prevent transition to chronic CRPS. Early and aggressive physical and occupational therapy is the cornerstone of therapy; pain avoidance behavior is deleterious.

a. Specific physiotherapeutic techniques include mirror therapy, graded motor imagery, and pain-exposure physical therapy/desensitization.

8. Psychotherapy: Only if psychological factors are felt to contribute to the presentation or if somatic-oriented therapy is unsuccessful. Evidence of

benefit is mostly extrapolated from other chronic pain conditions.

). Medications

a. Prednisolone 60 to 100 mg/d, with 25% dose reduction every 3 to 4 days, has good evidence for acute stage of CRPS (6 to 9 months) but is unhelpful beyond that time frame.

b. Oral and IV alendronate and IV clodronate, pamidronate, and neridronate show moderately good evidence to reduce pain and physical function in acute to subacute CRPS I (weeks to several months from onset).

c. Vitamin C, 500 mg daily for 50 days, might reduce the risk of developing CRPS after wrist fracture.

d. Other anti-inflammatory drugs (NSAIDs, cyclooxygenase [COX]-2 inhibitors [COXibs]) are likely less effective

e. Anticonvulsants (such as carbamazepine, topiramate, phenytoin), gabapentinoids, antidepressants, or opioids can sometimes be effective in reducing pain in CRPS-I patients and, despite lack of good evidence, can be tried on an individual basis along the treatment guidelines for neuropathic pain conditions.

f. Intravenous immunoglobulin (IVIG) 0.5 mg/kg might reduce pain in stable, chronic CRPS I.

g. Topical treatments

1) Dimethyl sulfoxide (DMSO) (50% cream for 2 months) with some evidence for pain relief

2) Less evidence for 5% lidocaine-impregnated patch, lidocaine cream, the eutectic mixture of local anesthetics (EMLA) cream, and capsaicin cream (often not tolerated)

). Interventions

a. Increased tone and dystonia can be treated with local botulinum toxin injections and, if severe, intrathecal baclofen pump in carefully selected patients.

b. Sympathetic nerve blocks, for example, stellate ganglion block for the upper extremity and lumbar sympathetic chain block for the lower extremity can be considered; however, the limited data available does not suggest any consistent benefit.

c. Spinal cord stimulation shows promising results for treatment of chronic CRPS; however, the therapeutic effect declines after 2 to 3 years.

Central Poststroke Pain

1. Diagnostic criteria (according to Klit et al., *Lancet Neurology* 2009)
   - **a.** Mandatory criteria
     - **1)** Pain within an area of the body corresponding to the lesion of the CNS
     - **2)** History suggestive of a stroke and onset of pain at or after stroke onset
     - **3)** Confirmation of a CNS lesion by imaging or negative or positive sensory signs confined to the area of the body corresponding to the lesion
     - **4)** Other causes of pain, such as nociceptive or peripheral neuropathic pain, are excluded or considered highly unlikely.
   - **b.** Supportive criteria
     - **1)** No primary relation to movement, inflammation, or other local tissue damage
     - **2)** Descriptors such as burning, painful cold, electric shocks, aching, pressing, stinging, and pins and needles, although all pain descriptors can apply.
     - **3)** Allodynia or dysesthesia to touch or cold
2. Prevalence in stroke patients is around 8% and up to 18% in patients presenting initially with sensory deficits.
3. The probability of a lesion, including ischemic and hemorrhagic stroke, to cause CPSP depends mainly on its location rather than its size or etiology, with lesions in the lower brain stem and thalamus having the greatest potential to cause CPSP.
4. Symptoms include a mixture of reduced temperature or pain sensation in addition to allodynia or dysesthesia typically to cold and mechanical stimuli in the affected area.
5. Confounding pain etiologies after stroke include musculoskeletal pain from decreased mobility, changes in posture, spasticity, frozen shoulder, chronic headaches, as well as coexisting painful conditions such as diabetic neuropathy.
6. Pharmacologic treatment is not specific for CPSP and follows the general algorithm for neuropathic pain. TCAs, and especially amitriptyline (up to 100 mg/d if tolerated), could be considered first-line treatment, followed by

gabapentinoids, SNRIs, lamotrigine (200 to 400 mg/d), and opioids. Drug combinations can often be helpful to improve pain control and reduce side effects. There is no evidence for preventative treatment after stroke.

7. Nonpharmacologic treatments such as repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), and motor cortex stimulation (MCS) have inconclusive evidence for effectiveness.

Phantom Limb Pain

1. Definitions
   - **a.** Phantom sensation: Any nonpainful sensation referred to the missing limb caused by cortical sensory perception of the amputated body part. Loss of any limb or organ such as the tongue, eye, breast, and tooth can trigger this phenomenon.
   - **b.** Phantom limb pain (PLP): Painful sensation referred to the missing limb.
   - **c.** Stump sensation: Pain referred to the amputation stump.

2. Epidemiology: Phantom limb sensations occur in almost all amputees; however, PLP occurs in up to 85% of amputees and can be severe in 10% to 15%. Risks include acute postoperative pain, pre-amputation pain, female sex, and upper limb involvement and is lower in young patients and congenital amputees.

3. Symptoms: Onset usually within a few days after amputation. The pain is neuropathic (burning, shocklike, paresthesias, etc.) and localizes to the distal part of a limb (arm: fingers, palm; leg: toes, foot, ankle). It occurs mostly episodic on a daily basis and decreases in frequency and intensity over time.

4. Prevention: There is weak evidence that pre-amputation anesthesia with epidural morphine and bupivacaine as well as perineural anesthesia can prevent PLP in the short term. Perioperative memantine in addition to brachial plexus anesthesia might also decrease PLP in the short term.

5. Medical treatment: Medications used for other neuropathic conditions are generally used for PLP, including TCAs, gabapentinoids, SNRIs, anticonvulsants, and opioids. For chronic PLP, best evidence exists for oral morphine and oral gabapentin; weak evidence exists for NMDA receptor antagonists such as intravenous (IV) ketamine and dextromethorphan (60 or 90 mg p.o. twice daily) as well as topiramate (800 mg daily). Minimal

evidence exists for the treatment of PLP with mirtazapine, pregabalin, midazolam, milnacipran, fluoxetine, and duloxetine.

6. Interventions: Spinal cord stimulation or peripheral nerve stimulation can be tried; however, data is conflicting, and the benefit is often only temporary. Botulinum toxin injections appear not to be effective.
7. Other therapies: Mind–body therapy including biofeedback, mirror therapy, mental imagery, hypnosis, and meditation are all valuable options, are generally easy to implement, and do not have side effects.

Opioid-Induced Hyperalgesia

1. A state of nociceptive sensitization caused by exposure to opioids and characterized by increasing pain of same or different nature as the initial pain. Pain increase is independent of disease progression and is not helped by increased opioid dosing. Clinical evidence for the existence of opioid-induced hyperalgesia (OIH) in chronic opiate therapy is lacking.
2. Pharmacologic tolerance is characterized by decreasing efficacy of the drug and can be overcome by increasing opioid dosing; in contrast, OIH is caused by CNS sensitization, represents a paradoxical response to the analgesic properties of opioids, and is treated by weaning.
3. Clinically, OIH typically produces diffuse pain, exceeding the areas of preexisting pain; can be associated with other features of opioid withdrawal; and gets worse with increasing opioid dose.
4. Treatment: The goal is to wean off the offending opioid medication and transition preferentially to nonopioid analgesics. If not possible, transition to methadone or buprenorphine can be tried.

General Treatment

Overview

1. Treatment of pain is most impactful if the underlying etiology is targeted. Given the lack of a diagnostic gold standard for most chronic pain conditions (i.e., the poor correlation of imaging findings with symptoms, the poor specificity of many physical exam findings, the large variability in pain questionnaires) and the nonspecific treatment mechanisms of most analgesics, pain precision medicine is often challenging and sometimes

impossible.

2. Therefore, pharmacologic pain treatment often remains empiric, and choice of agent is driven by side effect profile, existence of comorbidities, drug interaction, and patient preference rather than by proven efficacy and working mechanism.
3. Nonpharmacologic treatments, including physical and psychological interventions, are universally well tolerated and often impactful to decrease pain-related disability but often suffer from limited availability and lack of insurance coverage.
4. Interventions such as nerve blocks, spinal epidural steroid injections, facet blocks, Botox injections, and implantation of stimulators and intrathecal pumps in selected cases are not last-resort options. They can often be used in conjunction with pharmacologic therapy in anatomically well-defined pain phenotypes and allow for targeted, often efficient, and side effect–reduced treatment.
5. Neurolytic procedures, that is, plexus, nerve, root and spinal cord ablative procedures should be reserved for intractable and terminally ill patients, given the periprocedural risk as well as potential for recurrence of worsening neuropathic pain.
6. Patients are ideally evaluated and treated in a multidisciplinary pain clinic if they do not respond adequately in a reasonable time to individual therapies. Special situations include cancer and palliative care, work-related injuries, and the extremes of age.

Principles of Pharmacologic Management

1. Pharmacologic treatment is geared toward pain physiology, if possible: nociceptive, inflammatory, neuropathic, and centralized pain. Often, more than one of these conditions coexist, that is, inflammatory response of a herniated disc causing neuropathic radicular pain.
2. NSAIDs and steroids have anti-inflammatory effects; all other analgesic agents are not specific for a certain type of pain but rather affect nociceptive transmission at both peripheral and central sites.
3. Principles of analgesic administration for chronic pain
   a. Long-acting analgesics should be used on a daily, scheduled basis.
   b. Short-acting analgesics can be taken prophylactically before pain-

provoking activity or for breakthrough pain.

Simple Analgesics

1. Acetaminophen (or paracetamol)
   - **a.** The first step in any pharmacologic pain treatment of mild to moderate severity. It is the most commonly used analgesic worldwide, given its good tolerability especially in the very young and old, affordability, and availability.
   - **b.** Drug of choice in patients that cannot be treated with NSAIDs, such as people with bronchial asthma, peptic ulcer disease, hemophilia, salicylate-sensitized people, children under 12 years of age, and pregnant or breastfeeding women.
   - **c.** Can be effective in osteoarthritis, musculoskeletal pain, headaches, dysmenorrhea, pain after dental procedures/toothache, and others.
   - **d.** Dosage 500 to 1,000 mg p.o. every 6 hours, not to exceed 4 g/d
   - **e.** Side effects are minimal, but long-term use might result in renal impairment, high blood pressure, and increased risk of gastrointestinal (GI) bleeding. Doses exceeding 4 g/d can result in severe liver damage.
   - **f.** Mode of action is complex and not fully understood but includes COX inhibition and interacting with serotonergic descending neuronal pathway, L-arginine/nitric oxide (NO) pathway, and the cannabinoid system.
2. NSAIDs
   - **a.** Especially useful for inflammatory pain, such as rheumatoid arthritis, osteoarthritis, and radiculitis. Also widely used for many musculoskeletal conditions, headaches, and cancer-related pain.
   - **b.** Efficacy of different NSAIDs is similar, and nonselective NSAIDs are as effective as selective COXibs. However, a patient may respond better to one than another in an unpredictable fashion. Initial choice can depend on the patient's relative cardiovascular (CV) and GI risk (see "f"), availability, and cost. A sequential trial of various medications in this class may be attempted.
   - **c.** Mode of action is the inhibition of COX. COX I is constitutively expressed in most tissues and is involved in processes such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function. COX II is constitutively expressed in some tissues (brain, bone,

kidney) but is mostly induced in immune cells and neuronal cells in states of inflammation. Nonselective NSAIDs as well as COXibs exhibit their clinical effect by inhibition of COX II, therefore decreasing the inflammatory response and the associated sickness syndrome (fever, anorexia, sleepiness, hyperalgesia). Non-selective (NS) NSAIDs block nonselectively both COX isoforms, whereas COXibs preferentially block COX-2.

d. Most side effects are related to disruption of the homeostatic function of COX I and II; occur usually with chronic intake; and include significant GI toxicity (ranging from mild bloating/discomfort/reflux to ulcers and lethal bleeding), acute and chronic kidney malfunction, and CV risk (hypertension, myocardial infarction [MI], stroke).

e. NS NSAIDs and COXibs might have similar CV risks (direct comparison trial underway, PRECISION), but COXibs have lower GI toxicity than NS NSAIDs.

f. Reducing risk of toxicity

1) Avoid NS NSAIDs or COXibs as long-term therapy.

2) Use sparingly in the elderly and should be avoided in patients with history of GI bleeding/gastric ulcer, on anticoagulation or chronic steroid therapy, and with high CV risk factors, or renal disease.

3) Avoid NSAIDs with higher toxicity (e.g., piroxicam and ketoprofen) and use agents with lower toxicity (e.g. naproxen, ibuprofen and diclofenac).

4) For patients with low GI and high CV risk, naproxen may be preferred because of its lower CV risk compared with other NS NSAIDs or COXibs.

5) For patients with high GI and low CV risk, a COXib alone or NS NSAID with a proton pump inhibitor offers similar relative upper GI protection; however, only COXibs will reduce risk for lower GI tract toxicity.

6) With use of concomitant aspirin, COXibs might reduce GI bleeding compared to NS NSAIDs.

7) Topical diclofenac cream can be used to avoid major systemic side effects.

g. Typical dosing schedules are shown in Table 11-1.

Table 11-1 Typical Dosing Schedule for Nonsteroidal Inflammatory Drugs

Drug	Dose Range (mg)	Dosing Intervals (h)
Indomethacin	50–100	6–12
Diclofenac	25–150	8–12
Ibuprofen	200–1,600	6–8
Ketoprofen	100–200	12–24
Naproxen	250–1,000	12
Meloxicam	7.5–15	24
Celecoxib	100–200	12–24

Table 11-2 Onset, Peak, and Duration of Commonly Used Opioids

Opiate	Route	Onset (min)	Peak Effect (min)	Duration of Analgesia (h)
Morphine	IV	5–10	10–30	3–5
	p.o.	30–60	90–120	4
Hydromorphone	IV	5–20	15–30	3–4
	p.o.	15–30	90–120	4–6
Oxycodone	p.o.	15–30	30–60	4–6
Methadone	IV	10–20	60–120	4–6
	p.o.	30–60	90–120	4–12
Fentanyl	IV	<1	5–7	1–2
	Transdermal	12–24 h	20–72 h	15–20 h
Oxymorphone	IV	5–10	30–60	3–6
	p.o.	30–60	60	4–6

IV, intravenous; p.o., by mouth.

Table 11-3 Examples of Equivalence Values

Hydromorphone (mg/d)		Morphine (mg/d)		Fentanyl (µg/h)	Oxycodone (mg/d)
IV	p.o.	IV/IM	p.o.	TD	p.o.

1.25	6.25	8.5	25	12	15
2.5	12.5	17	50	25	30
5	25	33	100	50	65
7.5	37.5	50	150	75	100
10	50	67	200	100	130
12.5	62.5	83	250	125	165
15	75	100	300	150	200

IV, intravenous; p.o., by mouth; IM, intramuscular; TD, transdermal.

Opioids

See Table 11-2 for opioid pharmacodynamics and Table 11-3 for equianalgesic dosing of commonly used opioids.

Overview

1. For cancer-related and palliative care situations, opioids play an essential part in pain control and should be used according to the World Health Organization (WHO) ladder principles to achieve rapid and effective pain control (see Fig. 11-2 for modified WHO pain ladder).
2. For nonmalignant pain, evidence supports short-term pain relief and functional improvement (<12 weeks) in nociceptive and neuropathic pain, and opioids are likely as effective as NSAIDs for osteoarthritis; however, evidence for long-term benefit is scarce and remains controversial.
3. Long-term opioid therapy for nonmalignant pain remains problematic given often ill-defined and usually irreversible pathology, resulting in lack of any end point for opioid therapy. From 1999 to 2014, more than 165,000 persons died from opioid overdose in the United States alone, and this has markedly increased in the last years, in parallel with increasing opioid prescriptions. In 2013, roughly 2 million people in the United States were abusing or dependent on opioids.
4. Safety concerns
   a. Correlation of opioid dose for chronic nonmalignant pain and overdose: Compared with <20 morphine milligram equivalent (MME)/d, odds of overdose are 1.5 to 2 times (20 to <50 MME/d), 2 to 4.5 times (50 to <100 MME/d), and up to 9 times (≥100 MME/d). Absolute risk difference

(compared to <20 MME/d) for any/lethal overdose: 1.40%/0.15% (50 to <100 MME/d) and 4%/0.25% (≥100 MME/d). Opioid-related overdose mortality rates rise rapidly up to prescribed doses of 200 MME/d, with more gradual increase thereafter.

b. Concurrent use of benzodiazepines and multiple prescribers further increase risk for potentially fatal overdose.

c. Methadone and oxycodone have the highest rates of overdose death.

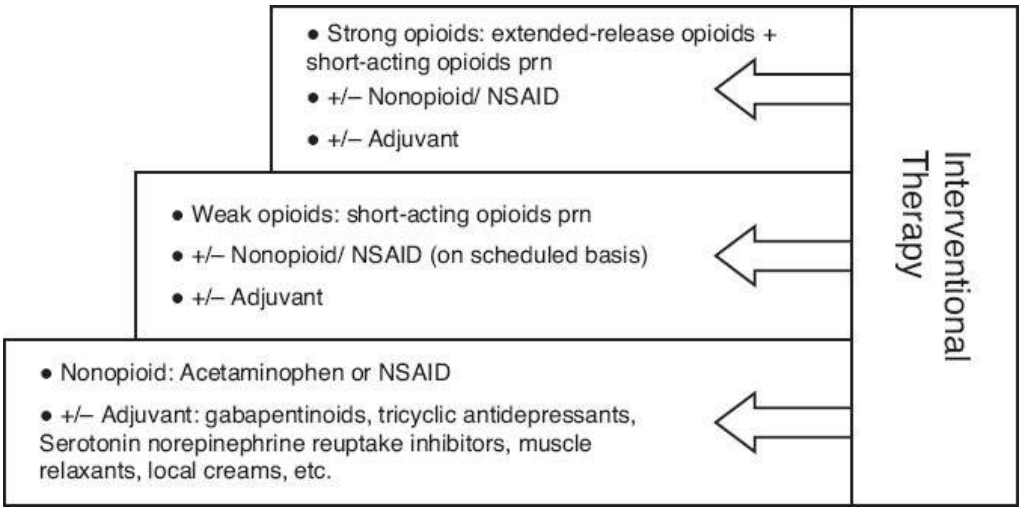

Figure 11-2. Proposed modified World Health Organization pain ladder for malignant and nonmalignant pain. Note that interventions at any step can help reduce oral medications and prevent a "step up" to the next level.

d. Factors associated with increased risk for misuse included history of substance use disorder, younger age, major depression, and use of psychotropic medications.

e. Conditions increasing the risk for greater harm include sleep apnea and other sleep-disordered breathing, renal or hepatic insufficiency, age >65 years, pregnancy, depression and other mental health conditions, and alcohol or other substance use disorders.

f. No study evaluated the effectiveness of risk mitigation strategies (use of risk assessment instruments, opioid management plans, patient education, urine drug testing, use of Prescription Drug Monitoring Program [PDMP] data, more frequent monitoring intervals, pill counts, or use of abuse-deterrent formulations) for improving outcomes related to overdose, addiction, abuse, or misuse.

Prescribing Principles for Nonmalignant Chronic Pain (modified, from the Centers for Disease Control and Prevention; Recommendations and Reports / March 18, 2016 / 65(1);1–49)

1. *When and how to initiate opioids for chronic pain*
   - **a.** Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred. Use opioids only if expected benefit for *both* pain and function outweigh risk. Opioids should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate.
   - **b.** Treatment goals: Establish realistic goals for pain and function and exit strategy if opioids are not beneficial or benefit does not outweigh risk. Continue therapy only if clinically meaningful improvement in pain and function occurs.
   - **c.** Before starting and periodically during opioid therapy, discuss risks and realistic benefits as well as patient's and clinician's responsibilities for managing therapy. An opiate treatment agreement is often signed.
   - **d.** Identify risk for harm. A psychological assessment can help to identify the risk for drug-related harm and addiction. Questionnaires such as the Opioid Risk Tool (ORT) and Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) can help. Urine toxicology screening before prescribing can sometimes identify patients with opioid use disorder.

2. *Opioid selection, dosage, duration, follow-up, and discontinuation*
   - **a.** For initiation, use short-acting/immediate-release (IR) instead of extended-release (ER)/long-acting opioids. Once stable dosage is reached, dosage might be converted to its ER equivalent.
   - **b.** There is insufficient data to assess which dosing strategy has best long-term effect: ER alone versus IR alone versus a combination of ER and IR. In common practice, an ER formula is typically given on a fixed dosing regimen, and IR formula is used for breakthrough pain or before a pain-evoking activity. Time-scheduled opioid use is associated with substantially higher average daily opioid dosage than as-needed opioid use.
   - **c.** Individuals may have to try different opioids to determine the one with the

best efficacy and least side effects.

d. Prescribe lowest effective dose. Carefully reassess benefit versus risk when increasing dose to ≥50 MME/d and try avoid or carefully justify doses ≥90 MME/d.

e. Long-term opioid use begins with treatment of acute pain. For acute pain, prescribe opioids only if pain is severe enough to justify opioids. Three days or less will often suffice; more than 7 days are rarely needed.

f. Evaluate benefit/harm within 1 to 4 weeks of starting opioid therapy, with reevaluation at least every 3 months. If benefit/risk ratio unsatisfactory, optimize other therapies and gradually decrease dose or discontinue.

b. *Assessing risk and addressing harms of opioid use*

a. Evaluate risk factors before starting and periodically during therapy (see earlier), such as history of overdose or substance use disorder, higher opioid dosages (≥50 MME/d), or concurrent benzodiazepine use.

b. Consider prescribing naloxone (handheld naloxone autoinjector [Evzio] or intranasal spray) to patient/caregiver if risk is high.

c. Review initially and periodically every 3 months the use of all controlled substance prescriptions using, for example, state PDMP data. Identify multiple prescribers or dangerous medication combinations (multiple opioids, benzodiazepines).

d. Use urine drug testing before starting opioid therapy and at least annually to assess for intake of prescribed opioids, other controlled prescription drugs, and illicit drugs.

e. Other risk mitigation strategies: Use of risk assessment instruments such as Current Opioid Misuse Measure (COMM), opioid management plans, more frequent monitoring intervals, shorter prescriptions, pill counts, or use of abuse-deterrent formulations.

f. Offer or arrange treatment with buprenorphine or methadone in combination with behavioral therapies for patients with opioid use disorder.

g. Driving, operating heavy machinery, and performing tasks that require delicate psychomotor skills should be avoided during dose titration but are not contraindicated when stable doses are reached.

Opioid Side Effects and Its Specific Treatment

1. Common side effects include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, myoclonus, and respiratory depression. No tolerance develops toward miosis and constipation.
   a. Constipation: Can be severe enough to require cessation of opioid therapy
      1) Increase in dietary fiber, fluid intake, and physical activity
      2) Scheduled senna-docusate 8.5 to 50 mg 2 tablets b.i.d.
      3) As needed (prn): Magnesium hydroxide (Milk of Magnesia) 30 mL p.o. b.i.d.; polyethylene glycol (Miralax) 17 g daily; bisacodyl (Dulcolax) 10 mg daily
      4) For refractory constipation
         a) *Lubiprostone (Amitiza)*: 24 μg twice daily p.o.; induces Cl^- influx into intestinal lumen
         b) *Methylnaltrexone (Relistor)*: 12 mg s.c. daily; in advanced illness, administer every other day: 38 kg to <62 kg: 8 mg; 62 to 114 kg: 12 mg. Peripherally acting opioid antagonist does not cross blood–brain barrier and therefore does not cause withdrawal or interfere with analgesic effect.
         c) *Naloxegol (Movantik)*: Peripherally acting opioid antagonist ; 12.5 or 25 mg qd orally
2. Nausea: Prochlorperazine, metoclopramide, or ondansetron in typical dosing
3. Itch: Typically not allergic reaction; mediated partially by peripheral histamine release (especially from Morphine) but mostly through central mu opioid receptors. Treatment with ondansetron or antihistamines; opiate rotation if intractable.
4. Endocrine dysfunction (typically low testosterone or estrogen, respectively; erectile dysfunction): Estrogen and testosterone replacement therapy and use of phosphodiesterase-5 inhibitors (e.g., sildenafil)
5. Myoclonus: Decrease or switch to other opioid; if not successful, low-dose benzodiazepine, for example, clonazepam (0.5 mg p.o. q6–8h)
6. Respiratory depression: hold all opiates, supportive measures
   a. Naloxone should be reserved for symptomatic respiratory depression or for progressive obtundation suggestive of imminent respiratory failure: 0.4 mg per dose; repeat as necessary and titrate toward respiratory rate.
   b. Given naloxone's short half-life compared to almost all other opioids, repeat injections or infusions (for extended release opioids and

methadone) are often necessary.

c. For lay people administration: 0.4 mg per dose can be safely administered using a handheld naloxone autoinjector (Evzio) or intranasal spray (Narcan).

7. OIH (see section on Opioid-Induced Hyperalgesia)

How to Taper Down Chronic Opioid Therapy

1. Indications

a. Clinically meaningful pain and functional improvement could not be achieved despite reasonable dose escalation.

b. Intolerable adverse effects at the minimum effective analgesic dose

c. Nonadherence with patient treatment agreement/aberrant behavior

d. Deterioration in physical, emotional, or social functioning because of opioid therapy.

e. Resolution of underling pathology (rare)

2. How to taper

a. Daily dose to prevent acute withdrawal is approximately 25% of the previous day's dose (i.e., 20 mg of oxycodone for a patient taking 80 mg daily).

b. Patients with less than once daily rescue doses do not need to taper.

c. Taper speed: No data to suggest superiority of any specific taper plan; emphasis should be given to patient adherence and withdrawal symptoms.

1) Very fast protocol: Daily decrease by 20% to 50% of the initial dose down to a threshold (30 to 45 mg of MME daily), followed by decreases every 2 to 5 days

2) Fast: Reduction by 20% to 50% of the original dose per week

3) Slow: Decrease of 10% of original dose every 5 to 7 days until 30% of the original dose is reached, followed by a weekly decrease by 10% of the remaining dose

4) Very slow (preferred if opioid therapy more than 2 years): 10% to 20% decrease every 2 to 4 weeks

d. For extended-release (ER) formulas, the opioid is first decreased to the smallest available unit dosage, after which dosing frequency is spaced out (e.g., ER morphine given as q8h is decreased to 15 mg ER morphine first, before decreasing frequency to q12h). Transdermal formulas will

similarly be decreased to the smallest available dose unit (e.g., fentanyl patch 12.5 μg/h).

e. An immediate-release (IR) opioid can be introduced toward the end of an ER formula taper (e.g., from oxycodone 10 mg ER to oxycodone 5 mg IR).

Opioid Withdrawal and Its Treatment

1. Withdrawal symptoms: Tolerance and physical and psychological dependence occur after several weeks of daily usage. Withdrawal symptoms usually are triggered by abrupt decrease or discontinuation of daily opioid usage. Onset and length of withdrawal is proportional to half-life of used opioid (e.g., ER formulas or methadone have later onset but longer lasting withdrawal symptoms). Symptoms are rarely dangerous, but the combination of increased pain and withdrawal makes it a challenge for most patients to adhere.

a. 3 to 4 hours: Craving, anxiety, fear of withdrawal

b. 8 to 12 hours: Anxiety, restlessness, insomnia, yawning, rhinorrhea, lacrimation, diaphoresis, stomach cramps, mydriasis

c. 2 to 4 days: Tremor, muscle spasms, vomiting, diarrhea, hypertension, tachycardia, fever, chills, and piloerection

d. After 7 to 10 days: Resolution of acute withdrawal

e. Up to 6 months: Secondary/protracted withdrawal syndrome with reduced well-being, fatigue, intermittent opioid craving

2. Treatment of withdrawal

a. Treatment of increased sympathetic activity (α_2-adrenergic agonists)

1) Clonidine, lofexidine, guanfacine, and tizanidine (best available evidence for clonidine and lofexidine)

2) Typically administered orally 2 to 4 times per day, with total dose adjusted daily according to withdrawal symptoms and side effects (sedation, low blood pressure).

3) Maximum doses only given during peak withdrawal time (2 to 4 days after opioid cessation), and medication is stopped after 7 to 10 days, when resolution of acute withdrawal typically occurs.

4) Clonidine: 0.1 to 0.2 mg per dose, maximum 1 mg/d

5) Lofexidine: 0.4 mg to 0.6 mg per dose, maximum 2 mg/d

6) Tizanidine: 2 to 8 mg per dose, maximum 16 to 24 mg/d

7) Guanfacine: 0.03 to 1.75 mg/d at night

b. Other symptoms
   1) Diarrhea: Loperamide (Imodium): 4 mg × 1, then 2 mg p.o. after each loose stool; maximum of 16 mg/d
   2) Nausea/vomiting: Promethazine (12.5 to 25 mg p.o. q4h prn), ondansetron: 4 mg p.o. q6–8h)
   3) Anxiety/restlessness: Hydroxyzine (50 to 100 mg p.o. q6h prn), clonazepam (1 mg p.o. t.i.d. prn)
   4) Insomnia: Trazodone (50 to 100 mg p.o. qhs prn)
   5) Muscle aches, malaise: NSAIDs and acetaminophen (Tylenol)

c. Psychological support: Cognitive behavioral therapy (CBT) and group therapy for a few weeks to months after acute withdrawal might decrease risk for relapse.

Addiction and Abuse

1. Definitions

a. Opioid use disorder (OUD) (formerly substance abuse and substance dependence disorder): A problematic pattern of opioid use leading to clinically significant impairment or distress and manifested by increasing doses; trouble to cut down/control intake; craving; impairment of personal, social, and professional life and physical well-being; and continued behavior despite knowledge of consequences (refer to *DSM-5* for details).

b. Tolerance: Pharmacologic concept where the subjective response to the same drug dose is reduced following repetitive exposure. Increasing doses are needed to achieve the same reaction.

c. Physical dependence: A neuroadaptive state in which abrupt cessation or reduction of a substance can cause predictable withdrawal symptoms.

d. Psychological dependence: Abrupt cessation or reduction of a substance can cause emotional–motivational withdrawal symptoms (e.g., dissatisfaction, anxiety, decreased sensation of pleasure) and engagement in certain behaviors to obtain substance.

e. Addiction: Dysfunctional/problematic behavior related to a specific substance (see, e.g., OUD)

2. Major aberrant behavior, which can be indicative of opioid use disorder, or overt criminal acts

a. Stealing, borrowing, forging, repeatedly "loosing" drugs
b. Using drugs in aberrant routes (IV, snorting, etc.)
c. Obtaining prescriptions from nonmedical sources, different providers ("doctor shopping") or emergency room without disclosure, or "loosing" prescriptions repeatedly
d. Concurrently using other controlled substances without permission, abusing alcohol, using illegal drugs, or *not* taking prescribed drugs (e.g., not present in urine screen)
e. Repeatedly increasing dose without approval
f. Repeatedly avoiding changes to treatment despite physical or psychological side effects
g. Deteriorating function that appears to be drug-related

b. Minor aberrant behaviors include
a. Aggressively complaining about the need for more drugs
b. Drug hoarding during periods of reduced symptoms
c. Requesting specific drugs
d. Openly acquiring similar drugs from other sources
e. Increasing the dose without approval
f. Using drugs to treat other symptoms without approval

4. Management of aberrant behavior
a. Major aberrant behavior requires weaning and ceasing opioids, often with the help of an addiction medicine specialist. Frequent, small supplies (e.g., daily or weekly) are best suited. Withdrawal should be treated appropriately.
b. Minor aberrant behavior requires reassessment of the appropriateness for opioid therapy and increased vigilance, which can include more frequent urine testing, reducing script duration and psychological evaluation. Also, consideration should be given to development of drug tolerance, worsening disease process (both might require an increased dose or opioid rotation), or OIH (requiring to decrease dose).

Main Opioids

See Table 11-2 for opioid pharmacodynamics and Table 11-3 for equianalgesic dosing of commonly used opioids.

Tramadol

1. Weak μ-opioid receptor agonist with SNRI properties
2. Available as IR, orally disintegrating tablet (for both, dose 50 to 100 mg q4–6h; maximum 400 mg/d), or ER (100 mg daily, maximum 300 mg/d)
3. Specific side effects: serotonin syndrome (especially when used with SSRIs, monoamine oxidase inhibitors [MAOIs], and TCAs) and seizures

Codeine

1. Weak opioid receptor agonist; also causes cough suppression by central mechanism
2. IR (15 to 60 mg q4h prn; maximum 360 mg/d), ER (50 mg q12h, maximum 600 mg/d). Conversion from IR to ER has to be decreased by 25% of daily IR dose.
3. Metabolized to morphine in the body, which is the active compound. Ten percent of Caucasians are unable to metabolize codeine and will not experience analgesia.

Morphine

1. Opioid receptor agonist, functions as reference opioid for all other opioids (MME)
2. Relatively hydrophilic, therefore slower diffusion into brain, slower onset of action, and less euphorizing compared to, for example, oxycodone
3. Analgesic effect (4 to 5 hours) outlasts plasma half-life, therefore less prone to overdosing.
4. Needs liver and renal dosing
5. Hepatic metabolites
   a. Morphine-3-glucuronide (M3G): No opioid receptor function, causes CNS hyperexcitability (can cause seizure and myoclonus), accumulates in renal failure, and cannot be reversed with naloxone.
   b. Morphine-6-glucuronide (M6G): Opioid agonist, contributes to analgesia.
6. Routes of administration include oral, buccal, subcutaneous, intramuscular, IV, intrathecal, and epidural.
7. Initial dosing: IR (10 to 20 mg q4h), ER (30 mg daily or 15 mg b.i.d., depending on formulation; 1:1 conversion from IR formulation), and IV (2.5 to 5 mg q3–4h)

Oxycodone

1. Opioid receptor agonist with rapid onset and short half-life
2. Less histamine release than morphine, therefore better tolerated
3. Mostly prodrug, metabolized via P450 2D4 to oxymorphone; 10% of population have genetically low levels of P450 2D4 and will have reduced analgesia from oxycodone.
4. Dosing: IR (5 to 10 mg q4–6h), ER OxyContin (10 mg q12h, 1:1 conversion from IR formulation)
5. Renally excreted, needs renal adjustment
6. Very high abuse potential because of rapid onset and therefore euphorizing effect; oxycodone is the most abused opioid in the United States and is responsible for more than 20% of all opioid deaths.

Oxymorphone

1. Direct μ-opioid agonist, active metabolite of oxycodone.
2. Minimal interaction with cytochrome P450 (CYP), therefore less interpatient variability and less drug–drug interactions.
3. Rapid onset of action, therefore high abuse potential (see section on Oxycodone).
4. Concomitant food (1 hour prior and 2 hours after intake) as well as alcohol should be avoided, as it increases plasma concentration by up to 300%.

Hydromorphone

1. Strong opioid agonist, approximately 5 times as potent as morphine, is a hydrogenated ketone analogue of morphine.
2. Similar length of analgesic effect than morphine (4 to 5 hours); rapid analgesic effect; less pruritus, sedation, nausea, vomiting than morphine
3. Can be infused subcutaneously, making it a great choice for hospice patient care
4. Hepatic metabolite
   a. M3G: No opioid receptor function, causes CNS hyperexcitability (can cause seizure and myoclonus), accumulates in renal failure, and cannot be reversed with naloxone. Much lower amounts are generated from hydromorphone metabolism than from morphine. Therefore, hydromorphone is preferred over morphine in renal failure.

Fentanyl

1. Strong opioid agonist, rapid onset of action
2. Applied as buccal, transdermal, parenteral, and transmucosal formulations.
3. Transdermal patches are available starting at 12.5 µg/h all the way up to 100 µg/h concentrations.
   a. Only recommended for opioid tolerant chronic pain patients
   b. Absorption speed is controlled by rate-controlling membrane of patch as well as skin integrity.
   c. Takes mean 13 hours (large variability) for therapeutic serum levels, about two consecutive patches for steady state, and 15 to 20 hours for drop of serum concentration after patch removal
   d. Apply patch to upper body on hairless spot with fat and intact skin.
4. Rapid-onset fentanyl formulas (transmucosal, buccal film, disintegrating tablet) have onset of analgesia in less than 15 minutes and are only approved for cancer-related break through pain.
5. No renal or hepatic dosing needed.

Buprenorphine

1. Partial opioid receptor agonist; slow onset of action, long half-life
   a. Increasing doses result in ceiling effect for both analgesia as well as side effects such as respiratory depression and euphoria.
   b. Administration to patients currently on opioid agonist can trigger withdrawal.
   c. Because of buprenorphine's high affinity to µ-opioid receptors and its long half-life, high doses of opioid agonists are needed to achieve additional analgesia in patients on buprenorphine.
2. Administration: Sublingual, buccal film, transdermal patch, IV and intramuscular injection; is available as a combination drug with naloxone (Suboxone) for abuse deterrence.
3. Used as maintenance therapy for opioid use disorder, for opioid withdrawal, as well as chronic pain management.
4. Before starting buprenorphine, the patient should be at least 24 hours off any short-acting and 48 hours off any long-acting opioid in order to prevent precipitated withdrawal.
5. For use in opioid dependence, buprenorphine should be started when patient

is in mild to moderate withdrawal.

6. Typical dosing
   a. For opioid dependence: Day 1: 8 mg sublingual (sl) per day; day 2: 16 mg sl per day; maintenance dose: 4 to 24 mg/d with goal to suppress opioid withdrawal symptoms and reduce craving
   b. For chronic pain: Start at 5 µg/h patch applied transdermally every 7 days; patient on >30 MME/d might need higher dose for equianalgesic effect; available as 7.5 µg, 10 µg, 15 mcg, and 20 µg/h patches

7. Buprenorphine versus methadone for opioid dependence. Advantages of buprenorphine: less abuse potential and toxicity given ceiling effect, less withdrawal when stopped; advantages of methadone: more effective in patients with higher tolerance, cheap, higher treatment retention rates.

Methadone

1. Strong opioid receptor agonist with long half-life, weak NMDA receptor antagonist.
2. Analgesic onset about 1 hour after oral intake, duration of analgesic effect 22 to 48 hours after repeated dosing with great interindividual variability, and very slow elimination (because of slow release from liver and other tissues).
3. Available as oral and IV formulation. Because of its unpredictable metabolism, dosing should be very conservative when switching from other opioid therapy (typically 10% to 20% of MME).
4. Metabolized through the CYP pathway; typically does not require renal or hepatic dosing.
5. Used for chronic pain therapy and as maintenance therapy for opioid dependence
6. Because of its long-lasting effect and unpredictable half-life, methadone is responsible for most opioid deaths of all opioid drugs, often caused by concomitant use of other opioids.

Opioid Rotation

1. Opioid rotation is a strategy that takes advantage of the fact that there is incomplete cross-tolerance among opioids. It should be considered in cases of tolerance or dose-related side effects.

2. The total 24-hour dose of the current opioid is converted into the equivalent oral MME. Typically, 50% to 75% of the MME of the new opioid is used.
3. For methadone, more conservative calculations apply given its unpredictable metabolism and long half-life (typically 10% to 20% of MME)
4. For fentanyl, given mean 13-hour duration to reach analgesic effect, allow for one-time intake of long-acting or 2 to 3 doses of short-acting opioid at time of first patch application.
5. Examples of equivalence values are given in Table 11-3.

Antidepressants

Most effective for neuropathic pain conditions as well as centralized pain states. Their analgesic effects are independent of mood-modifying effects and largely related to their inhibition of presynaptic serotonin and noradrenaline reuptake. TCAs are the most effective medications to treat neuropathic pain (number needed to treat [NNT] 3.6), followed by SNRIs (NNT 6.4). SSRIs do not have an established role in pain management. SNRIs and TCAs are the preferred drugs in pain patients with comorbid depression. In general, it will take several weeks on an appropriately high dose for the patient to have the full therapeutic effect.

Tricyclic Antidepressants

1. Amitriptyline is the best studied drug with highest efficacy for neuropathic conditions (and certain headache disorders). Other commonly used TCAs are nortriptyline and desipramine.
2. Desipramine and nortriptyline have generally less side effects and are less sedating than amitriptyline but might not be as efficient.
3. Dosing
   a. *Amitriptyline*: Start dose 10 to 20 mg at night, increase by 10 to 20 mg q4–7d until maximum dose of 75 to 100 mg.
   b. Similar dosing is used for nortriptyline and desipramine.
4. Common side effects (very common in elderly) are anticholinergic (constipation and urinary retention, dry mouth) as well as postural hypotension, sedation, nausea, blurred vision, and weight gain.
5. Electrocardiogram (ECG) should be done to look for arrhythmias and

conduction blocks in patients with cardiac risk factors and the elderly prior to initiation and once dosages above 50 mg are reached.

Serotonin Norepinephrine Reuptake Inhibitors

1. Commonly used SNRIs include duloxetine and milnacipran; venlafaxine has only anecdotal evidence. SNRIs are mostly helpful in neuropathic conditions such as diabetic peripheral neuropathy, centralized pain states such as fibromyalgia, and chronic musculoskeletal pain.
2. Typically used in patients with comorbid depression or anxiety.
3. Should be avoided in end-stage renal disease and used cautiously in angle closure glaucoma and liver disease including patients with alcohol abuse.
4. Dosing
   a. *Duloxetine*: Start dose 30 mg/d, increase to 30 mg b.i.d. in 7 days, and if needed, gradually increase by 30 mg/d every 2 to 4 weeks until maximum dose of 120 mg daily is reached.
   b. *Milnacipran*: Start dose 12.5 mg/d on day 1, increase to 12.5 mg twice daily on days 2 to 3, 25 mg twice daily on days 4 to 7 and then 50 mg twice daily thereafter until maximum dose of 100 mg twice daily.
   c. *Venlafaxine* (ER): Start dose 37.5 mg/d or 75 mg/d; increase by 75 mg each week to a maximum dosage of 225 mg/d.
5. Common side effects include nausea, dizziness, diaphoresis, agitation, diarrhea, hypertension (not duloxetine), sexual dysfunction, and serotonin syndrome.

Antiepileptic Drugs

1. Antiepileptic drugs (AEDs) decrease neuronal excitability by interfering with Na^- and Ca^+ ion channels as well as enhancing GABA-ergic tone.
2. From the diverse group of AEDs, gabapentin and pregabalin have the best evidence, and conditions include neuropathic pain conditions such as painful diabetic neuropathy, postherpetic neuralgia, and centralized pain states (e.g., fibromyalgia). Carbamazepine (stronger evidence) and the related drug oxcarbazepine (better tolerability) have traditionally been first-line therapy for trigeminal neuralgia. All other AEDs, including phenytoin, sodium valproate, lamotrigine, lacosamide, levetiracetam, and topiramate lack convincing evidence for their benefit in pain treatment.

Gabapentinoids

1. Bind to the α2δ-1 subunit of presynaptic voltage-gated calcium channels causing changes in release of excitatory neurotransmitters.
2. Of all AEDs, gabapentinoids have the best evidence for any neuropathic pain condition, especially painful diabetic neuropathy, postherpetic neuralgia, and centralized pain states (e.g., fibromyalgia). In practice, gabapentinoids are used extensively for almost all types of painful conditions, including headache and facial pain disorders, peripheral neuropathies, radiculopathies, central poststroke pain, and other central neuropathic pain conditions.
3. Common side effects include dizziness, somnolence, peripheral edema, and gait disturbance.
4. Gabapentin
   - **a.** Often used as first-line agent for a variety of neuropathic pain conditions. Preferred for patients with anxiety and restless legs, as it can treat both conditions.
   - **b.** Dosing: Start dose 300 mg at night (100 mg in the elderly) and increase by 300 mg every 3 to 5 days. Typical dosing is three to four times per day, and dose increases are often done at nighttime first to decrease sedating effects. Maximum dose is 3,600 mg/d, daily doses >1,800 mg do often not show greater benefit, but increase risk for side effects.
   - **c.** Gabapentin ER formulation
     - **1)** Gabapentin enacarbil (Horizant): 600 mg once daily in the morning, increase to 600 mg twice daily in 3 to 5 days, and further if needed
     - **2)** Gabapentin ER (Gralise): Comes in 300 mg and 600 mg tablets. Rapid taper is often tolerated if taken at night (daily doses): day 1: 300 mg, day 2: 600 mg, days 3 to 6: 900 mg, days 7 to 10: 1,200 mg, days 11 to 14: 1,500 mg, days ≥15: 1,800 mg
   - **d.** Renal dosing
     - **1)** CrCl >30 to 59 mL/min: 200 to 700 mg twice daily
     - **2)** CrCl >15 to 29 mL/min: 200 to 700 mg once daily
     - **3)** CrCl 15 mL/min: 100 to 300 mg once daily
     - **4)** CrCl <15 mL/min: cautious use, minimal dosing
     - **5)** ESRD requiring hemodialysis: based on CrCl plus single supplemental dose of 100 to 300 mg given after each 4 hours of hemodialysis

e. Pregabalin
   a. Shows stronger binding affinity to its target receptor and increased potency compared to gabapentin, resulting often in better efficacy and fewer side effects. Patients who do not respond or do not tolerate gabapentin should therefore be considered to try pregabalin.
   b. Dosing: Start at 75 mg twice daily (once daily in the elderly), increase to 150 mg twice daily in 1 week, and increase further weekly to maximum dose of 600 mg daily (typically no addition effect beyond 450 mg daily).
   c. Conversion from gabapentin to pregabalin is roughly 6:1 for total daily dose and is usually well tolerated without taper:
      1) Gabapentin 900 mg/d → pregabalin 150 mg/d
      2) Gabapentin 1,800 mg/d → pregabalin 300 mg/d
      3) Gabapentin 3,600 mg/d → pregabalin 600 mg/d
   d. Renal dosing
      1) CrCl >30 to 59 mL/min: 50% of indicated dose, divided 2 to 3 doses
      2) CrCl >15 to 29 mL/min: 25% of indicated dose, divided in 1 to 2 doses
      3) CrCl 15 mL/min: About 12.5% of indicated dose, single daily dose

Carbamazepine and Oxcarbazepine

1. Used for a variety of neuropathic pain conditions, including trigeminal neuralgia, painful diabetic/HIV/cancer-related neuropathy, postherpetic neuralgia, PLP, CRPS, and centralized pain states. No high-quality evidence exists; best available evidence in descending order exists for trigeminal neuralgia, diabetic neuropathy, and poststroke pain.
2. Given mood-stabilizing effect, this medication might be particularly helpful in patients with comorbid bipolar disease.
3. Oxcarbazepine is typically better tolerated than carbamazepine but has a higher risk for hyponatremia. Switch from one to the other can be considered but lacks evidence.
4. Carbamazepine: Start dose 200 mg/d in two divided doses; gradually increase by not more than 200 mg/d every 2 to 4 weeks. Typical maintenance dose 400 to 800 mg/d, maximum dose 1,600 mg/d.
5. Oxcarbazepine: Start dose 300 mg/d, increase after 3 to 7 days to 300 mg

twice daily, and increase in increments of 300 mg/d every 2 to 4 weeks; maximum dose 1,800 mg/d.

5. Extended-release formulations for both carbamazepine (twice daily) and oxcarbazepine (once daily) are available.
6. Side effects commonly include CNS toxicity (sedation, nausea, dizziness, ataxia, and diplopia), rash, hyponatremia, and hepatic toxicity.
7. Serious side effects
   a. Toxic epidermal necrolysis and Stevens–Johnson syndrome; patients of Asian ancestry are at particularly high risk. The HLA-B*1502 haplotype, present almost exclusively in the Asian population, is strongly linked to increased risk and should be tested for before starting therapy in this population.
   b. Rare aplastic anemia, agranulocytosis, and other blood dyscrasias: Monitor complete blood count (CBC) before start of therapy and 1 to 2 months after any dose increase. If decreased white or platelet counts are present, monitor closely. If significant bone marrow depression develops, discontinue medication.
   c. Hyponatremia (more common with oxcarbazepine): Dose-dependent, more common in elderly. Monitor Na level 1 to 2 months after dose increase. Na >130 does not require intervention. Symptomatic hyponatremia (headache, nausea, fatigue, confusion, seizure) or Na <130 requires discontinuation.

Topical Agents

1. Topical agents should be used for focal conditions wherever possible either alone or in conjunction with systemic medication, and especially in the sick and elderly, to decrease side effects.
2. Various factors influence penetration and absorption of topical analgesics, including the biochemical properties of adjuvants used in the preparation, skin thickness, skin integrity, and temperature. Topical analgesics work both at local sites as well as systemically to a certain degree, but systemic concentrations are much lower compared to oral intake, and absorption varies greatly.
3. The most established topical agents are NSAIDs, lidocaine, and capsaicin. Other agents include amitriptyline, gabapentin, glyceryl trinitrate, opioids,

menthol, etc., and are typically prepared by special compounding pharmacies.

4. Strong evidence exists for the use of topical diclofenac and topical ibuprofen for acute soft-tissue injuries and chronic joint-related conditions, such as osteoarthritis. Reasonable evidence supports the use of topical lidocaine for postherpetic neuralgia and diabetic neuropathy as well as capsaicin for neuropathic pain and particularly in postherpetic neuralgia.

Lidocaine

1. Best evidence for diabetic neuropathy and postherpetic neuralgia but can be used in a wide range of neuropathic conditions, and to lesser degree, for musculoskeletal pain
2. Available as cream/gel/lotion/ointment as well as patch
3. Dosing: Applied two to three times daily to painful area. Up to three patches may be applied in a single application and can remain in place for up to 12 hours in any 24-hour period.

Capsaicin

1. Works by activation of the TRPV1 ligand-gated cation channels on nociceptive nerve fibers, resulting initially in strong activation (burning sensation) and eventually in desensitization and substance P depletion of neurons.
2. Indication: Desensitization for any kind of neuropathic pain, including postherpetic neuralgia, diabetic/HIV/chemotherapy-related and other polyneuropathy, postsurgical/scar pain, and mononeuropathies. Sometimes also helpful for local musculoskeletal pain.
3. Capsaicin 8% patch (Qutenza) is specifically approved for postherpetic neuralgia and HIV-polyneuropathy (Europe only). It requires pretreatment with local lidocaine cream as well as simple analgesic treatment during the application. Occasionally, rescue medications such as opioids are needed for intense pain. Common, transient side effects are skin erythema, pain, edema, and pruritus.

Intravenous Infusions

Ketamine

1. Ketamine produces strong analgesia in neuropathic pain states by inhibition of the NMDA receptor and by other mechanisms.
2. Short-term infusion produces rapid and potent analgesia during administration only. Few randomized controlled trials (RCTs) have shown long-term analgesic effects up to 3 months after prolonged infusion for 4 to 14 days in chronic pain states such as CRPS and spinal cord injury. Anecdotally, it has been successfully used in fibromyalgia, migraines, trigeminal neuralgia, postherpetic neuralgia, neuropathies, and other chronic neuropathic pain states.
3. There is no uniform administration protocol, but ketamine infusion always requires close inpatient monitoring; successful protocols used in RCTs include
   a. IV infusion of ketamine at 0.35 mg/kg/h for 4 hours (25 mL/h), not to exceed 25 mg/h daily for 10 days
   b. Four-day continuous IV infusion of low-dose ketamine, starting at 1.2 μg/kg/min (i.e., 5 mg/h for a 70-kg patient) with titration three times daily based on pain control and side effects to a maximum dose of 7.2 μg/kg/min (i.e., 30 mg/h for a 70-kg patient).
4. Common side effects of low-dose ketamine infusion include psychedelic symptoms (hallucinations, memory defects, panic attacks), nausea/vomiting, somnolence, CV stimulation, and rarely, hepatoxicity.

Lidocaine

1. Blocks both peripheral and central sodium ion gate channels and thus inhibits neuronal discharges; in addition, may have anti-inflammatory properties
2. Lidocaine infusions have been used successfully in small RCTs in various conditions, including central neuropathic pain, peripheral neuropathies, postherpetic neuralgia, fibromyalgia, and persistent postsurgical pain. Pain relief can sometimes extend for days and even a few months after treatment.
3. There is no uniform administration protocol, but lidocaine infusion generally requires close cardiac monitoring, typically done in an outpatient facility. Protocols include
   a. 5 mg/kg of body weight (maximum of 500 mg) over 1 to 4 hours diluted in

0.9% normal saline. Vital signs are typically obtained in regular intervals during infusion. Repeat infusions are based on duration of analgesic effect and are typically done every 1 to 3 months.

4. Common side effects during infusion are metallic taste, tremor, dry mouth, insomnia, allergic reactions, and mild tachycardia. Others include somnolence, confusion, headache, nausea, numbness, and tingling. Serious, rare adverse events are cardiac arrhythmias, hemodynamic instability, and seizure.
5. Precautions before lidocaine infusion should include routine ECG to look for conduction abnormalities and electrolyte testing to minimize cardiac adverse events.

Physical Therapies

1. Physical exercise is an intrinsic part of most successful pain management programs. The goal is to restore or improve function and to prevent disability. Referral is appropriate when pain impairs a patient's optimal functional ability or inhibits a patient's independence in activities of daily living.
2. Physical therapy includes active modalities (i.e., exercise) and passive modalities (i.e., massage, joint mobilization, electrotherapy, heat, and cold).
3. Transcutaneous electrical nerve stimulation (TENS): A TENS unit is connected to the skin using two or more electrodes and delivers an electric current of customizable pulse width, frequency, and intensity to the tissue to decrease pain. Impulses can be applied at high frequency (>50 Hz) with an intensity below motor contraction or low frequency (<10 Hz) with an intensity that produces motor contraction.
   a. TENS has been successfully used in chronic pain conditions including rheumatoid and osteoarthritis, low back pain, myofascial pain, as well as acute and postsurgical pain.
   b. For migraine prevention, a specifically designed TENS unit is available (Cefaly), which has been shown to prevent migraine headaches with daily use.
4. Therapeutic ultrasound is often used as a form of mechanotherapy and has both thermal and nonthermal effects, including increased blood flow,

increased extensibility of collagenous tissues, and decrease in pain and muscle spasm. It is used for a range of musculoskeletal pain symptoms as well as to promote soft-tissue healing. There is some evidence for short-term benefit in chronic low back pain.

Cognitive Behavioral Therapy and Other Psychological Therapies

1. The cognitive behavioral concept of chronic pain purports that cognitions (appraisals, beliefs, and expectancies) modify the relationship between a nociceptive stimulus and pain-associated behaviors, mood changes, and their social consequences.
2. CBT helps the patient identify maladaptive thoughts and behaviors and develop adaptive strategies. The patient is thus assigned an active role in the treatment process.
3. Methods include behavioral techniques (goal setting, graded activity, goal-contingent activity) and cognitive strategies (cognitive reconceptualization). The patient is also taught coping strategies such as attentional control, relaxation, sleep hygiene, and problem solving. Maladaptive strategies are discouraged.

Invasive Therapies

1. Interventions can often be helpful for anatomic-diagnostic purposes and to reduce systemic medications and their side effects.
2. Simple interventions include trigger point injections for myofascial pain and peripheral nerve block for mononeuropathies, e.g., occipital neuralgia or lateral femoral cutaneous neuropathy.
3. Fluoroscopy-guided procedures should be done by a pain specialist and include injection of steroids in vicinity of cervical/thoracic/lumbar nerve roots or in the epidural space for radiculopathies, facet joint injections for facetogenic spine pain and cervicogenic headaches, large joint injections for arthritis, trigeminal nerve blocks, etc.
4. Radiofrequency lesioning (RFL) is often applied to the medial branches of the facet joints (for facetogenic axial back or neck pain) and other peripheral nerves if injections are successful but of short effect.

5. Neurolytic/neurodestructive procedures are typically reserved for cancer patients or severe, intractable pain and include alcohol or phenol injections to the celiac, superior/inferior hypogastric plexus, or nerve roots to disrupt visceral and somatic afferents, respectively. Neurosurgical procedures for this patient population include spinal anterolateral tractotomy, dorsal rhizotomy, or cutting of peripheral nerves.
6. Spinal dorsal column stimulation using one or several percutaneously placed electrodes can be helpful for intractable cases of radiculopathy, "failed back surgery syndrome," and CRPS. A psychosocial assessment is mandatory especially in patients with chronic nonmalignant pain. Complications of lead migration/failure and infection necessitate revision, and the therapeutic benefit might decrease after some time (typically years). The latest stimulators are MRI compatible.
7. Intrathecal application of opioid medications (for pain) or baclofen (for spasticity) is sometimes used if oral medications at sufficiently high doses cause inacceptable side effects. While this can be an efficient and sometimes cost-effective method of pain control in cancer patients with reasonable life expectancy, this therapy remains controversial for non-malignant pain. Intrathecal baclofen for intractable spasticity can be highly efficient but requires high surveillance for pump refill and pump failure to avoid potentially lethal baclofen withdrawal.

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12 Headache and Facial Pain

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MIGRAINE HEADACHE

Background

1. The most common cause of episodic severe headache
   a. Forty-three percent of women and 18% of men experience migraine during their lifetime.
   b. Half of all cases begin before age 25 years; 75% begin before age 35 years.
   c. Migraine is among the top 20 causes of disability worldwide; the disability is disproportionately concentrated in women of reproductive age.
2. When preceded by transient focal neurologic symptoms, the syndrome is termed "migraine with aura"; otherwise, it is known as "migraine without aura." When headaches occur 15 or more days per month for at least 3 months with features of migraine headache on at least 8 days per month, it is termed "chronic migraine."

Pathophysiology

1. Positron emission tomography shows activation of the dorsal midbrain, including the periaqueductal gray matter and dorsal pons, during migraine.
2. The primary sensory nerve terminals that innervate dural vessels release substances that cause inflammation and dilation of meningeal arteries and sensitization of peripheral trigeminal neurons. Distension and pulsation of meningeal vessels is perceived as painful and throbbing by these sensitized neurons. Evidence suggests that the migrainous brain does not habituate to

sensory signals in a normal way.

3. Presumed interictal cortical hyperexcitability to sensory stimuli, or at least destabilization of control of cortical excitability with lack of inhibitory control, may give rise to waves of cortical spreading depression (CSD) that produce clinical symptoms, especially aura (see section on Migraine with Aura).
4. Many neurotransmitters are suspected of involvement in migraine. These include serotonin, substance P, vasoactive intestinal peptide, glutamate, and nitric oxide. Calcitonin gene-related peptide (CGRP) is now thought to play a major role in migraine pathophysiology, and drugs currently in development target this substance or its receptors.
5. Pain-triggered activation of the sympathetic nervous system and ascending reticular arousal system probably cause associated autonomic symptoms.

Prognosis

1. Migraine is a condition of long duration. Frequency and severity commonly wax and wane, but over time, the disorder will follow one of three patterns:
   - **a.** Migraine may remit. Remission increases with age and in women is often attributed to menopause. Over a 1-year period, 10% of subjects in one study experienced complete remission, although 3% had partial remission.
   - **b.** Attacks of headache may become more frequent over time but lose characteristic migraine features such as vomiting and may no longer meet criteria for migraine.
   - **c.** In a small percentage of patients, migraine progresses and becomes chronic. Longitudinal studies suggest that roughly 3% of patients with baseline episodic headache progress to chronic headache over the course of a year. Risk factors for progression include medication overuse and obesity.

Diagnosis

1. In episodic migraine, there are discrete episodes of headache lasting 4 to 72 hours if untreated, on average occurring once or twice a month.
2. Two of the following four features are present: The headache is unilateral, pulsating, has moderate or severe intensity, and is aggravated by or causes

avoidance of routine physical activity.

3. At least one of the following must be present during headache: nausea and/or vomiting, photophobia, or phonophobia.
4. Headache is not attributed to another disorder.
5. In chronic migraine, headaches occur 15 or more days per month for 3 or more months and meet criteria for migraine on at least 8 of these days; milder headaches that do not fully meet criteria for migraine may be present as well.
6. When provoked by emotional stress, the headache typically comes afterward: so-called "letdown" headache. In women, migraine may be provoked by estrogen withdrawal and be more likely to occur in the pill-free week of combination oral contraceptive regimens or in the late luteal phase of the natural menstrual cycle.
7. Other common triggers of migraine headache in susceptible individuals are
   - **a.** Substances or their withdrawal
     - **1)** Alcohol
     - **2)** Nitroglycerin
     - **3)** Phosphodiesterase inhibitors used to treat erectile dysfunction, such as sildenafil
     - **4)** Caffeine withdrawal
   - **b.** Chronobiologic challenges
     - **1)** Over- or undersleeping; changes in sleep schedules
     - **2)** Shift work or travel to different time zones
     - **3)** Irregular or skipped meals; fasting
     - **4)** Sensory stimuli such as bright light, loud noises, or strong odors

Treatment

1. Sufferers rarely go without acute treatment of some kind for individual attacks. Use of acute treatment should generally be limited to no more than 2 to 3 d/wk in order to avoid medication-overuse headache.
2. The goal of abortive therapy is to provide rapid, well-tolerated, complete relief of headache and associated symptoms with minimal impairment of functional ability.
3. The choice of abortive treatment depends on headache characteristics and patient preference.

a. Oral therapies are convenient and preferred by most patients. They are appropriate for headaches that develop gradually and when nausea and vomiting are not prominent.

b. Nonoral therapies are more effective and reliable when headaches evolve rapidly or are accompanied by early nausea or vomiting. Gastric stasis may impair the efficacy of oral therapies, even in patients who do not experience nausea, so suboptimal results from an oral therapy should prompt a trial of nonoral treatment.

c. All forms of treatment are most effective when used early while the headache is still mild.

4. The triptans (serotonin agonists with activity at 1B and 1D receptors) are first-line medications for the abortive therapy of migraine headache; seven available triptans are listed, but not all are available in every country.

a. Almotriptan

b. Eletriptan

c. Frovatriptan

d. Naratriptan

e. Rizatriptan

f. Sumatriptan

g. Zolmitriptan

5. All triptans are available in oral formulations; rizatriptan and zolmitriptan are also available as orally disintegrating tablets that dissolve in the mouth but are absorbed intestinally. A fixed-dose combination of sumatriptan and naproxen is available. Sumatriptan and zolmitriptan are available as nasal sprays as well, and sumatriptan for subcutaneous (s.c.) injection is available in two fixed doses in an autoinjector. A sumatriptan–naproxen sodium combination tablet is also available. Sumatriptan is also available in an iontophoretic transdermal system and a nasal powder in a breath-activated delivery system. Sumatriptan is available without a physician prescription in some countries, although interaction with a pharmacist is usually required.

6. The oral and orally disintegrating tablets are best administered at mild or mild-to-moderate headache intensity to ensure their absorption. They should be administered in their optimum doses and may be repeated every 2 hours (for naratriptan every 4 hours), until headache is relieved or the maximum

daily dose is reached.

7. Table 12-1 lists the tablet sizes and optimum, maximum single, and maximum daily doses of the oral triptans.
8. Almotriptan, eletriptan, rizatriptan, sumatriptan, and zolmitriptan, in their optimum doses, have similar 2-hour efficacy rates. They also have similar recurrence rates of approximately one-third.
9. Frovatriptan and naratriptan have 2-hour efficacy rates approximately half those of the other triptans. However, their duration of action is prolonged because of their longer plasma-elimination half-lives.
10. Triptans are generally well tolerated. The most common side effects of oral triptans are dizziness, paresthesias, and flushing. Neck or chest tightness can occur; the latter is generally not thought to be caused by myocardial ischemia, with multiple hypothesized causes including esophageal spasm. These "triptan sensations" are usually mild and transient. If a particular triptan is not effective or tolerated, another should be tried.

Table 12-1 Oral Triptans

Triptans	Tablet Sizes (mg)	Optimum Doses (mg)	Maximum Single Doses (mg)	Maximum Daily Doses (mg) or Tablet
Almotriptan	6.25 and 12.5	12.5	12.5	25 mg
Eletriptan	20 and 40	20	40	80 mg
Frovatriptan	2.5	2.5	2.5	7.5 mg
Naratriptan	1 and 2.5	2.5	2.5	5 mg
Rizatriptan	5 and 10	10[a]	10[a]	30[a] mg
Sumatriptan	25, 50, and 100	50	100	200 mg
Sumatriptan-naproxen	Fixed-dose tablet with 80 mg sumatriptan and 500 mg naproxen sodium			2 tablets
Zolmitriptan	2.5 and 5	2.5	5	10 mg

[a] In patients on propranolol, 5 and 15 mg, respectively.

11. Triptans are selective for the cranial circulation, but a small degree of coronary artery constriction can occur. Thus, they are contraindicated in

patients with known coronary artery disease or those at high risk for coronary artery disease. Uncontrolled hypertension is a contraindication to use. Rizatriptan, sumatriptan, and zolmitriptan are also contraindicated with the concomitant use of a monoamine oxidase inhibitor. The concomitant use of propranolol requires a 50% reduction in rizatriptan dose because of interference with the breakdown of the triptan. Eletriptan should not be used within 72 hours of taking medications that are inhibitors of CYP3A4 activity (mycin antibiotics, antifungal and antiviral medications).

2. The U.S. Food and Drug Administration has issued a safety alert about the risk of serotonin syndrome when triptans are used with selective serotonin or serotonin/norepinephrine reuptake inhibitors. It recommends weighing the potential risk of the syndrome with the expected benefit of using the combination, discussing this with patients, and following them closely during such treatment. There is little experimental support for this purported interaction.

3. When oral medications do not reliably relieve headache within a reasonable time, nonoral routes of administration should be considered.

4. Parenteral, nasal, or rectal routes can be used to administer migraine medications.
   - **a.** The following nasal sprays are used to treat migraine:
     - **1)** Sumatriptan (5 and 20 mg)
     - **2)** Zolmitriptan (5 mg)
     - **3)** Dihydroergotamine (2 mg)
     - **4)** Butorphanol
   - **b.** The following rectal suppositories are sometimes used:
     - **1)** Indomethacin (50 mg)
     - **2)** Ergotamine with caffeine

5. Dihydroergotamine and ergotamine are nonselective serotonin agonists with activity at a variety of other receptors including adrenergic and dopaminergic receptors. This accounts for their tendency to produce or aggravate nausea and the possibility of more pronounced or prolonged vasoconstrictive effects. Thus, they are also contraindicated in patients with coronary artery disease or risk factors for coronary artery disease and should not be used concurrently with the triptan medications.

6. The sumatriptan and zolmitriptan nasal sprays can, if necessary, be repeated

after 2 hours, with a maximum of 40 and 10 mg in 24 hours, respectively. In adults, sumatriptan nasal spray is used in a dose of 20 mg and zolmitriptan nasal spray in a dose of 5 mg. Dihydroergotamine nasal spray is given only once in 24 hours, in a dose of four times 0.5 mg. Side effects of the nasal sprays are nasal congestion, nasal irritation, and a bad taste in the mouth.

7. The indomethacin rectal suppository is given in a dose of 50 or 100 mg, if necessary, repeated after 0.5 to 1 hour, with a maximum of 200 mg in 24 hours. Its most common side effect is orthostatic light-headedness because of a systemic vasodilator effect. The medication is contraindicated in peptic ulcer disease and bleeding disorders.

8. The ergotamine–caffeine suppository contains 2 mg ergotamine in combination with 100 mg caffeine to improve its absorption. Nausea and vomiting are its most common side effects, and therefore, it is important to administer the medication with care. Patients are advised to take only one-fourth or one-third of a suppository at a time and repeat it, if necessary, every 30 minutes to 1 hour, with a maximum of two suppositories a day.

9. Injection is another route through which a medication can be administered for the abortive therapy of migraine headache. The two medications that are available for parenteral administration are
   a. Dihydroergotamine (1 mg/mL)
   b. Sumatriptan (6 or 4 mg)

10. The usual dose of dihydroergotamine is 1 mg given s.c., intravenously (IV), or intramuscularly (IM). If given IV, the drug should be mixed with 5% dextrose in water (D5W) and not saline. Patients should be pretreated with an antiemetic drug to prevent worsening or precipitation of nausea or vomiting. Metoclopramide 10 mg, given IM or IV, is commonly used as pretreatment.

11. Sumatriptan is available for patient self-administration with an autoinjector. The injection is given s.c. in a dose of 6 or 4 mg, which can be repeated, if necessary, after 1 hour. Parenteral use of sumatriptan during aura does not prolong or worsen aura symptoms but has no effect on the subsequent headache. Thus, patients with aura may wish to delay its use until just before or after the headache begins. The most common side effects of the sumatriptan injection are a hot, tight, or tingling sensation, generally in the upper chest, anterior neck, and face, and light-headedness.

2. When abortive therapy is contraindicated, poorly tolerated, or ineffective, or when headaches occur more frequently than once a week, preventive therapy should be considered.
3. Preventive therapy does not have to mean drugs. There is some evidence of benefit from nonpharmacologic treatments such as biofeedback-assisted relaxation or lifestyle alterations.
4. The quality and quantity of evidence supporting the use of preventive medications varies considerably. Medications, herbal preparations, or vitamins that show benefit in at least one reasonably large, well-conducted, double-blind, randomized controlled trial include
   a. β-Blockers
      1) Atenolol
      2) Bisoprolol
      3) Metoprolol
      4) Nadolol
      5) Propranolol
      6) Timolol
   b. Tricyclics
      1) Amitriptyline
      2) Pizotifen
   c. Calcium-entry blockers
      1) Flunarizine
      2) Verapamil
   d. Anticonvulsants
      1) Divalproex sodium
      2) Topiramate
   e. Angiotensin-converting enzyme inhibitors
      1) Lisinopril
   f. Angiotensin receptor blockers
      1) Candesartan
   g. Vitamin B_2 (riboflavin)
   h. Petasites (butterbur)
5. β-Blockers with intrinsic sympathomimetic activity, pindolol, penbutolol, and acebutolol, are not effective in migraine. The mechanism of action of β-blockers in migraine is unknown but probably is not caused by blood pressure reduction.

6. Tricyclics such as amitriptyline and pizotifen may work by acting on the serotonergic system. The neurotransmitter serotonin inhibits the transmission of pain signals.
7. The calcium-entry blockers are a disparate group of drugs; not all show benefit in migraine. Those that do might work through effects on calcium-dependent processes involved in migraine, including synaptic transmission and neuronal membrane stability.
8. Divalproex sodium and topiramate are thought to be effective in part because they potentiate the inhibitory effects of γ-aminobutyric acid-ergic (GABA-ergic).
9. The choice of preventive medication depends on the features of the headaches and also on the risks, side effects, and possible benefits taking in consideration coexisting conditions.
10. When one preventive medication fails to provide relief or cannot be tolerated, another should certainly be tried. Clinical experience suggests that starting doses should be low and the dose gradually increased.
11. Headache activity normally waxes and wanes, so a treatment period of 2 to 3 months is necessary to be certain of a drug's effect. This is best judged through the use of a headache diary or other objective measurements of headache activity.
12. Although single-drug therapy is preferred, some patients with resistant headache syndromes may benefit from combinations of two or even three preventive drugs.
13. β-Blockers are contraindicated in sinus bradycardia, atrioventricular block, obstructive pulmonary disease (asthma), and diabetes mellitus.
14. Apart from sedation, amitriptyline can cause dry mouth, constipation, and weight gain; pizotifen can cause weight gain, and flunarizine occasionally causes depression. Amitriptyline is contraindicated in glaucoma, prostate hypertrophy, epilepsy, and cardiac disease; flunarizine and pizotifen do not have contraindications.
15. Verapamil in its sustained-release form can be given twice daily; its most common side effects are constipation and hypotension. Verapamil is contraindicated in atrioventricular block and sick sinus syndrome because it slows down atrioventricular conduction.
16. The anticonvulsants divalproex sodium and topiramate are often not well tolerated. Divalproex sodium can cause nausea, tremor, weight gain, and

hair loss, and topiramate can cause sedation, cognitive dysfunction, paresthesias, weight loss, and kidney stones. Divalproex sodium is contraindicated in liver disease or when liver function is abnormal. Exposure during the first trimester of pregnancy can cause neural tube defects. It should thus be used with caution or avoided in women of childbearing age.

7. In the absence of clinical trial evidence guiding the length of treatment, most experts continue the medications for 4 to 6 months and then taper them slowly. They can be resumed if headaches recur. The medications should be prescribed for at least 6 months, after which the dose is gradually decreased and the medication, if possible, discontinued.
8. Injectable monoclonal antibodies to CGRP or its receptor are in clinical development and show promise for preventive treatment of both episodic and chronic migraine.
9. Devices are becoming more widely used in migraine management. Current U.S. Food and Drug Administration–approved devices include a transcutaneous supraorbital nerve stimulator (Cefaly) and a transcranial magnetic stimulator (Spring TMS).

MIGRAINE WITH AURA

Background

1. Migraine with aura is also known as classic migraine. It is headache preceded by transient focal neurologic symptoms, generally referred to as aura symptoms. The majority of patients who have migraine with aura also have attacks of migraine without aura.
2. When the aura symptoms occur by themselves, not followed by headache, the condition is called migraine aura without headache. In the older patient, this condition is an important differential diagnostic consideration in transient ischemic attack (TIA).
3. Occurrence in the general population
   - **a.** Lifetime prevalence is 5%; male-to-female ratio is 1 to 2.
   - **b.** One-year prevalence is 3%; male-to-female ratio is 3 to 4.

Pathophysiology

1. Aura is caused by CSD, which is a wave of neuronal and glial depolarization that spreads across the cortex at a rate of 3 mm/min.
2. Modest reductions in cerebral blood flow occur in the wake of CSD, but they do not correlate with aura symptoms and are unlikely to be their cause. It is more likely that both the blood flow reductions and aura symptoms are caused by CSD-triggered electrophysiologic changes.
3. A variety of genetic mutations may increase susceptibility to CSD by affecting the stability of neuronal membranes.
4. A causal link between aura and headache is uncertain. Some believe that "silent" CSD can trigger headache in the absence of clinically apparent aura; others believe that aura and headache are independent, although often parallel, processes.

Prognosis

1. Migraine with aura is a risk factor for ischemic stroke, but the attributable risk is small. The relationship is particularly strong in the posterior circulation as evidenced by a 15-fold increased risk of cerebellar lesions in migraine patients both with and without aura.
2. Migraine with aura is a relative contraindication to the use of estrogen-containing contraceptives. Migraine with aura may increase the risk of cardiovascular disease.
3. Migrainous infarction is uncommon; when it occurs, it usually consists of ischemic infarction of an occipital lobe, resulting in homonymous hemianopia.

Diagnosis

1. The symptoms of typical migraine aura are visual or sensory. When aura consists of weakness, it is called hemiplegic migraine. Three mutations associated with hemiplegic migraine have been identified.
2. A common presentation of typical visual aura is the scintillating scotoma, also known as teichopsia or fortification spectra. Digitolingual paresthesias, also called cheiro-oral syndrome, represent the typical presentation of the somatosensory aura.

3. The aura symptoms usually last approximately 20 minutes, with a range from 10 to 30 minutes. When they last longer than 60 minutes, they are referred to as prolonged aura, and when they last longer than 24 hours, they are called migraine aura status.
4. The scintillating scotoma usually begins near the center of vision as a twinkling star that develops into a circle of bright, and sometimes colorful, flickering zigzag lines. The circle opens up on the inside to form a semicircle or horseshoe that further expands into the periphery of one visual field or the other. On the inside of the visual disturbance, a band of dimness follows in the wake of the crescent of flickering zigzag lines. The disturbance of vision ultimately disappears as it fades away in, or moves outside of, the visual field in which it developed.
5. The digitolingual paresthesias typically start in the fingers of one hand, extending upward into the arm and, at a certain point, also involving the nose/mouth area on the same side. The progression of the somatosensory disturbance, similar to that of the scintillating scotoma, is slow and usually takes 10 to 30 minutes.
6. A progressing somatosensory disturbance similar to the digitolingual paresthesias of migraine can occur with stroke, although this is rare. What differentiates one from the other is the resolution of the disturbed sensation, to which the first–last rule applies: In migraine, what is involved first resolves first, whereas in stroke, what is involved first resolves last.
7. When the aura symptoms are fixed in their lateralization, neurologic illness should be suspected, especially when occurring with contralateral headache. Occipital arteriovenous malformation is a notorious cause of symptomatic migraine with aura.

Treatment

1. Migraine with aura is treated as migraine in general, except that in its preventive therapy, β-blockers are often avoided because of theoretical worry that they may aggravate the neurologic symptoms.
2. There is no well-validated, practical acute treatment for aura symptoms. Experimentally, ketamine seems to abort aura in about half the cases. Anecdotal accounts suggest benefit from magnesium, furosemide, Compazine suppositories, or rebreathing into a paper bag. When frequent

auras are troublesome, some experts suggest preventive therapy with aspirin and/or a calcium-entry blocker.

TENSION-TYPE HEADACHE

Background

1. Tension-type headache is sometimes called muscle-contraction or tension headache.
2. In its episodic form (fewer than 15 d/mo), it is among the most common pain syndromes, with a lifetime prevalence of 69% in men and 88% in women. Chronic tension-type headache is diagnosed when headaches occur 15 or more days a month for at least 3 months.
3. Episodic tension-type headache is often self-treated; patients with chronic forms of the disorder are more likely to seek medical attention.
4. Although the burden of tension-type headache may be modest at the level of the individual, its prevalence means that it is the largest single cause of headache-related disability at the population level.

Pathophysiology

Sustained contraction of the craniocervical muscles, caused by such trivial issues as stress, fatigue, and lack of sleep, which may lead to sensitization of central pain pathways as well.

Prognosis

In the absence of medication overuse, prognosis for the episodic form of the disorder is generally good. In a subset of patients, episodic headaches may gradually increase in frequency and become chronic. The prognosis in these cases is less favorable unless a causal factor such as medication overuse can be identified and eliminated.

Diagnosis

1. Mild or moderate intermittent headaches occur, lasting hours to days.

2. Headaches are generally bilateral and diffuse in location.
3. Pain is described as tightness or pressure and is usually not associated with other symptoms.
4. Migraine is commonly misdiagnosed as tension-type headache. Neck or muscle pains are common in both disorders and are not specific to tension-type headaches. Typical associated symptoms and features of migraine may not develop if attacks are treated early or do not progress. Confusion between these two headache types is minimized when diagnosis is based on records from headache diaries in which patients have recorded associated symptoms and other headache features.

Treatment

1. Headaches generally respond to simple nonprescription analgesics. Evidence is best for nonsteroidal anti-inflammatory drugs (NSAIDs), but acetaminophen may also be effective. If this treatment is helpful, well tolerated, and infrequent, no additional treatment is needed.
2. In episodic tension-type headache that responds well to simple analgesics, the main role of the doctor is to monitor the frequency of use of abortive medication. As a general rule, this should be limited to no more than 2 to 3 days of use per week to prevent development of medication-overuse headache.
3. Prescription combination analgesic medications such as fixed combination products of butalbital/acetaminophen/caffeine or isometheptene mucate/dichloralphenazone/acetaminophen are generally avoided, and use should be limited to avoid precipitation of medication-overuse headache. Judicious, infrequent use may be appropriate in patients for whom other treatments are contraindicated or ineffective.
4. The use of opioids or sedative medications, while effective for pain relief, is generally discouraged because of concerns about the development of tolerance or addiction.
5. Preventive treatment should be considered if headaches are troublesome or disabling despite optimal abortive therapy, or if headache frequency exceeds twice a week on a regular basis.
6. Effective preventive treatments include
   a. Amitriptyline

b. Doxepin
c. Imipramine

7. Amitriptyline and doxepin are particularly helpful when there is also insomnia because the medications are sedating. Imipramine is less sedating and has fewer anticholinergic side effects, including dry mouth and constipation, but may be less effective.
8. A good starting dose is 10 mg at bedtime, after which the dose is gradually increased as tolerated and as needed. Early evening administration, rather than bedtime dosing, may help reduce morning sedation. The dose of amitriptyline usually required to achieve a beneficial effect in tension headache lies between 10 and 75 mg/d.

HEADACHE ATTRIBUTED TO RHINOSINUSITIS

Background

1. Mild headache is common with acute sinusitis, but chronic sinusitis is thought to be an uncommon cause of chronic headache or facial pain.
2. The prevalence is unknown but probably high because mild, acute episodes may resolve spontaneously and sufferers may self-treat.

Pathophysiology

1. Headache is caused by pressure in the sinuses because of obstruction of the orifices, in particular the ostiomeatal complexes (maxillary sinuses) and nasofrontal ducts (frontal sinuses).
2. Obstruction is generally caused by swelling of the nasal mucosa, often on the basis of anatomically relatively narrow orifices, and it involves all sinuses.

Prognosis

Prognosis is generally good for acute uncomplicated sinusitis.

Diagnosis

1. Acute sinusitis can be caused by cold viruses and noninfectious conditions such as allergies. Bacterial sinusitis is also a possibility, particularly if symptoms persist beyond 10 days or worsen after initial improvement.
2. Headache is generally located in the frontal or maxillary region and described as pressure. If the sphenoid sinus is involved, pain may be occipital, frontal, temporal, or periorbital.
3. Symptoms are characteristic of a prolonged upper respiratory infection but last less than 4 weeks in acute sinusitis, 4 to 8 weeks in subacute sinusitis, and longer than 8 weeks in the chronic form. Facial tenderness, congestion, anosmia, purulent nasal discharge, fever, cough, or halitosis may occur.
4. The pain of sphenoid sinusitis may be aggravated by bending, standing, and walking, and nausea and vomiting may occur.
5. Sinus computed tomography (CT) scan with coronal cuts is recommended when episodes are recurrent or chronic bacterial sinusitis is suspected.

Treatment

1. Observation and symptomatic treatment without the use of antibiotics are appropriate in mild cases for up to 2 weeks, since many episodes resolve spontaneously.
2. The choice of antibiotic is based on the likely pathogen, cost, and adverse effects. A common treatment for acute sinusitis in adults is a 10- to 14-day course of amoxicillin 250 to 500 mg t.i.d.
3. Nasal corticosteroid sprays, saline irrigation, antihistamines, decongestants, and other symptom-relieving drugs may be helpful. Improvement with any treatment may take up to 7 days.
4. The use of antibiotics for chronic sinusitis is controversial, and referral to an allergist or otolaryngologist should be considered.

CLUSTER HEADACHE

Background

1. Cluster headache is also known as migrainous neuralgia or alarm clock headache.

2. It is relatively rare, with a population prevalence of less than 1%. The male-to-female ratio is roughly 14 to 1.

Pathophysiology

1. Cluster headache is caused by arterial vasodilation in combination with neurogenic inflammation, probably in the extracranial circulation, preferentially involving the ophthalmic artery, giving rise to the characteristically sharp, steady pain in and behind the eye. Hypothalamic activation may also play a role.
2. Autonomic symptoms are probably caused by a localized shift in autonomic balance in favor of the parasympathetic and to the detriment of the sympathetic system, suggesting hypothalamic involvement.

Prognosis

The episodic form may change into the chronic form and vice versa. Remission and worsening are not predictable. Patients may have a single period of cluster attacks or may experience them repeatedly over a lifetime.

Diagnosis

1. These are unilateral headaches generally located in and behind the eye and described as intense, sharp, steady pain.
2. Headaches last for 30 to 120 minutes and occur daily or almost daily, once or more per 24 hours, often waking the patient out of early sleep during the first period of rapid eye movement sleep.
3. Headache must be associated with one or more autonomic signs or symptoms involving the affected eye and/or ipsilateral nostril, such as tearing, ptosis, miosis, reddening, congestion, and running. Ipsilateral forehead sweating is usually impaired, although this history is difficult to elicit.
4. Headaches are often associated with agitation, leading to rocking, pacing, head banging, and so forth.
5. Headaches occur in discrete episodes of weeks to months with varying periods of remission (85%) or chronically without remission (15%). The chronic form can be primary (chronic from onset) or secondary (initially

episodic).

6. Diagnosis of this highly disabling form of headache is often delayed; in one series of patients, the median time to correct diagnosis was 3 years following the first attack.
7. Lesions of the middle cranial fossa can cause neuralgic pain or sensory change in the distribution of the first division of the trigeminal nerve with ptosis or miosis but no sweating abnormalities (paratrigeminal oculosympathetic syndrome). Careful imaging studies are necessary to exclude structural abnormalities.

Treatment

1. Common triggers of individual headaches are use of alcohol and daytime napping, which should be avoided when the condition is active.
2. Abortive therapy is most effective with
   a. Sumatriptan, 6 or 4 mg s.c. injection
   b. Oxygen, 100%, inhaled at a rate of 8 to 10 L/min
3. Preventive therapy is most effective with
   a. Verapamil
   b. Lithium
4. Steroids may be used as "bridging treatment," but care should be taken to avoid frequent or prolonged use, because they can cause osteonecrosis, and desperate patients are prone to overuse. If immediate headache prevention is required, a prednisone course generally provides relief within 24 to 48 hours. The starting dose is 60 mg/d, which should be given for 3 to 5 days, followed by a taper of 5 mg/d every 2 days.
5. Maintenance treatment with verapamil or lithium should be started when attacks begin. Many patients with cluster headache experience complete prevention of headache attacks on preventive therapy, in contrast to the partial improvement that is common with preventive therapy of migraine. A common starting dose of verapamil is 120 mg sustained release (SR) twice daily, with an increase of 120 mg SR/d/wk. The result of the dose increase is usually evident in 3 to 5 days.
6. It is prudent to obtain a baseline electrocardiogram (ECG) and to repeat this to determine atrioventricular conduction, within days, for every dose

increase beyond 480 mg SR/d.

7. The daily dose of verapamil required to obtain relief in cluster headache is generally much higher than doses used for the treatment of hypertension. Reports exist of patients who have required as much as 960 mg/d to obtain headache relief.
8. If full relief of headaches cannot be obtained with verapamil or the required dose cannot be tolerated because of hypotension or constipation, lithium should be added to the maximum tolerated dose. A small dose of lithium in addition to the verapamil often suffices, that is, 150 to 300 mg twice daily.
9. Alternatively, lithium may be tried by itself and verapamil added if the single drug is not effective. Lithium used alone is particularly effective in chronic cluster headache, but high doses may be required for relief. A typical starting dose is 300 mg t.i.d. of lithium carbonate.
10. Verapamil is contraindicated in atrioventricular block and sick sinus syndrome; constipation and hypotension are its most common side effects.
11. Lithium is contraindicated in electrolyte imbalance and when sodium restriction or diuretic therapy is required. Its most common side effects are nausea, tremor, and diarrhea. The serum level should be kept below 1.5 mEq/L; it should be determined regularly along with the electrolytes and kidney and thyroid functions. Symptoms of lithium toxicity range from tremor to convulsions.
12. Preventive treatment should be continued for the usual duration of the patient's cluster episodes, which is usually 2 to 3 months at a time, and then discontinued until the next cluster episode begins.

HEADACHES ASSOCIATED WITH EXERTION AND SEXUAL ACTIVITY

Background

1. Headache triggered by physical exertion may be caused by
   - **a.** Primary exercise headache, in which headache is brought on by and occurs only with physical exertion.
   - **b.** Primary headache associated with sexual activity. This is now regarded as

a single entity and no longer divided into the subforms of preorgasmic and orgasmic headache. Subarachnoid hemorrhage or arterial dissection must be ruled out in cases of sudden-onset orgasmic headache.

c. Preexisting migraine that is triggered by exertion, in which case the headache usually occurs after prolonged exertion rather than immediately.

Pathophysiology

1. The pathophysiology of exercise/sexual activity headaches is uncertain. A vascular pathophysiology has been suggested, with arterial or venous distension and neurogenic inflammation commonly mentioned as potential causes.
2. Primary exercise headache and sexual activity headaches may be caused by perivascular inflammation, which is neurogenic in origin, from vasodilation or vasodistention.

Prognosis

1. Prognosis is generally not predictable. Primary exercise headache or headache associated with sexual activity often improves over time without treatment.
2. Exertional headache occurring as part of migraine may respond to migraine-preventive therapy, particularly β-blockers.

Diagnosis

Pulsating headache triggered only by physical exertion is characteristic of primary exercise headache; it may be more likely to occur with exertion at high altitude or in warm temperatures. Sexual activity headache is a dull aching sensation in the head and neck region with a sensation of muscle tension or tightness. It increases with sexual excitement and escalates with orgasm, at which point it may suddenly intensify and become pulsating. Subarachnoid hemorrhage and arterial dissection should be excluded with appropriate imaging studies.

Treatment

1. Anti-inflammatory medications are generally most effective.

a. Primary exercise and sexual activity headaches may be preempted by taking an NSAID medication 30 minutes to 1 hour prior to expected exertion or intercourse. Indomethacin seems particularly effective. The typical starting dose is 25 mg; this can be increased to 50 mg if needed.

b. Propranolol 20 to 40 mg taken 30 minutes to 1 hour prior to exertion or intercourse is also reported to be effective; if needed, propranolol and indomethacin can be given together.

c. If long-term suppression of headaches is desired, β-blockers and calcium-entry blockers, in doses commonly used for migraine, can be tried.

HYPNIC HEADACHE

Background

Hypnic headache is an uncommon nighttime headache that occurs in persons over 50 years.

Pathophysiology

Pathophysiology is unknown, although possibly similar to cluster headache.

Prognosis

The natural history of the disorder has not been well characterized; clinical experience suggests the prognosis for eventual remission is good.

Diagnosis

There is bilateral or generalized headache, usually mild to moderate, that develops during sleep and wakes the patient. It is unassociated with cranial autonomic symptoms or restlessness. It typically lasts 15 minutes to 4 hours and occurs more than 10 d/mo.

Treatment

Lithium, 300 to 600 mg at bedtime.

Bedtime treatment with caffeine, usually a dose of 200 mg, may be effective.

Melatonin and indomethacin have also been reported to be effective.

PAROXYSMAL HEMICRANIA

Background

1. Attacks are similar in all respects to those of cluster headache except that frequency is increased and duration is reduced. Treatment is different from that of cluster headache, with a high percentage of patients responding completely to indomethacin.
2. Paroxysmal hemicranias may occur in episodic or chronic forms.

Pathophysiology

Pathophysiology is unknown, although possibly similar to that of cluster headache.

Prognosis

1. The condition can generally be very well controlled preventively. However, continuation of therapy may be required, although, sometimes, at a lower dose than is initially necessary to relieve the headaches.
2. The long-term therapy with indomethacin needs to be monitored from a gastric as well as a renal perspective; the former includes testing for the development of anemia (hemoglobin, ferritin).

Diagnosis

1. There is unilateral headache with pain described as intense, sharp, and located in the supraorbital, orbital, or temporal region.
2. Headaches last for 2 to 30 minutes and occur daily or almost daily, with a frequency of 5 or more every 24 hours at least half the time.
3. Headaches are associated with one or more ipsilateral autonomic signs or symptoms such as tearing, reddening, congestion, and rhinorrhea.
4. Headaches occur in episodes with remissions or chronically.

Treatment

1. Abortive therapy is generally ineffective because of the short duration of the headache.
2. Preventive therapy with indomethacin is usually effective. Doses of up to 150 mg/d should be tried before concluding that the drug is ineffective, but maintenance doses of 25 to 50 mg four times daily are usually effective. If indomethacin is contraindicated, ineffective, or poorly tolerated, typical preventive treatments for cluster headache may be tried.

PRIMARY STABBING HEADACHE

Background

This is also called jabs-and-jolts, or ice pick headache. It is more common in patients who also have migraine.

Pathophysiology

Pathophysiology is unknown but probably vascular.

Prognosis

Stabbing headaches are generally not serious, and the prognosis for remission is good.

Diagnosis

These are short unilateral or bilateral stabs of pain, singly or in volleys, in the first and second divisions of the trigeminal nerve. They last a few seconds and occur unpredictably.

Treatment

1. When the stabbing headaches occur occasionally, only reassurance is required, and patients often do not desire treatment.
2. When they occur frequently, they usually respond well to preventive therapy with NSAIDs. Indomethacin is usually used in doses of 25 to 50 mg three to

four times daily. The optimal duration of treatment is not known. Periodic cessation of the drug is prudent; it can be reinstituted if attacks recur.

TRIGEMINAL NEURALGIA

Background

Trigeminal neuralgia is also known as tic douloureux; incidence is 4 per 100,000 population per year.

Pathophysiology

1. Often, no cause can be identified, but in some cases, there may be compression of the trigeminal nerve by a tortuous vascular loop compressing the nerve and causing focal demyelination. Although this is properly a secondary form of the condition, many patients do not undergo surgical management, and thus, the secondary nature of the problem remains unproven. The term classical, rather than primary, trigeminal neuralgia has been applied to patients with a typical history and a possible vascular compressive source of compression. Trigeminal pain caused by other disorders producing neural damage, including trauma, herpes zoster, tumor, or multiple sclerosis plaque, is termed a "painful trigeminal neuropathy." In multiple sclerosis, it is probably caused by a demyelinating plaque at the trigeminal root entry zone.
2. Demyelination causes axonal hyperexcitability, and damaged axons near each other become susceptible to chemical coupling. Synchronous discharge of hyperexcitable axons, activated by light mechanical stimulation and recruiting adjacent pain fibers, causes intense pain.

Prognosis

Medical treatment is often effective, and spontaneous remissions occur. If medical therapy is ineffective or poorly tolerated, surgery to address a vascular loop should be considered, especially late in the course of illness when spontaneous remission is less likely.

Diagnosis

1. There are 1-second to 2-minute paroxysms of severe, lancinating pain in regions supplied by the maxillary and mandibular divisions of the trigeminal nerve. A dull ache may occur between episodes.
2. Multiple attacks may occur during the day.
3. Light touch or other stimulation of trigger zones may evoke pain, especially in the nasolabial fold or in the mouth. Severe pain may cause muscle spasm of the face mimicking a tic.
4. Contrast-enhanced cranial magnetic resonance imaging (MRI) may reveal vascular compression of the trigeminal ganglion.
5. A subgroup of patients report concomitant persistent moderate facial pain in between attacks (previously referred to as atypical trigeminal neuralgia).

Treatment

1. Table 12-2 shows the medications that are used to treat trigeminal neuralgia.
2. Carbamazepine is the drug of choice.

Table 12-2 Medications Used to Treat Trigeminal Neuralgia

Medications	Start Doses (mg/d)	Maintenance Doses (mg/d)	Pretreatment Precautions	Important Side Effects
Carbamazepine	300	1,500–2,000	Hematology, electrolytes, ECG	Sedation, hyponatremia, leukopenia
Phenytoin	300	300–400	Hematology, ECG	Hirsutism, gingival hypertrophy
Baclofen	15	80	None	Sedation
Lamotrigine	25	300–600	Kidney and liver function	Rash
Gabapentin	900	2,400–3,600	Kidney function	Sedation
Clonazepam	1.5	6–8	None	Sedation
Sodium valproate	500	1,500–2,000	Hematology, liver function	Weight gain, hair loss, nausea

ECG, electrocardiogram.

3. Surgical therapeutic options can be considered if medical therapy fails. Choices are
   a. Radiofrequency thermocoagulation
   b. Microvascular decompression
   c. Stereotactic radiosurgery
4. Patients in the concomitant persistent facial pain subgroup may respond less well to both medical and surgical management.

MEDICATION-OVERUSE HEADACHE

Background

1. Also known as "rebound" headache, this syndrome of escalating headache in the context of escalating use of acute headache treatment is more common in patients with preexisting headache disorders, especially migraine.
2. Definitions of medication overuse are based on evidence of variable quality and incorporate both frequency and regularity of use; they differ for various categories of medication. There is considerable controversy over which categories of acute medication can cause medication-overuse headache.

Pathophysiology

The pathophysiology of medication-overuse headache is not well understood but may be caused by changes in receptor density or sensitivity as a result of chronic drug exposure.

Prognosis

The prognosis for patients who comply with medication discontinuation is good, but entrenched patterns of medication use can be difficult to reverse, and recidivism is common.

Diagnosis

1. Headache quality and location are variable, but headache must have developed or worsened in the context of regular overuse of acute headache

medicines for 15 or more days per month for 3 or more months.

2. The clinical presentation is often a low- or moderate-grade background headache with features of tension-type headache, with superimposed migrainous exacerbations.
3. It is more common in patients with preexisting primary headache disorders such as migraine and may occur when offending medications are used for other reasons, such as arthritis.
4. Headache should resolve or revert to its previous pattern within 2 months of discontinuation of the suspect medication.

Treatment

1. It is important to identify and treat medication-overuse headache because it is a common cause of treatment failure; there is a strong clinical impression that it renders preventive treatment less effective.
2. Common offending medications include vasoconstrictors such as caffeine or decongestants. Caffeine is an ingredient in many acute headache medications. It remains in the system for up to 2 or 3 days and should not be used more often than 2 or 3 d/wk. A higher frequency of intake can be allowed for the shorter acting triptans, which have plasma-elimination half-lives of 2 to 4 hours. A lower frequency of intake has to be considered for the ergots, ergotamine, and dihydroergotamine because they induce vasoconstriction for 3 to 5 days.
3. For overused medications that do not provoke medically dangerous withdrawal syndromes, withdrawal is best accomplished quickly to avoid complex withdrawal regimens and bargaining behavior. When barbiturate-containing or opioid medications are overused, tapering is necessary and hospitalization may be necessary for supervision and treatment of withdrawal symptoms.
4. A common practice is to use short-term steroid therapy in conjunction with medication withdrawal in order to minimize the occurrence of severe withdrawal headaches. Decadron 4 mg t.i.d. for several days may be tried; some physicians use a 3- to 6-day tapering course of prednisone, beginning with 15 mg four times daily, with dose reductions of 5 mg every few days. For treatment of severe interval headaches, sedating phenothiazines are often helpful. Physical treatments such as occipital nerve blocks or massage

may also be helpful. It is best to avoid the use of opioids or triptans during the initial withdrawal phase.

5. Hospitalization is recommended if outpatient withdrawal is unsuccessful or contraindicated. In the hospital, parenteral protocols can be used to manage headaches. In the absence of cardiovascular contraindications, dihydroergotamine 1 mg IV every 8 hours for 3 days is often helpful; doses of ergotamine should usually be preceded by an antiemetic such as metoclopramide or a phenothiazine, given orally or parenterally. IV steroids such as hydrocortisone 100 mg can also be used for severe headaches.
6. Once the headaches have become intermittent, effective abortive therapy should be provided for the severe headaches, preferably using specific antimigraine medications such as triptans or ergots.
7. Concomitant with medication withdrawal, preventive therapy for the underlying headache disorder should be optimized. Combination therapy with more than one preventive agent may be useful in these cases, especially if a poor response to preventive treatment in the past led to medication overuse.
8. Scheduled maintenance treatment with long-acting opioids is sometimes recommended for patients whose headaches fail to respond to aggressive preventive therapy and medication withdrawal. Such decisions should be made on a case-by-case basis, but mounting evidence suggests that only a quarter or fewer of these patients experience durable relief from such treatment. The development of opioid-induced hyperalgesia is increasingly recognized as a potential problem, and inappropriate use of medications is a persistent risk even in patients who do not display problems early in therapy. Consultation with a physician who has experience in the treatment of nonmalignant pain syndromes with opioids is advised.

POSTTRAUMATIC HEADACHE

Background

1. Head and neck injuries are common, and a large variety of head pain syndromes can result. Most are mild and self-limited, but some persist.
2. The incidence of posttraumatic headache depends on the type and location of

injury but ranges from 30% to 90%. Headache is more common in mild injuries than generally appreciated, and some experts believe headache frequency is inversely related to the severity of head injury.

3. Posttraumatic headache is very common in returning soldiers who have survived blast injuries.
4. Posttraumatic head and neck pain is often associated with other symptoms including cognitive impairment, labile mood, and attentional abnormalities.

Pathophysiology

1. The pathophysiology of posttraumatic headache is incompletely understood. Neural damage, particularly axonal shearing because of trauma, or movement of the brain within the skull, may underlie some of the symptoms. The condition may also have pathways in common with primary headache disorders.
2. Neck complaints are common in posttraumatic headache, and cervical injuries from flexion-extension injuries (whiplash) may contribute to the pain.

Prognosis

1. The prognosis of posttraumatic headache is extremely variable and may differ from country to country depending on compensation systems.
2. Other risk factors for a poor outcome include aging, female sex, and preexisting psychiatric disorders.

Diagnosis

1. Headache location, intensity, and associated features are variable. Some patients have low-grade headaches resembling tension-type headache, with prominent muscle and neck pain; others have episodes that resemble migraine, including associated nausea, vomiting, and photo- and phonophobia. A mixed pattern of headaches is common.
2. Headaches typically begin within 7 days of the injury. Persistent posttraumatic headache is diagnosed when headaches persist for at least 3 months.

Treatment

Treatment depends on the headache characteristics and consists of therapies employed for migraine and tension-type headache. Associated neck pain may respond to physical treatments such as massage or exercise. In chronic forms of the disorder, treatment results are commonly unsatisfactory, especially since many headache therapies may worsen cognitive complaints.

HEMICRANIA CONTINUA

Background

Hemicrania continua is a persistent unilateral headache without side shift that is completely responsive to indomethacin treatment.

Pathophysiology

The pathophysiology is unknown, but similarities with cluster headache and other trigeminal cephalgias suggest a shared etiology.

Prognosis

The natural history of the disorder has not been well studied. Remissions may occur but are not predictable.

Diagnosis

1. The headache is a persistent moderate headache with flares of severe pain, limited to one side of the head.
2. Complete or almost complete relief is obtained with NSAIDs, especially indomethacin, in appropriate doses.
3. Local ipsilateral autonomic symptoms such as tearing, reddening, congestion, and rhinorrhea are present during exacerbations.

Treatment

1. Preventive therapy is necessary because of the unremitting nature of the headache. A common treatment is indomethacin 25 to 50 mg three times

daily. Other NSAIDs may be helpful but are generally less effective. The optimal duration of treatment is unknown.
2. The principal risk of long-term therapy is gastrointestinal ulceration and bleeding.

HEADACHE ATTRIBUTED TO ARTERIAL HYPERTENSION

Background

1. Headache and hypertension are both common conditions and will frequently coexist.
2. However, mild or moderate chronic hypertension is unlikely to produce headache. More severe hypertension not only can cause headache by itself but can also aggravate a preexisting headache condition, such as migraine.

Pathophysiology

1. Acute headache can be caused by hypertensive crisis, presumably because the abrupt increase in pressure is transmitted to the large, pain-sensitive cerebral arteries. Preeclampsia and eclampsia probably also produce headache through similar mechanisms.
2. Pheochromocytoma may produce abrupt, intermittent increases in blood pressure with resultant headache.
3. Hypertensive encephalopathy may also produce headache as a result of extravasation of plasma and erythrocytes.

Prognosis

If blood pressure control is achieved or the underlying cause of the hypertension is eliminated, the prognosis is good.

Diagnosis

1. Hypertensive headaches are usually bilateral and throbbing in nature. They are worsened with physical activity.

2. Specific causes of hypertensive headaches may be suspected based on the clinical situation and accompanying features. For example, preeclampsia is a likely diagnosis when hypertensive headaches occur in late pregnancy or the puerperium, while pheochromocytoma should be suspected when such headaches occur in paroxysms with sweating, palpitations, or anxiety.

Treatment

Treatment is aimed at the presumed underlying cause; most often, it includes traditional measures to control blood pressure.

MENINGITIS

Background

The incidence of infectious meningitis, and causative organisms, varies depending on age, sex, and geographic location. In the United States, approximately two-thirds of cases are caused by viral causes and one-third to bacterial causes.

Pathophysiology

1. Headache is caused by inflammation of the meninges by infectious agents that have penetrated the blood–brain barrier.
2. Viral meningitis can be caused by a large number of viruses. Common causes are enteroviruses, herpes simplex type 2, and varicella-zoster virus.
3. The epidemiology of bacterial meningitis has changed with the introduction of the *Haemophilus influenzae* type B, varicella, and pneumococcal vaccines. Some causes are group B streptococci, *Listeria* organisms, and mycobacteria.

Prognosis

The prognosis depends on the causative organism, underlying status of the patient, and the promptness of treatment. For many forms of viral meningitis, the long-term prognosis is good, although in bacterial meningitis, mortality is higher and persistent neurologic morbidity can occur in up to a quarter of

survivors. Persistent headache can occur with all forms of meningitis and may sometimes prove intractable.

Diagnosis

1. The headache associated with meningitis typically develops in close association with meningeal inflammation and resolves within 3 months of effective treatment or disappearance of the infection.
2. Headache characteristics are variable. The head pain may be severe, and neck pain and stiffness are often prominent associated symptoms.
3. Diagnosis depends on lumbar puncture (LP) and spinal fluid analysis, preceded by neuroimaging (CT scanning or MRI) if space-occupying lesion (abscess) or hydrocephalus is suspected.
4. Spinal fluid analysis in aseptic (noninfectious) meningitis typically shows lymphocytic pleocytosis, mildly elevated protein, and normal glucose with no infectious organisms.
5. In infectious meningitis, analysis reveals an increased leukocyte count, higher in bacterial infection (1,000 to 5,000/mm^3) than in viral meningitis (100 to 1,000/mm^3).
6. The putative pathogen is identified through
   a. Spinal fluid Gram stain
   b. Spinal fluid and blood cultures (bacterial meningitis), or antibody titer determinations in acute and convalescent serum samples (viral meningitis)

Treatment

1. Viral meningitis is treated with supportive therapy only in the absence of specific antiviral therapy.
2. Suspected bacterial meningitis should be treated promptly and empirically with antibiotics. Treatment can be adjusted based on identification of the bacteria. Typical initial empiric treatments depend on the suspected organism as described in Chapter 19 and for adults include
   a. Ceftriaxone, 2 g IV every 12 hours
   b. Cefotaxime, 2 g IV every 4 hours
   c. Chloramphenicol 12.5 mg/kg IV every 6 hours plus trimethoprim/sulfamethoxazole 5 mg/kg IV every 6 hours (if allergic to penicillin)

3. Symptomatic treatment of associated headache is accomplished with simple analgesics such as acetaminophen or NSAIDs. For more severe headaches, opioids may be needed and appropriate.
4. Antibiotic therapy is often combined with corticosteroid treatment, usually dexamethasone. The use of corticosteroids in meningitis remains controversial.

SUBARACHNOID HEMORRHAGE

Background

1. Subarachnoid hemorrhage is an important diagnostic consideration in headache of very acute onset because of the high morbidity and mortality associated with it.
2. Incidence is 10 per 100,000 population per year; mean age is 50 years.
3. Risk factors
   a. Cigarette smoking
   b. Hypertension
   c. First-degree relative with subarachnoid hemorrhage

Pathophysiology

1. Headache is caused by chemical inflammation of the pia-arachnoid from blood in the subarachnoid space.
2. Bleeding into the subarachnoid space generally occurs from an aneurysm but occasionally from an arteriovenous malformation or as the result of a bleeding disorder.

Prognosis

1. Twelve percent of patients die before receiving medical care.
2. Forty percent of hospitalized patients die within the first month.
3. One-third of those who survive have major neurologic deficits.

Diagnosis

1. There is headache of very acute onset, usually severe in intensity and associated with nausea and vomiting; sometimes, this occurs also with (temporary) loss of consciousness and with meningeal irritation on examination.
2. One-third to one-half of the patients have a history of similar acute-onset headaches in the days or weeks before the presenting hemorrhage occurs (sentinel headaches).
3. Cranial CT scanning is the preferred diagnostic test; it detects blood in the subarachnoid space in
   a. Ninety percent to 95% within 24 hours
   b. Eighty percent at 3 days
   c. Seventy percent at 5 days
   d. Fifty percent at 1 week
   e. Thirty percent at 2 weeks
4. With clinical suspicion of a subarachnoid hemorrhage and negative findings on cranial CT scan, LP should be performed.

Treatment

1. Surgical clipping or endovascular coiling of the aneurysm, resulting in obliteration by thrombosis.
2. Obliteration of the arteriovenous malformation by endovascular coiling causing thrombosis, by resection, or by Gamma Knife radiation.

SUBDURAL HEMATOMA

Background

1. In subdural hematoma, blood collects beneath the dura when bridging veins tear. Acute subdural hematoma may occur following head trauma, while chronic subdural hematoma is more common in older adults and may occur after minor head injury.
2. The incidence of chronic subdural hematoma is approximately 1.5 to 3 per 100,000 population per year. Acute subdural hematoma occurs in 5% to 25% of patients with severe head injuries.

3. Predisposing factors include
   a. Anticoagulation
   b. Head trauma
   c. Advancing age
   d. Bleeding disorders or anticoagulation
   e. Intracranial hypotension

Pathophysiology

Blood collects when bridging veins tear and the resultant hematoma puts pressure on adjacent pain-sensitive meningeal blood vessels.

Prognosis

1. Mortality is roughly 30% at 6 months and depends on age and neurologic status at the time of diagnosis.
2. Diagnosis may be delayed in cases with minor head trauma or insidious development.

Diagnosis

1. The clinical presentation can be subtle and easily confused with other disorders. Headache is a common symptom, but cognitive impairment or altered mental status makes the history difficult to elicit.
2. Other symptoms may include balance problems, hemiparesis, aphasia, and cognitive impairment.
3. Hemiparesis, hyperreflexia, mental status changes, papilledema, or a third or sixth cranial nerve palsy may be present on examination.
4. Cranial CT scanning is the preferred diagnostic test if acute hematoma is suspected; the hematoma should be hyperdense to brain tissue. In older hematomas, the lesion may be isodense to brain tissue, and MRI may be required if midline shift is not present.

Treatment

1. Surgical evacuation through burr hole or craniotomy is indicated in most symptomatic cases or where a mass effect is present. The outcome of

surgery is unpredictable, and complications can occur (see Chapter 1).
2. Small hematomas in stable patients may be observed without surgical intervention.

OPHTHALMIC ZOSTER

Background

1. Head or facial pain may be caused by zoster outbreaks in the distribution of the trigeminal nerve, especially the ophthalmic division.
2. The disorder becomes more common with age.
3. Childhood varicella vaccination may someday decrease the incidence of the disorder, but at this time, children are not routinely vaccinated. A varicella vaccine is now available and is indicated in adults above the age of 60 years.

Pathophysiology

1. Zoster is caused by reactivation of dormant varicella-zoster virus in the trigeminal ganglion. It is manifested by a vesicular eruption in the territory of the affected nerve.
2. In addition to age, risk increases with
   a. Neoplastic disease, especially lymphoproliferative cancers
   b. Immunosuppression because of human immunodeficiency virus or chronic immunosuppressive therapy for a variety of disorders

Prognosis

1. Ophthalmic zoster causes ocular complications in about half the patients. These include iritis, keratitis, and episcleritis.
2. Up to three quarters of patients may develop postherpetic neuralgia, which is pain that persists for more than a month following healing of the skin lesions.

Diagnosis

1. Pain may precede the herpetic eruption by up to a week. It may range from mild itching to severe pain and is unilateral on the side of the reactivated infection.
2. Within 7 days, a maculopapular rash appears in the territory of the affected nerve and progresses to a vesicular stage with the developments of pustules, ulceration, crusting, and eventual clearing.
3. Healing occurs over about a month, but residual scarring may result.

Treatment

1. Antiviral therapy should be started as soon as possible since it may reduce the risk of persistent pain and ocular complications.
2. Drugs used include
   a. Acyclovir, 800 mg five times daily
   b. Famciclovir, 500 mg every 8 hours
   c. Valacyclovir, 1,000 mg every 8 hours
3. Treatment is usually continued for 7 days.
4. Ophthalmologic consultation should be sought to evaluate ophthalmic complications.
5. Tricyclic antidepressants, such as amitriptyline or doxepin, may be started along with antivirals to help reduce or prevent postherpetic neuralgia.
6. Other treatment choices for postherpetic neuropathy include
   a. Opioids (short- and long-acting)
   b. Gabapentin 300 to 600 mg p.o. t.i.d.

TEMPORAL ARTERITIS

Background

1. Also called giant cell or cranial arteritis, this is a systemic vasculopathy that typically affects the temporal arteries.
2. Other large-sized vessels such as the aorta and carotid artery may also be affected.
3. It is most common in women over 50 years, and incidence increases with age.

Pathophysiology

1. Affected arteries show transmural inflammation of arterial walls with infiltration by lymphocytes and giant cells. Luminal narrowing occurs with resulting distal ischemia.
2. Visual loss is caused by ischemic damage to the retina and optic nerve.
3. The inciting event is unknown, but viral or other infectious causes are suspected triggers. Genetic factors may play a role in susceptibility.

Prognosis

1. Partial or total loss of vision is the most feared complication and occurs in up to a third of untreated patients.
2. Early identification and treatment is important to prevent visual complications.

Diagnosis

1. Headache is present in a majority of patients and occurs in close temporal relationship with other symptoms such as thickened temporal arteries and visual changes. It typically resolves within 3 days of appropriate steroid treatment.
2. The headache usually begins insidiously, is persistent and moderate in intensity, and may be associated with skin or scalp tenderness or areas of necrosis. Headache location is variable.
3. Fever, pelvic and shoulder muscle stiffness (polymyalgia rheumatica), and jaw claudication and pain on chewing are other common symptoms.
4. Temporal artery pulsations may be absent.
5. Temporal artery biopsy is recommended for definitive diagnosis, which is desirable because of the potential harms of steroid treatment. Most experts believe biopsies can be obtained up to a week after initiation of steroid treatment. Because some areas of vessels are not affected, multiple biopsies may be needed to obtain a diagnosis.
6. An erythrocyte sedimentation rate above 80 mm/h is found in the majority of patients with temporal arteritis, but values can be difficult to interpret because of variations based on age, sex, and comorbidity. C-reactive protein levels are less variable and are above 2.45 mg/dL in most patients; they may

be elevated even if the sedimentation rate is normal. Anemia is also common.

7. Duplex sonography of the temporal arteries may show a "halo sign" around the affected vessel.

Treatment

1. Prednisone, 60 mg/d, should be started as soon as possible to prevent visual loss. Improvement of most symptoms is evident within 3 days, and the dose is very gradually decreased thereafter.
2. Long-term treatment with steroids for up to a year may be needed and is guided by symptoms, sedimentation rate, and C-reactive protein levels.
3. Immunosuppressive therapy with drugs such as azathioprine and methotrexate is sometimes attempted.
4. Ophthalmologic consultation is indicated.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Background

1. Also referred to as pseudotumor cerebri or benign intracranial hypertension, this is a disorder of unknown cause marked by chronically increased intracranial pressure (ICP). Headache is present in the vast majority of patients and may be the presenting symptom.
2. Annual incidence ranges from 1 to 2 per 100,000 people. It is more common in women and those who are overweight. Incidence peaks in the third decade.

Pathophysiology

1. The underlying cause of the elevated ICP is not known, but it is thought to result from a mismatch between spinal fluid production and absorption or increased resistance to absorption or functional lateral venous sinus obstruction.
2. Traction from swelling or pressure of dilated venous sinuses on pain-sensitive, large cerebral vessels may produce headache.

3. Obesity, anemia, and use of substances such as estrogen-containing contraceptives, vitamin A, or tetracycline may affect spinal fluid balance and provoke the condition.

Prognosis

The most feared complication is visual loss, which can occur in up to a quarter of untreated patients.

Diagnosis

1. Daily diffuse, nonpulsating headache is present in over 90% of patients.
2. It may be aggravated by coughing, sneezing, or other Valsalva maneuvers.
3. Mental status is normal, but papilledema, an enlarged blind spot, a sixth nerve palsy, or visual-field defect may be found on examination.
4. ICP of over 200 mm H_2O in nonobese and over 250 mm H_2O in obese patients is demonstrated on LP in the recumbent position; spinal fluid composition is normal, although low protein content may be seen.
5. Headache occurs in close temporal relationship to the development of increased ICP and resolves within 72 hours of successful lowering of pressure.
6. Cranial MRI with gadolinium enhancement is useful to assess for other causes of symptoms such as hydrocephalus or venous thrombosis.
7. Neuroimaging findings are usually normal with the exception of small ventricles or an empty sella in some cases.
8. Intracranial noises, facial numbness, tinnitus, transient visual obscurations, and double vision can occur.
9. About half the patients have visual-field deficits, most commonly enlargement of the blind spot and constriction of peripheral vision.
10. Ophthalmologic consultation is essential for careful assessment of visual fields, acuity, and papillary function.

Treatment

1. Medical therapy is used for patients without visual loss and includes
   - **a.** A medication, usually acetazolamide, to lower ICP
   - **b.** Weight loss if appropriate

c. Steroids are used by some clinicians if visual loss is present.

2. Surgical therapy is reserved for patients with visual loss or poor response to medical therapy and includes
   a. Cerebrospinal fluid (CSF) shunting procedures, especially lumboperitoneal shunt
   b. Optic nerve sheath fenestration, which some believe to be the best procedure to preserve vision
   c. Stenting of functional lateral venous sinus obstruction is under study.

LOW CEREBROSPINAL FLUID PRESSURE HEADACHE

Background

Headache attributable to low CSF pressure may occur spontaneously or as a result of dural trauma that allows leakage of CSF. LP or other trauma is a common cause.

Pathophysiology

Decreased CSF volume causes compensatory dilation of cerebral veins and sinuses with resulting traction on pain-sensitive cerebral vessels. This is accentuated by upright posture.

Prognosis

If the cause of the CSF leak can be corrected, the headache resolves within 48 hours, and often much sooner. Spontaneous resolution may also occur.

Diagnosis

1. Headache is typically generalized and severe. When caused by LP or inadvertent dural puncture from anesthesia, it usually develops within 5 days of the procedure.
2. It worsens within minutes of standing or sitting and improves within minutes of lying down.

3. It may be associated with tinnitus, hyperacute hearing, photophobia, and nausea.
4. LP shows an opening pressure of less than 60 mm H_2O.
5. Gadolinium-enhanced cranial MRI may show pachymeningeal enhancement and, occasionally, small subdural hematomas.
6. Evidence of CSF leakage may be seen on CT myelogram, conventional myelogram, or radionuclide cisternography.

Treatment

1. Conservative treatment with bed rest, IV hydration, and oral caffeine may be tried initially.
2. Epidural blood patch, ideally performed near the site of the leak, may be performed if conservative treatment is not effective. Repeated blood patches may be needed.
3. Fibrin sealant injections are sometimes performed.
4. In refractory cases where the site of the leak is known, surgical repair of the dura may be undertaken.

CEREBRAL VENOUS THROMBOSIS

Background

Cerebral venous thrombosis is an uncommon cause of stroke with headache, but its incidence is increased during pregnancy and in the postpartum period in women using estrogen-containing contraceptives and in those with chronic inflammatory diseases or hyperviscosity syndromes.

Pathophysiology

1. Blood clots form in the cortical veins and the venous sinuses of the brain (rarely in the cortical veins alone).
2. Local alterations in blood flow, vessel wall injuries, or hypercoagulability can predispose to formation of a clot.
3. Venous congestion because of the clot causes interruption in the blood supply to adjacent areas of the brain, and cerebral edema and hemorrhage

may result, producing headache.

Prognosis

A quarter to a third of patients have full recovery; mortality in untreated cases is at least 10%. Some patients have residual neurologic impairment, seizures, or headache.

Diagnosis

1. Onset can be acute or insidious. In about half the patients, the syndrome evolves over 2 days to a month.
2. Headache and seizure are the most common presentation. Focal neurologic deficits, especially sixth nerve palsy, signs of increased ICP, and altered consciousness can also occur.
3. Cavernous sinus thrombosis should be suspected with painful third or sixth nerve palsy.
4. Headache is present in most patients with cerebral venous thrombosis but has no particular characteristics and can mimic primary headache disorders such as migraine.
5. Diagnosis is based on neuroimaging.
   a. Cranial MRI is preferred and shows an infarct whose distribution does not correspond with an arterial occlusion.
   b. MR venography visualizes the dural sinuses and large cortical veins.
   c. Cranial CT scan with contrast may show the "empty delta sign" with enhanced superior sagittal sinus collateral veins surrounding the nonenhanced sinus thrombus.
6. D-dimer levels less than 500 μg/L are associated with a low likelihood of cerebral venous thrombosis.

Treatment

1. IV heparin is used (with the goal of obtaining a partial thromboplastin time 2 to 2.5 times the control).
2. Systemic thrombolytic therapy is used in some specialized centers.
3. Most experts recommend continued anticoagulation with oral warfarin for 3 to 6 months.

CAROTID ARTERY DISSECTION

Background

Incidence is 2.5 to 3 per 100,000 population per year. It is most common in midlife.

Pathophysiology

A small tear in the intima of the artery allows blood to enter and dissect the inner layers of the artery, forming an intramural hematoma. This causes stenosis or complete occlusion of the artery. Dissection can be spontaneous, perhaps because of inherent weakness in the vessel wall from connective tissue disorders, or can result from mechanical trauma. Headache is presumably caused by direct irritation of the sensory fibers of the trigeminal nerve that innervate the carotid and travel in a plexus with autonomic fibers.

Prognosis

1. Headache associated with dissection resolves spontaneously in most patients, usually within a week.
2. The majority of patients with extracranial dissections make good recovery following treatment, although early mortality rates can approach 10%, and some patients have persistent neurologic impairment.

Diagnosis

1. The following ipsilateral symptoms or signs are common.
   - **a.** Pain, especially in the anterior neck, face or eye, or temporal area
   - **b.** Miosis and ptosis (partial Horner syndrome)
   - **c.** Lower cranial nerve palsies
2. Cerebral ischemia, in the form of TIA or infarction, occurs in 75% of patients.
3. Cervical MR angiography with axial T1 sequences through the vessel lumen may show a bright “crescent sign” surrounding a flow void.

Treatment

1. Anticoagulation with heparin, followed by 3 to 6 months of warfarin therapy, is usually recommended.
2. IV tissue plasminogen activator treatment has been used in patients presenting for treatment within 3 hours of onset.
3. Surgical procedures such as angioplasty with stenting, embolization, coiling, or ligation are used rarely.

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13 Stroke and Cerebrovascular Disorders

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ARTERIAL ISCHEMIC STROKE AND TRANSIENT ISCHEMIC ATTACK

Background

1. Stroke is the fifth leading cause of death in the United States and the most common cause of serious long-term disability.
2. Completed stroke and transient ischemic attack (TIA) have the same vascular pathophysiology and are distinguished by the duration of ischemia and presence or absence of permanent tissue injury.
3. TIA is defined as a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction. Diffusion-weighted magnetic resonance imaging (MRI) has revealed that many events that fit the former definition of vascular symptoms lasting <24 hours were, in fact, associated with acute infarction; therefore, this tissue-based definition of TIA is now most widely used.

History

1. The onset of stroke is typically sudden, and symptoms vary according to the site of ischemia.
2. History is directed at distinguishing stroke and TIA from other causes of sudden focal deficits such as migraine and focal seizures.
3. Underlying factors in the history that suggest the possible cause of stroke are
   - **a.** Heart disease, including atrial fibrillation, and peripheral arterial disease.
   - **b.** Atherosclerotic risk factors (hypertension [HTN], diabetes,

hypercholesterolemia, smoking, sedentary lifestyle, family history of stroke and atherosclerotic disease).

c. History suggesting thrombophilia; cranial or cervical trauma or neck, face, and head pain that suggest arterial dissection and history of fever, chills, cardiac symptoms, or drug abuse that suggest endocarditis.

4. When acute thrombolytic or endovascular therapies are being considered, the precise time of symptom onset and problems that might contraindicate such therapies should be determined.

Pathophysiology

1. Most cases of focal cerebral ischemia are caused by blockage of a cerebral artery. The most common causes of occlusion are

a. Embolism of thrombotic material from the heart chambers or valves or from another source such as the aorta

b. Atherosclerosis in a large or medium artery, particularly a carotid artery, causes either stenosis with reduction of distal blood flow or local thrombosis that causes artery-to-artery embolism to a cerebral vessel

c. Hypertrophy and ultimately luminal stenosis of small cerebral vessels, typically the result of chronic exposure to HTN, diabetes mellitus (DM), and hyperlipidemia

2. Less common causes of vascular occlusion include cervical arterial dissection; arteritis of small or large vessels; vasospasm; thrombophilia; and embolism of material other than thrombus, such as fat, air, tumor, amniotic fluid, or intravascular medical devices. The main disorders underlying stroke are listed in Table 13-1, but most are infrequent compared to the big three: cardioembolism, large vessel atherosclerosis, and small vessel disease.

Prognosis

1. The outcome of an individual ischemic event depends on the location, magnitude, and duration of the ischemia, hence ultimately on the size and location of the completed stroke. The outcome after stroke can be improved by the early use of intravenous (IV) tissue plasminogen activator (tPA) and by early revascularization with endovascular clot retrieval.

Table 13-1 Some Causes of Stroke

Large-vessel disease
- Atherosclerotic disease of large and medium arteries: hyperlipidemia, HTN, DM, hyperhomocysteinemia, radiotherapy, pseudoxanthoma elasticum
- Nonatherosclerotic disease of large and medium arteries: arterial dissection, fibromuscular dysplasia, moyamoya disease, sarcoidosis, fungal and tuberculous vasculitis, varicella zoster vasculitis, systemic vasculitic syndromes, isolated CNS angiitis

Small-vessel disease
- Lipohyalinosis, atherosclerosis, infections (syphilis, TB, aspergillosis), vasculitis

Cardioembolism
- HTN, atrial fibrillation, valvular heart disease, cardiomyopathy, paradoxical embolism, left atrial thrombus, ventricular mural thrombus after MI, bacterial endocarditis, nonbacterial thrombotic endocarditis (cancer, antiphospholipid antibody syndrome), left atrial myxoma

Prothrombotic states
- Cancer; oral contraceptives; pregnancy and the puerperium; antiphospholipid antibody syndrome; sickle cell disease; polycythemia vera; essential thrombocytosis; TTP; DIC; markedly elevated prothrombotic factors; deficiency or dysfunction of protein C, protein S, or antithrombin III; activated protein C resistance (factor V Leiden genotype or acquired); factor II G20210A mutation; dysfibrinogenemias; disorders of fibrinolysis

Drug abuse
- Vasospasm, vasculitis, cardiac arrhythmias, endocarditis, mycotic aneurysm, injection of infected or thrombogenic material

Miscellaneous
- CADASIL, Fabry disease, Sneddon syndrome, MELAS

HTN, hypertension; DM, diabetes mellitus; CNS, central nervous system; TB, tuberculosis; MI, myocardial infarction; TTP, thrombotic thrombocytopenic purpura; DIC, disseminated intravascular coagulation; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

Table 13-2 $ABCD^2$ Score for Predicting Early Stroke Risk After Transient Ischemic Attack

Score	Age (years)	Blood Pressure	Clinical Features	Duration	Diabetes
0	<60	Normal	No speech disturbance; no unilateral weakness	<10 min	No
1	≥60	≥140/90	Speech disturbance; no unilateral weakness	10–59 min	Yes
2	—	—	Unilateral weakness	≥60 min	—

Interpretation of $ABCD^2$ Scores

Score	2-Day Risk (%)	7-Day Risk (%)

1–3	1.0	1.2
4–5	4.1	5.9
6–7	8.1	11.7

2. The risk of a completed stroke after a TIA depends on the mechanism of the TIA and the success of appropriate acute and preventive therapies. The ABCD^2 score has been used to predict the risk of stroke in the days after TIA (Table 13-2). Predictive power is enhanced by consideration of dual TIAs, that is, recent prior TIA, and brain MRI and carotid imaging. The ABCD^2 score is commonly used by emergency departments to triage patients with TIA.

Diagnosis

Examination

1. The examiner should note the temperature, blood pressure (BP), cardiac rhythm, the quality of carotid pulses and the presence of bruits, the quality of heart sounds and presence of murmur, and any findings that might suggest a special mechanism, such as splinter hemorrhages (endocarditis) or petechiae (thrombotic thrombocytopenic purpura and other causes).
2. The neurologic examination should define the localization and clinical stroke syndrome. This allows prediction of the vessel involved and the mechanism of vascular occlusion.

Major Stroke Syndromes

1. Middle cerebral artery (MCA) territory syndrome: Contralateral gaze paresis, hemiparesis, hemisensory loss, often with contralateral visual field loss, and cortical signs (aphasia with left hemispheric lesions; neglect with right).
2. MCA branch (partial) syndromes: Nonfluent aphasia (Broca aphasia if perisylvian and transcortical motor aphasia if sparing the perisylvian area) if involving anterior division branches and fluent aphasia (Wernicke aphasia if perisylvian and transcortical sensory aphasia if sparing the perisylvian area) if involving posterior division branches of the left MCA.
3. Anterior cerebral artery (ACA) syndrome: Predominant leg weakness and

sensory deficits, sparing of vision. Bilateral frontal signs suggest a common origin of the two anterior cerebral arteries.

4. Posterior cerebral artery (PCA) syndrome: Contralateral homonymous hemi- or quadrantanopsia, typically with intact motor and somatosensory function or with associated cortical deficits, such as
   a. Memory loss from medial temporal infarction
   b. Alexia without agraphia from dominant visual cortex and splenium of corpus callosum infarction
   c. Agnosias, such as color naming and recognition disorders and prosopagnosia (facial recognition disorder), from infarction of the inferior temporo-occipital cortex
5. Mid-basilar artery syndrome implying atherosclerotic stenosis or occlusion of the mid-basilar artery with pontine (dysarthria, horizontal diplopia, vertigo, quadriparesis) and cerebellar dysfunction.
6. Top-of-the-basilar syndrome implying embolic occlusion of the distal basilar artery with midbrain (decreased arousal, vertical and horizontal diplopia, bilateral ptosis, unequal and irregular poorly reactive pupils), thalamic, and occipital dysfunction.
7. Lacunar syndromes usually indicate occlusion of a small cerebral vessel (e.g., pure motor or pure sensory syndromes without visual loss or cortical findings [aphasia or neglect]) or isolated hemiparesis with ataxia. Dysarthria is common when such lacunar infarcts are in the pons or the internal capsule.
8. Borderzone (watershed) infarcts occur when a large region of the cerebrum is subjected to reduced blood flow either from proximal vascular occlusion or from global reduction in perfusion because of systemic hypotension.
   a. Anterior watershed stroke typically produces the "man-in-a-barrel" syndrome characterized by leg and proximal upper extremity weakness with relative sparing of the distal upper extremities from infarction of the ACA and MCA border zone in the high frontal convexity.
   b. The posterior watershed stroke may produce Balint syndrome (simultanagnosia, optic ataxia, and ocular apraxia) from infarction of the MCA and PCA border zone in the parieto-occipital region.

Neuroimaging

1. The goals of acute neuroimaging after the stroke are
   a. To define the site and location of an established infarct and the extent of ischemic tissue at risk
   b. To identify the site of an acute vascular occlusion
   c. To identify potential source of the embolus
   d. To identify hemorrhage or unexpected lesions mimicking acute cerebral infarction

2. Computed tomography (CT) and CT angiography
   a. Noncontrast CT dependably identifies acute hemorrhage. It is insensitive to infarction within hours of stroke onset. However, subtle changes are sometimes detected: "dense MCA sign" of thrombus in the MCA stem; sylvian fissure dot sign indicating thrombus in the more distal MCA branches; or hypodensity, loss of gray-white differentiation, and sulcal effacement, all of which indicated early infarction. Early loss of gray-white differentiation is most commonly seen in the basal ganglia capsular region and insula ("insular ribbon sign").
   b. CT angiography allows evaluation of the patency of cerebral vessels from the aortic arch through the neck and for large intracranial vessels at least to the first branching beyond the circle of Willis.
   c. CT perfusion techniques give acute information about the size of established infarct and of hypoperfused tissue at risk of infarction.

3. MRI and magnetic resonance angiography (MRA)
   a. The diffusion-weighted imaging (DWI) sequence of MRI is far more sensitive than CT for detecting early infarction. Acute infarction becomes bright on this sequence within minutes of tissue infarction. Correlation with low signal on apparent diffusion coefficient (ADC) images differentiates acute infarction from other causes of bright signal on DWI.
   b. MRA defines flow in the cerebral vessels from the aortic arch to the intracranial arteries.
   c. MRI perfusion techniques can give information about the size of established infarct and of hypoperfused tissue at risk.

4. Conventional angiography
   a. Angiography is more sensitive and specific than either CT angiography or MRA and remains the gold standard for diagnostic vascular imaging; although infrequently used for solely diagnostic reasons, conventional

angiography is now routine for the application of acute endovascular therapies.

5. Carotid duplex ultrasound
   a. Carotid duplex ultrasound includes Doppler assessment of blood flow velocities and anatomic imaging by gray scale and color flow techniques.
   b. It is widely available, noninvasive, and, in good hands, reliably defines and quantifies most proximal atherosclerotic carotid lesions.
   c. Doppler waveforms can also give indirect information about upstream and downstream stenosis that is outside of the field of carotid ultrasound.

6. Transcranial Doppler (TCD) ultrasound
   a. TCD allows imaging of the flow of the major vessels of the circle of Willis; the proximal middle, anterior, and posterior cerebral arteries; the ophthalmic artery; and the vertebral and basilar arteries. Information about direction, velocity, and turbulence of flow allows identification of stenosis of intracranial vessels or vasospasm and assessment of pathways of collateralization. Embolic signals may also be detected.
   b. High flow velocities suggest vascular narrowing from stenosis or vasospasm, or elevated flow, as in generalized high flow states, such as arteriovenous malformations or collateral flow in the setting of stenosis or occlusion at another site. Because ultrasound is safe and noninvasive, it can be used serially for repeated examinations. Its most valuable application has been serial evaluation of the severity of cerebral vasospasm after subarachnoid hemorrhage (SAH).

Other Tests for Stroke Assessment

1. Electrocardiogram (ECG), chest radiograph (CXR), glucose, electrolytes, blood urea nitrogen (BUN), creatinine, complete blood count (CBC) with platelets, prothrombin time (PT), international normalized ratio (INR), and an activated partial thromboplastin time (aPTT) should be part of the initial evaluation to help determine the cause of the event and to provide information critical to the planning of acute therapy.
2. If fever or cardiac murmur is present, or if there are other reasons to suspect endocarditis, then C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR), blood cultures, and echocardiogram are important to pursue this diagnosis.

3. If there is reason to suspect drug abuse, toxicology screening is valuable.
4. In the postacute phase, echocardiography, cardiac rhythm monitoring, further definition of the cerebral vasculature, and laboratory tests directed at stroke risk factors are indicated as follows:
   a. Fasting serum glucose and HgA1C, total low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and triglycerides.
   b. High-sensitivity CRP elevation and hyperhomocysteinemia have been identified as modifiable risk factors for atherosclerosis.
   c. Patients in whom hypercoagulability is suspected should be evaluated for underlying cancer, and, in some cases, with immunoglobulin G (IgG) and immunoglobulin M (IgM) anticardiolipin antibodies, beta-2 glycoprotein 1 antibodies, lupus anticoagulant assay including, dilute Russell's viper venom test, screening for factor V Leiden, prothrombin G20210A mutation, and levels and activities of proteins C and S and antithrombin III.
   d. Where aortic atheroma, valvular, or left atrial appendage visualization, or definition of a patent foramen ovale (PFO) will alter secondary preventive therapy, transesophageal echocardiography should be considered because the sensitivity of transthoracic echocardiography is low for lesions at these sites.

Treatment

Acute Therapy of Ischemic Stroke

Hemodynamic Considerations

1. Cerebral perfusion depends on the mean systemic arterial pressure (MAP) based on the basic hemodynamic relationship (CBF = [MAP − CVP] / CVR, where CBF = cerebral blood flow, CVP = cerebral venous pressure, and CVR = cerebrovascular resistance).
2. Areas of brain distal to narrowed or occluded arteries may be supplied by collateral vessels. When fully dilated (i.e., autoregulated to maximize CBF), flow in these vessels becomes passively dependent on the MAP. Therefore, it is desirable to maintain MAP high in the setting of acute stroke.
3. It is common for patients with acute stroke to have acute BP elevations on presentation.

a. In general, BP should not be lowered, unless

1) BP lowering is necessary to fulfill criteria for safe thrombolysis (see the section on Intravenous Thrombolysis and Tables 13-3 and 13-4), or unless acute medical issues demand it:

a) Acute myocardial infarction

b) Aortic dissection

c) Hypertensive crisis with end-organ involvement (congestive heart failure, acute renal failure, hypertensive encephalopathy)

b. A threshold above which BP should be treated acutely has not been established outside of these complications; however, consensus guidelines from the American Stroke Association suggest that therapy should be withheld unless diastolic BP is above 120 mm Hg or systolic BP is above 220 mm Hg.

Table 13-3 Acute Antihypertensive Therapy for Administration of Intravenous Tissue Plasminogen Activator

Management of BP Before Treatment with IV tPA
For systolic BP >185 mm Hg or diastolic BP >110 mm Hg
• Labetalol 10–20 mg IV over 1–2 min; may repeat once, or
• Nicardipine 5 mg/h IV; titrate up by 2.5 mg/h every 5–15 min; maximum dose 15 mg/h; when desired BP reached, adjust to maintain proper BP limits, or
• Other agents (hydralazine, enalaprilat, etc.) may be considered when appropriate
If BP is not maintained at or below 185/110, do not administer tPA.
Management of BP During and After Treatment with tPA or other Acute Reperfusion Therapy to Maintain BP at or Below 180/105 mm Hg
Monitor BP every 15 min for 2 h from the start of tPA, then every 30 min for 6 h, and then every hour for 16 h.
If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg:
• Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min or
• Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h
If BP is not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside starting at 0.5 1 μg/kg/min

BP, blood pressure; IV, intravenous; tPA, tissue plasminogen activator.

From Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for early management of patients with acute ischemic stroke. *Stroke*. 2013;44(3):870–947.

c. Patients with excessive BP elevation who are otherwise suitable for tPA should be treated acutely to achieve tolerable BP for therapy (systolic BP <185 mm Hg, diastolic BP <110 mm Hg). The antihypertensive goals and regimen modeled after the practice in the National Institute of Neurological Disorders and Stroke (NINDS) trial of IV tPA and recommended by the American Stroke Association are shown in Table 13-3.

Metabolic Considerations

1. Patients may be monitored with pulse oximetry and given supplemental oxygen for desaturation to less than 95%.
2. Both hyperthermia and hyperglycemia may increase the size of the ultimate infarct in experimental models and some clinical studies; therefore, patients should receive antipyretic medications and external cooling, if needed to maintain normal body temperature, and insulin to avoid excessive glucose elevation.

Intravenous Thrombolysis

1. All patients who present within 3 hours of onset of stroke symptoms should be considered for IV thrombolytic therapy with tPA.

Table 13-4 Indications and Contraindications for Intravenous Tissue Plasminogen Activator for Acute Ischemic Stroke

Inclusion Criteria
• Acute ischemic stroke causing measurable neurologic deficit • Onset within 3 h (and within 3–4.5 h with the added exclusion criteria noted below under "Exclusion Criteria," item 1)[a] • Age ≥18 y
Exclusion Criteria
• For 3- to 4.5-h window only: age >80 y, NIHSS >25; taking oral anticoagulants regardless of INR, history of both diabetes and prior ischemic stroke • Significant head trauma or prior stroke in previous 3 mo

- Symptoms suggesting SAH
- Arterial puncture at noncompressible site in previous 7 d
- History of previous intracranial hemorrhage
- Intracranial neoplasm (other than incidental meningioma), AVM, or aneurysm
- Recent intracranial or intraspinal surgery
- Elevated BP (SBP >185 mm Hg or DBP >110 mm Hg)
- Active internal bleeding
- Active bleeding diathesis, including but not limited to
  - Platelet count <100,000/mm^3
  - Heparin received within 48 h, resulting in abnormally elevated aPTT, greater than the upper limit of normal
  - Current use of anticoagulant with INR >1.7 or PT >1.5 seconds
  - Current use of direct thrombin inhibitor or direct factor Xa inhibitor with elevated sensitive laboratory tests (such as aPTT, INR, ECT, TT, or appropriate factor Xa activity assays)
  - Blood glucose concentration <50 mg/dL (2.7 mmol/L)[b]
- Head CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Relative Exclusion Criteria (consider risk to benefit carefully if any of these is present)

- Seizure at onset with postictal residual neurologic impairments[b]
- Major surgery or serious trauma within previous 14 days
- Recent GI or urinary tract hemorrhage (within previous 21 days)
- Recent acute MI (within previous 3 months)

[a] The American Stroke Association has endorsed this expansion of the therapeutic window for intravenous tissue plasminogen activator based on results of the European Cooperative Acute Stroke Study III (ECASS III) trial and the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) registry data (see Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329 and Wahlgren N, Ahmed N, Davalos A, et al. Thrombolysis with alteplase 3- 4.5 hours after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet*. 2008;372:1303–1309.)

[b] This contraindication is intended to prevent treatment of patients with focal deficits caused by causes other than vascular occlusion. If the deficit persists after correction of the abnormal glucose, or ideally if rapid diagnosis of vascular occlusion can be made by CT angiography or magnetic resonance angiography, then treatment may be indicated.

NIHSS, National Institutes of Health Stroke Scale Score; INR, international normalized ratio; SAH, subarachnoid hemorrhage; AVM, arteriovenous malformation; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; aPTT, activated partial thromboplastin time; PT, prothrombin time; ECT, ecarin clotting time; TT, thrombin time; CT, computed tomography; GI, gastrointestinal; MI, myocardial infarction.

2. Patients who can be treated within 3 to 4.5 hours should be considered for IV tPA therapy if they do not meet these added exclusion criteria: Older than 80 years, National Institutes of Health Stroke Scale (NIHSS) more than 25, taking oral anticoagulants, history of both prior stroke and DM.
3. Indications and contraindications for IV thrombolysis are listed in Table 13-

4.

4. For suitable patients, IV tPA should be given as soon as the essential evaluation can be completed. The dose of tPA is 0.9 mg/kg to a maximum total dose of 90 mg. Ten percent of this dose is given as a bolus over about 1 to 2 minutes. The remainder is infused over 1 hour. It is advised that emergency departments establish protocols for administration to speed up preparation and minimize errors.
5. BP should be controlled within recommended parameters for 24 hours after administration (see Table 13-3), and patients should be closely monitored for evidence of hemorrhage with serial neurologic examinations and follow-up CT scanning.
6. No adjunctive antiplatelet or anticoagulant medication should be given for 24 hours after IV thrombolysis.

Endovascular Therapies

1. There is clear evidence that urgent endovascular therapy is highly beneficial to patients presenting within 6 hours of stroke onset with internal carotid artery (ICA) or proximal MCA (M1) arterial occlusions within the anterior circulation.
2. IV tPA should be given without delay to all qualifying patients who might also be considered for endovascular therapy.
3. Although less well studied, patients with acute basilar artery occlusions should also be considered for urgent endovascular therapy.
4. Proper concurrent use of heparins, antiplatelet agents, and induced HTN has not been established by systematic study and at this time are based on institutional protocols.

Early Use of Antiplatelet Therapies and Anticoagulants

1. Acute administration of aspirin and other antiplatelet agents has not been shown to decrease stroke size; although in large trials, early institution of low-dose aspirin has slightly improved outcome, probably by reducing the incidence of early recurrent events within approximately 2 weeks.
2. There is evidence that, if started within 24 hours after TIA and minor stroke, short-term (21 days) dual antiplatelet treatment with aspirin and clopidogrel (300 mg load, then 75 mg daily) followed by antiplatelet monotherapy reduces the risk of early recurrent stroke.

3. Early use of unfractionated heparin and low molecular weight heparins (LMWHs) has been studied with variable results. There may be some benefit in preventing early recurrent events in patients with severe carotid stenosis and atrial fibrillation.
4. Patients with prosthetic heart valves requiring anticoagulation and other cardiac lesions representing clear embolic risks are best placed back on anticoagulants as early as judged to be safe.
5. Anecdotal data suggest that reperfusion of infarcted tissue is more likely to undergo hemorrhagic conversion when anticoagulants are given, when strokes are large, when bolus doses of heparin are used, and when the level of anticoagulation is excessive. Therefore, care should be taken when anticoagulants are begun early after acute ischemic stroke.

Deep Vein Thrombosis Prophylaxis

1. Patients immobilized after acute strokes should be placed on low-dose subcutaneous heparin or LMWH and be provided with pneumatic compression boots to minimize the risk of deep vein thrombosis (DVT).
2. Patients who cannot receive anticoagulants may benefit from aspirin for DVT prevention.

Hemicraniectomy

1. In patients with large hemispheric infarcts and malignant cerebral edema for whom medical therapy of the cerebral edema and mass effect may prove inadequate, hemicraniectomy, removal of a large segment of the overlying cranial bone and incision of the dura, may directly relieve intracranial pressure (ICP) and midline shift and herniation by allowing the swollen infarcted tissue to herniate through the surgical defect. This therapy has been shown to increase survival after large strokes.
2. Hemicraniectomy may be lifesaving, but the patient and family should understand that the underlying disabling stroke is not altered.

Secondary Prevention of Ischemic Stroke

Antiplatelet Therapies

Low-dose aspirin (81 to 650 mg/d), aspirin combined with dipyridamole (aspirin 25 mg/dipyridamole 200 mg twice a day), and clopidogrel (75 mg/d) have been shown to reduce the risk of recurrent events after stroke and TIA.

Long-term combination of aspirin and clopidogrel has not been shown to confer benefits in excess of monotherapies or of aspirin with dipyridamole for secondary prevention in general. However, for patients with atrial fibrillation who cannot take warfarin, the combination of aspirin and clopidogrel does confer added protection from ischemic stroke, although with added hemorrhagic risk (see the section on Atrial Fibrillation). Aspirin is typically used in doses of 81 to 325 mg, although higher doses may be more effective in some patients with relative aspirin resistance. Lower doses confer less hemorrhagic risk.

Early use of short-term dual antiplatelet therapy with aspirin and clopidogrel decreases risk of early recurrent stroke (see section on Early Use of Antiplatelet Therapies and Anticoagulants).

Atrial Fibrillation

1. It has been demonstrated in several studies that warfarin reduces the risk of stroke in patients with atrial fibrillation and that strokes occurring in these patients tend to occur during lapses in anticoagulation.
2. All patients with persistent or paroxysmal atrial fibrillation who have had a prior stroke or have a CHADS2 score ≥2 should be given chronic anticoagulation therapy, unless there are decided contraindications to its use.
3. Options for anticoagulation for nonvalvular atrial fibrillation have broadened with the introduction of oral direct inhibitors of thrombin and factor Xa. Available agents are listed in Table 13-5.
4. Aspirin probably slightly lowers the risk of stroke in patients with atrial fibrillation, although its benefit has been inconsistently shown in trials. The combination of aspirin and clopidogrel is more effective than aspirin at preventing strokes in the setting of atrial fibrillation, however, at the cost of increased risk of hemorrhage, mostly gastrointestinal.
5. Patients with lone atrial fibrillation (younger than 60 years, no prior stroke or TIA, normal ECG and echocardiogram, no HTN, no DM) are the sole exception. Such patients appear to have a risk of stroke comparable to that of the general population, and anticoagulation is not indicated for them for *primary* prevention. Such patients should receive low-dose aspirin or other antiplatelet therapy.

Table 13-5 Oral Anticoagulation for Nonvalvular Atrial Fibrillation

Agent	Standard Dose	Comments
Warfarin	Variable	Maintain goal INR 2–3
Apixaban	5 mg b.i.d.	2.5 mg b.i.d., if two of these three conditions are met: age ≥80 y, weight ≤60 kg, creatinine ≥1.5 mg/dL
Rivaroxaban	20 mg daily	15 mg daily, if CrCl = 15–50 mL/min; avoid if CrCl <15 mL/min
Edoxaban	60 mg daily	30 mg daily, if CrCl = 15–50 mL/min; avoid if CrCl <15 mL/min
Dabigatran	150 mg b.i.d.	Reduce dose or avoid in patients ≥75 y and those with reduced renal function, on strong P-gp inhibitors, or with prior GI bleeding

INR, international normalized ratio; b.i.d., twice a day; CrCl, creatinine clearance; P-gp, P-glycoprotein; GI, gastrointestinal.

Intracranial Arterial Stenosis

For patients with symptomatic intracranial stenosis, a trial comparing warfarin to aspirin found an increased risk of major hemorrhage to outweigh the benefit of warfarin for ischemic stroke prevention, and two trials of intracranial stenting versus medical therapy found an increased hazard with stenting. Therefore, most patients with symptomatic intracranial stenosis should be treated with antiplatelet agents and optimal risk factor management.

Valvular and Other Heart Disease

1. Patients with rheumatic and other valvular disease and evidence of embolic stroke or TIA may benefit from anticoagulation; however, the subsets of patients who should be treated with long-term anticoagulation have not been clearly defined.
2. Patients with mechanical valve prostheses and increased embolic risk have a clear indication for anticoagulation. The optimal INR range for anticoagulation varies based on the valve type and position. Table 13-6 shows the optimal INR ranges recommended by the American College of Cardiology and the American College of Chest Physicians for patients with mechanical and biologic heart valve prostheses. Neither oral direct thrombin nor factor Xa inhibitors should be used for anticoagulation in patients with mechanical valve prostheses.

3. Patients with dilated cardiomyopathy have an increased risk of embolic stroke. A trial of patients with left ventricular ejection fraction (LVEF) ≤35% showed that warfarin therapy was associated with a reduced risk of ischemic stroke, however, with a competing increase in risk of major hemorrhage, but not of intracranial hemorrhage. Risk and benefit must be weighed individually. It is reasonable to anticoagulate patients with reduced left ventricular (LV) function who are judged to be at a high risk of thromboembolism and relatively low risk of hemorrhage.

Table 13-6 Recommended Anticoagulation and Antiplatelet Therapy for Patients with Mechanical and Biologic Heart Valve Prostheses

Valve Type/Position/Complicating Condition	Recommended INR Goal (Range)
Mechanical AVR (bileaflet or current generation single tilting disc) and no additional thromboembolic risk factors[b]	2.5 (2.0–3.0) + low-dose aspirin[a]
Mechanical AVR plus addition risk factors	
Mechanical AVR, older generation (e.g., ball in cage)	3.0 (2.5–3.5) + low-dose aspirin
Mechanical MVR	
Bioprosthetic AVR or MVR	
Mechanical bileaflet AVR and no risk factors during intervals when warfarin must be discontinued	3.0 (2.5–3.5) + low-dose aspirin
Mechanical AVR with any risk factor or older generation AVR or mechanical MVR during intervals when warfarin must be discontinued	3.0 (2.5–3.5) + low-dose aspirin
	Low-dose aspirin
	No bridge
	Bridge with UFH or LMWH

[a] 75–100 mg daily.

[b] Atrial fibrillation, previous thromboembolism, myocardial infarction, left ventricular dysfunction, left atrial enlargement, hypercoagulable state.

INR, international normalized ratio; AVR, aortic valve replacement; MVR, mitral valve replacement; UFH, unfractionated heparin; LMWH, low molecular weight heparin.

4. Clear standards for the treatment of cryptogenic stroke or TIA in the setting of a PFO have not been established. With PFO, risk of infarct may be increased in the presence of an accompanying atrial septal aneurysm or a

large right-to-left shunt. The high frequency of PFO in the healthy population makes this a difficult and important therapeutic issue.

5. At this time, it is reasonable to advise that patients with stroke or TIA and PFO receive antiplatelet agents, those with identified venous thrombus receive anticoagulation for at least 3 months, those with hypercoagulable states be treated with long-term anticoagulation, and those with recurrent strokes or TIAs despite anticoagulation be considered for closure of the PFO. Whether large size or the presence of atrial septal aneurysm alone justifies closure has not been established.

Carotid Stenosis and Other Indications for Surgical Therapy

1. Patients with TIA or with partial strokes in the ICA territory and with significant atherosclerotic carotid stenosis should be considered for carotid endarterectomy as soon as possible in the case of TIAs and as soon as it is deemed safe after partial territory strokes.
   - **a.** The benefit of carotid endarterectomy in symptomatic patients (prior stroke or TIA) with stenosis of 70% or greater has been clearly established in several trials. These early studies failed to show a benefit in patients with less than 30% stenosis. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) data suggest that those with stenosis of 30% to 69% have an intermediate risk and that, in those with stenosis above 50%, a small surgical benefit accumulates statistical significance after 5 years.
   - **b.** In asymptomatic patients, primary stroke prevention by carotid endarterectomy remains an uncertain issue. Two studies show, after 5 years of follow-up, a small benefit in favor of carotid endarterectomy in patients with stenosis of 60% to 70% or greater. These studies were done before statin agents were widely used, and they gave the same weight to early strokes which are more highly represented in the surgical group because of the perioperative stroke risk, although early strokes confer a higher burden of cumulative disability. The studies did not find an increased risk of stroke and benefit of carotid endarterectomy with increasing degrees of stenosis above 60%. Therefore, it is difficult to give broad advice about thresholds for carotid endarterectomy in asymptomatic patients. With the available data, it is reasonable to recommend carotid endarterectomy in asymptomatic individuals with severe asymptomatic

stenosis who are at low surgical risk, especially if serial ultrasound or imaging shows progressive stenosis. Statin drugs and aspirin may be a reasonable alternative.

2. Trials comparing angioplasty and stenting of stenotic carotid lesions with endarterectomy suggest reasonable safety of stenting and slightly lower or similar overall efficacy in patients with high surgical risk. In patients of average risk, endarterectomy and stenting appear to be comparable for symptomatic and asymptomatic disease, with a higher risk of periprocedural stroke with stenting and of myocardial infarction with endarterectomy. Therefore, carotid stenting has become an alternative to endarterectomy.

Risk Factors for Atherosclerosis and Small-Vessel Disease

1. Antihypertensive therapy
   a. HTN is a major stroke risk factor even at levels beneath the conventionally defined normal thresholds. Both systolic and diastolic elevations increase stroke risk. Therefore, all patients at risk should receive optimal BP control. Consensus guidelines recommend maintenance of systolic BP <140 mm Hg and diastolic BP <90 mm Hg, with stricter goals of 130/80 mm Hg for those with history of diabetes and other risk factors. Various agents might be used to accomplish this. The Heart Outcomes Prevention Evaluation (HOPE) trial suggests that angiotensin-converting enzyme inhibitors may confer a measure of stroke prevention beyond their BP-lowering effect.

2. Statins and cholesterol-lowering therapy
   a. Elevation of LDL cholesterol and triglycerides and low HDL cholesterol are risk factors for atherosclerotic vascular disease, including stroke. The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) have been shown to decrease LDL cholesterol and may lower triglycerides and elevate HDL cholesterol in some patients. These agents have been shown to lower the risk of atherosclerotic mortality and vascular events, including stroke. They may also confer benefits in addition to those of lipid lowering. Triglycerides may respond to glycemic control and fibrates, although statins may also contribute benefit. Niacin and fibrates are most effective in elevating HDL cholesterol, although these agents must be used with caution in diabetics. When combined with

statins, niacin may cause hyperglycemia; fibrates may cause myositis. Consensus guidelines recommend maintenance of LDL <100 in all patients with past stroke or presumed atherosclerotic origin. In those with other multiple vascular risk factors, intensive statin therapy is recommended following the 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines.

b. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial showed lowered recurrent stroke risk in patients treated with intensive lipid lowering (atorvastatin 80 mg daily with target LDL <70) beginning soon after an acute ischemic stroke. Statin therapy requires surveillance for myopathy and liver disease.

3. Other risk factors and interventions

a. In all cases, weight loss, proper nutrition, moderation of alcohol use, smoking cessation, and regular physical exercise should be encouraged as first or concurrent steps in therapy of modifiable risk factors.

b. Fluoxetine 20 mg daily initiated 5 to 10 days after stroke onset and continued for 3 months has been shown to improve motor recovery when combined with physical therapy.

4. Hyperhomocysteinemia

a. Hyperhomocysteinemia contributes to stroke risk by two mechanisms: promoting atherosclerosis and promoting thrombosis. Although trials have not shown stroke reduction from lowering of homocysteine levels with high-dose vitamin therapy, for patients with hyperhomocysteinemia (>10 μmol/L), it is reasonable to recommend daily multiple vitamins (B_6 1.7 mg daily, B_{12} 2.4 μg daily, folate 0.4 mg daily). Some subgroups at high risk of atherosclerosis may benefit from more aggressive vitamin therapy.

Other Arterial Lesions

1. Many diseases other than atherosclerosis may lead to stroke (Table 13-1).

a. The most common of these is arterial dissection. Dissection of the carotid or vertebral arteries is most common and may cause symptoms by compromise of the vessel lumen and distal flow or by embolization from thrombus formed at the site of endothelial tear. The risk of the latter is probably decreased by anticoagulation and antiplatelet agents. A large trial showed strokes to be rare after dissection and no difference in

efficacy of aspirin and anticoagulation for stroke prevention. There is a risk of SAH from rupture of a pseudoaneurysm when a dissection extends intracranially.

b. Headache or systemic illness, especially with elevated ESR or CRP, could suggest cerebrovascular vasculitis as a possible cause of a stroke or TIA.

1) When giant cell arteritis is strongly suspected, prednisone 60 to 80 mg daily should be started without delay to minimize risk of visual loss. Diagnosis can be confirmed with temporal artery biopsy after treatment has been started.

2) When visual loss has already occurred in one eye because of temporal arteritis, there is anecdotal evidence that early use of high-dose methylprednisolone minimizes risk of visual loss in the other eye.

3) Systemic vasculitis with neurologic manifestations and primary central nervous system (CNS) angiitis are treated with corticosteroids (e.g., prednisone 60 to 80 mg daily) with or without other immunosuppressive agents.

4) Primary CNS vasculitis is rare but usually requires more potent immune suppression with cyclophosphamide or other agents.

5) It is important to differentiate isolated CNS vasculitis from intravascular lymphoma or other mimicking disorders to ensure the selection of appropriate therapies.

6) CNS angiitis should be distinguished from reversible cerebral vasoconstriction syndrome based on the acute presentation, normal or near-normal cerebrospinal fluid (CSF) findings, and reversibility of angiographically demonstrated stenosis and dilations characteristic of the latter.

Thrombophilic States

l. The two most important thrombophilic states to consider when evaluating patients with arterial stroke are the thrombophilia of malignancy and the antiphospholipid antibody syndrome (APAS).

a. Cancer, especially adenocarcinomas of the gastrointestinal tract, lungs, or breast, may induce a state of hypercoagulability characterized by activation of the thrombin generation and fibrinolytic systems. Patients may show laboratory evidence of this (elevated D-dimer and fibrin

degradation products); however, frank disseminated intravascular coagulation with consumption of fibrinogen, platelets, and clotting factors with prolongation of INR, aPTT, and thrombin time is uncommon.

b. Strokes in such patients may be because of *in situ* thrombosis in cerebral vessels, embolization from cardiac lesions such as marantic endocarditis, or embolization from a venous source through a PFO or other arteriovenous shunt. Anticoagulation may reduce thrombotic risk in such patients until more definitive therapy for the cancer can be given.

c. There is evidence that LMWH is more effective than warfarin in patients with cancer.

2. The major features of the APAS are recurrent venous or arterial thrombotic events, thrombocytopenia, and, in women, recurrent second-trimester miscarriages. Other symptoms and signs include migraines, livedo reticularis, and, rarely, chorea. Laboratory evidence is most commonly elevation of anticardiolipin antibodies at high titers (IgG, IgM, or immunoglobulin A [IgA]), anti-β2-glycoprotein 1 antibodies, evidence of a circulating (lupus) anticoagulant on various functional tests of coagulation (e.g., Russell viper venom, modified aPTT, mixing study, platelet neutralization test for phospholipids dependence), thrombocytopenia, positive antinuclear antibody (ANA), and false-positive rapid plasma reagin (RPR). Stroke is the most common manifestation of arterial thrombosis, and there is a tendency for a single patient to have recurrences in the same vascular bed (arterial or venous) as prior events. Patients with APAS and a history of a single stroke or TIA should receive either moderate-intensity warfarin (INR 1.4 to 2.8) or aspirin 325 mg daily. With recurrent events, full anticoagulation (INR 2 to 3) or LMWH with or without antiplatelet agents should be given.

3. Other causes of thrombophilia include inherited and acquired deficiency or dysfunction of antithrombin III, proteins C and S, factor V Leiden mutation, acquired activated protein C resistance, and the prothrombin *G20210A* mutation. These states have been clearly linked to venous thrombosis. The association with arterial events such as stroke has been harder to confirm. Some studies of young stroke populations have found a statistical association. When these disorders are implicated by association with otherwise unexplained strokes and TIAs, then it is reasonable to consider

long-term antiplatelet therapy or anticoagulation; however, no systematic study of this issue guides clinical choice.

CEREBRAL VENOUS SINUS THROMBOSIS

Background

Stroke may also occur from occlusion of cerebral venous sinuses or cerebral cortical veins by thrombus. Although much less common than arterial occlusion, this is an important mechanism of stroke to keep in mind, especially in late pregnancy, the postpartum period, and in other thrombophilic states.

History

The important history is the presence of conditions that predispose the patient to venous thrombosis. Women in late pregnancy or the postpartum period or patients with other evidence of thrombophilic states should raise suspicion. Patients may present with headache, focal deficits, and focal seizures. Some patients will have headaches with or without progressive visual loss or visual obscurations, and venous sinus thrombosis should be considered as a possible underlying cause in all patients with the pseudotumor cerebri syndrome.

Pathophysiology

Most venous sinus thromboses occur in the context of hypercoagulability, such as pregnancy or the puerperium, cancer, or the other thrombophilias listed above (see section on Thrombophilic States). Trauma, adjacent tumor or inflammation, dural arteriovenous fistulas, or anatomic abnormalities may contribute in some cases. The infarcts that ensue are thought to be caused by the congestion of capillary blood flow that results from elevated venous pressures. Hemorrhagic conversion is common in venous infarcts.

Prognosis

As with arterial strokes, prognosis depends on the size, location, and degree of infarction and hemorrhage, but venous strokes are typically less complete within the territory of the infarct, and in many cases, neurologic recovery is

excellent.

Diagnosis

Examination

As with arterial strokes, focal neurologic signs are the most prominent findings. Bilateral signs, seizures, headache, papilledema, and other evidence of elevated ICP should all raise suspicion of venous infarction.

Neuroimaging

1. Head CT may show hyperdensity in the region of a thrombosed venous sinus or at the site of a thrombosed cortical vein. With contrast, the surrounding dural wall of the superior sagittal sinus will enhance, while the area of the thrombosis will not, creating the empty delta sign. In addition, a venous infarction may be visualized as hypodensity, swelling, or hemorrhage in the region of the affected sinuses, for example, parasagittal (superior sagittal sinus thrombosis) or in the temporal lobe (transverse sinus thrombosis). These infarcts may cross boundaries of typical arterial territories providing a clue that they are caused by venous occlusion. CT venography may show absence of contrast filling in thrombosed sinuses.
2. MRI may show signal intensities consistent with acute (isointense on T1- and hypointense on T2-weighted images) or subacute (hyperintense on T1- and T2-weighted images) thrombosis within affected sinuses as well as features of venous infarction, often with hemorrhagic conversion. Magnetic resonance (MR) venography may show absence of flow in thrombosed sinuses. Blooming hypodensity on susceptibility or gradient-echo images may be helpful in identifying venous sinus and elusive cortical vein thrombosis.
3. Angiography is more specific than MR or CT venography, but, where these latter are available, it is usually not needed to establish the diagnosis.

Lumbar Puncture

Findings on lumbar puncture (LP) are nonspecific. CSF pressure may be elevated, protein may be elevated, and there may be increased numbers of red and white blood cells.

Laboratory Tests

Laboratory tests may help reveal evidence of underlying thrombophilia, infection, or inflammation (see section on Thrombophilic States).

Treatment

1. Anticoagulation with heparin is indicated for most cases of venous sinus thrombosis. Patients with and without hemorrhage into venous infarcts appear to benefit. Duration of chronic anticoagulation with warfarin is not standardized, and decisions should be based on the reversibility of the underlying cause and the anatomic issues of recanalization and collateral flow.
2. Transvenous cannulation of the affected sinus with catheter-directed thrombolysis and mechanical removal of thrombus may be indicated when patients have severe deficits from involvement of the deep venous system or extensive involvement of superficial sinuses.

HEMORRHAGIC STROKE (CEREBRAL HEMORRHAGE)

Background

Intracranial hemorrhage accounts for about 15% of strokes. These strokes may be because of SAH or of hemorrhage into the brain parenchyma or ventricles.

History

SAH typically presents with sudden onset of a severe, explosive headache; stiff neck; photophobia; nausea; and vomiting. Patients may have focal loss of function and sudden loss of consciousness, which may be transient.

As with other strokes, the symptoms of intraparenchymal hemorrhage depend on the site of the stroke. The typical symptoms are sudden focal loss of function with early headache. Symptoms will often worsen in the first minutes and hours after onset. Patients with hemorrhages in critical upper brainstem and diencephalic structures will have loss of consciousness at onset. Those

with large hemispheric hemorrhages in the basal ganglia or lobar areas or in the cerebellum may progress to coma rapidly as the hemorrhage expands and mass effect increases.

Pathophysiology

There are many causes of intracranial hemorrhage. Epidural and subdural hematomas are not usually classified as strokes, and they are not discussed here.

1. Large SAH is usually caused by rupture of an intracranial saccular aneurysm.
2. Small SAH over the cerebral convexities are most commonly caused by trauma, thrombocytopenia or other coagulopathies, reversible cerebral vasoconstriction syndrome, or cerebral amyloid angiopathy (CAA).
3. Intraparenchymal hemorrhage is most commonly because of long-standing HTN. Such hypertensive hemorrhages are typically located in the basal ganglia, thalamus, pons, or cerebellum.
4. Lobar hemorrhages (located in the subcortical white matter) in elderly patients are often the outcome of CAA. In younger patients, coagulopathy and arteriovenous malformations are the usual causes.
5. Various cerebral vascular malformations may cause hemorrhage. These include aneurysms, arteriovenous malformations, dural arteriovenous fistulas, and cavernous malformations. Venous malformations and capillary telangiectasias rarely cause hemorrhage.
6. Coagulopathies, such as those from warfarin or thrombocytopenia because of various hematologic and malignant disorders, may cause hemorrhages that are often multifocal.
7. Tumors may give rise to spontaneous hemorrhage, especially glioblastoma multiforme, oligodendrogliomas, and certain metastatic tumors, particularly lung, breast, melanoma, renal cell carcinoma, thyroid carcinoma, and choriocarcinoma.
8. Hematomas may occur in the context of drug abuse, especially of stimulants such as cocaine, which cause marked increases in BP and, rarely, vasculitis.
9. Venous infarctions caused by venous sinus thrombosis often have a hemorrhagic component or frank clot. Secondary hemorrhage may also complicate arterial infarctions.

Prognosis

Prognosis varies greatly with the site, size, and cause of the hemorrhage and with the occurrence and management of complications.

Diagnosis

1. SAH
   - **a.** All patients with sudden severe headache should be evaluated for possible SAH. The examiner should check for nuchal rigidity, subhyaloid retinal hemorrhages, and subtle neurologic deficits, especially cranial neuropathies.
   - **b.** The sensitivity of cranial CT to acute blood depends on the size of the SAH and the time since its occurrence. Table 13-7 provides estimates from one study. These estimates may be high because subtle changes were interpreted as positive, and no patients had mild headaches felt to be small warning leaks.

Table 13-7 Sensitivity of Computed Tomography in Subarachnoid Hemorrhage

Time After SAH of CT	Positive CT (%)
2 d	96
5 d	85
1 wk	50
2 wk	30
3 wk	Almost nil

SAH, subarachnoid hemorrhage; CT, computed tomography.

From van Gijn J, van Dongen KJ. The time course of aneurysmal haemorrhage on computed tomograms. *Neuroradiology*. 1982;23(3):153–156, with permission of Springer.

Table 13-8 Hunt and Hess Clinical Classification of Patients with Subarachnoid Hemorrhage

Grade I—Asymptomatic or minimal headache and slight nuchal rigidity
Grade II—Moderate to severe headache, nuchal rigidity, no neurologic deficit except cranial nerve palsies

Grade III—Drowsiness, confusion, mild focal deficit
Grade IV—Stupor, moderate or severe hemiparesis, possibly early decerebrate rigidity, vegetative disturbances
Grade V—Deep coma, decerebrate rigidity, moribund appearance
Grade VI—Dead

From Hunt WE, Hess RM. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *J Neurosurg*. 1968;28:14–20, with permission.

c. Because a small but significant number of cases may be missed by CT, when the history is suggestive but CT is negative, LP should be done to eliminate the diagnosis definitively. The findings of SAH on LP are red blood cells (RBCs) and xanthochromia (in a spun specimen). Although many ways to differentiate traumatic LP from true SAH have been proposed, such as declining number of RBCs in serially collected tubes, the opinion of the physician performing the LP, RBC crenation, and cytology for erythrophages, none of these methods, except complete clearing of the CSF, is reliable.

d. Xanthochromia is nearly 100% sensitive for up to 2 weeks but only if spectrophotometry is used for detection. It may take several hours for xanthochromia to develop.

e. When the clinical context suggests SAH and CT and LP are not definitive, angiography should be done to look for an aneurysm.

f. Patients with SAH should be classified by the Hunt and Hess and Fisher grading systems to facilitate therapeutic decisions (Tables 13-8 and 13-9). After stabilization, patients should undergo four-vessel angiography to look for intracranial aneurysms.

Table 13-9 Fisher Grading of SAH

Grade 1—No evident hemorrhage on CT
Grade 2—Hemorrhage <1 mm thick
Grade 3—Hemorrhage >1 mm thick
Grade 4—Any thickness with intraventricular hemorrhage or parenchymal extension

CT, computed tomography.

From Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery*. 1980; 6:1–9.

2. Intraparenchymal hemorrhage
   a. Intraparenchymal hemorrhage is reliably identified as a density on head CT and as a signal that varies in intensity with time on MRI.
   b. Susceptibility-weighted or gradient-echo MRI sequences are most sensitive for the residual hemosiderin of small old hemorrhages, and they may be useful in revealing CAA when it is suspected, although many patients with presumed CAA do not have evidence of multiple hemorrhages on these sequences.
   c. For classification and prognosis, the volume of the hemorrhage can be estimated by the formula (ABC)/2, where letters represent the length, width, and the height of the clot.*
   d. In addition to noting the size and location of the hemorrhage, the examiner should scrutinize the images for evidence of intraventricular extension, edema, midline shift, uncal, tonsillar, and transfalcine herniation, underlying vascular lesions, primary or secondary infarction, or tumor.
   e. When CT and MRI do not provide an adequate explanation of the cause of the hemorrhage, conventional angiography should be strongly considered.

Treatment

General Principles

(See also Chapter 1.)

1. Correction of coagulopathies
   a. For all patients with intracranial hemorrhage, PT (INR), aPTT, and platelets should be checked, and abnormalities should be corrected as quickly as possible. Available therapies for correction of elevated INR include prothrombin complex concentrates (PCC), fresh frozen plasma (FFP), vitamin K, and recombinant activated factor VII (rFVIIa).
      1) Four-factor PCC and vitamin K are now the preferred method to correct warfarin-associated coagulopathy in a setting of intracranial hemorrhage. PCC corrects the INR more rapidly and with much lower volumes than FFP. Preparations of four-factor PCC contain the vitamin K–dependent coagulation factors II, VII, IX, and X, the anticoagulant proteins C and S. The dose, measured in factor IX units, is calculated based on the INR, the patient's weight, and the factor IX

units per milliliter. Because the potency varies, the dose volume must be calculated for each vial. PCC very rapidly corrects the INR. Vitamin K should be given simultaneously to sustain INR correction. Some centers may offer three-factor PCC, with low levels of factor VII. If three-factor PCC is given, then FFP and vitamin K should be given with it.

2) Vitamin K, 10 mg IV, should be given to those with elevated INR. The effect is delayed by at least 6 hours; therefore, other therapies must be given at the same time to achieve more immediate correction. The IV infusion rate should be less than 1 mg/min to minimize risk of anaphylaxis.

3) If four-factor PCC is not available, then FFP 2 to 6 units should be given as quickly as possible to begin rapid correction of elevated INR or aPTT. This therapy also replaces depleted coagulation factors, and its action begins rapidly; however, full correction requires 15 to 20 mL/kg. It takes many hours to administer this volume, and it confers a risk of volume overload.

4) rFVIIa (15 to 90 μg/kg) can correct an elevated INR almost immediately as well. However, its half-life is short (2.6 hours), so repeated doses may be needed, and the risk of thromboembolic complications is high.

b. Defibrinogenation is best corrected with cryoprecipitate or fibrinogen concentrates.

c. Heparin's effect is reversed with protamine sulfate 10 to 50 mg IV over 1 to 3 minutes (1.0 to 1.5 mg/1,000 U heparin, if given within 30 minutes of cessation of heparin infusion; 0.5 mg/1,000 U heparin, if given between 30 and 45 minutes of cessation of heparin infusion; the maximum dose is 100 mg; 50 mg in 10 minutes). Patients receiving protamine sulfate should be observed closely for signs of hypersensitivity.

d. Thrombocytopenia (<100,000/μL) should be corrected with transfusion of platelets. More modest goals for ongoing correction of platelets may be necessary in disorders resistant to platelet transfusion.

e. Idarucizumab is a monoclonal antibody that specifically binds and neutralizes the action of the thrombin inhibitor dabigatran. The dose is 5 g IV.

f. Andexanet alfa is a recombinant modified inactive factor Xa with a much

higher affinity for factor Xa inhibitors and thus acts as a competitive inhibitor of this class of drugs, including apixaban, rivaroxaban, edoxaban, LMWH, and fondaparinux. It is currently under study and available as an investigational agent only.

2. Correction of elevated BP: Many patients with intracranial hemorrhage will have elevated BP. Those with SAH should have their BP normalized using IV agents such as nicardipine, labetalol, esmolol, or sodium nitroprusside.
   a. Nicardipine is started at 5 mg/h and titrated up to the desired effect by increments of 2.5 mg/h every 5 minutes to a maximum dose of 15 mg/h.
   b. Labetalol is given by intermittent dosing (10 to 20 mg IV over 2 minutes, then 40 to 80 mg IV every 10 minutes until desired BP is achieved or 300 mg has been given, and then repeat effective dose every 6 to 8 hours) or by continuous infusion (1 to 8 mg/min). Care should be taken to avoid excessive bradycardia. It can be converted to oral dosages of 200 to 400 mg every 6 to 12 hours.
   c. Esmolol is given as a loading dosage of 20 to 30 mg/min IV over 1 minute followed by a maintenance dose starting at 2 to 12 mg/min and increasing by 2 to 3 mg/min every 10 minutes until desired BP is achieved (maximum dose 20 mg/min or 300 μg/kg/min).
   d. Hydralazine may be given IV 10 to 20 mg every 4 to 6 hours.
   e. Enalaprilat may be given IV 0.625 to 1.2 mg every 6 hours.
   f. Sodium nitroprusside should be avoided in neurologic emergencies because it can raise ICP; however, it may be used when urgent BP reduction is needed and other agents are not effective. It is given as a continuous infusion at 0.25 to 10 μg/kg/min. The initial dose should be low to avoid the excessive abrupt lowering that some patients experience when the drug is started. Cyanide toxicity can occur with rapid and prolonged infusion. Metabolic acidosis, elevated lactate levels and lactate/pyruvate ratios, and increased mixed venous oxygen content suggest clinical toxicity. Cyanide levels increase with increasing infusion rate, and sustained infusion rates of more than 4 μg/kg/min risk toxicity. Symptoms of toxicity emerge at blood cyanide levels of 0.05 to 0.1 mg/dL. Thiocyanate levels vary with the cumulative dose. Toxic levels are not well established. Levels should remain below 1.75 μmol/L. Although levels may be useful to confirm diagnostic suspicion, diagnosis and a

decision to proceed with therapy should be based on history of exposure and clinical findings.

3. Maintenance of cerebral perfusion pressure (CPP): Patients with intraparenchymal hemorrhage should have their BP controlled without excessive reduction. Definitive optimal values have not been established; however, one large trial suggests that targeting systolic BP of 140 mm Hg is safe and possibly beneficial compared to a target of 180 mm Hg without apparent adverse effects. Where elevated ICP is suspected, ICP monitoring allows measurement of the CPP based on the relationship: CPP = MAP − ICP. When the ICP is monitored, the CPP should be kept above 60 to 70 mm Hg. This is ideally achieved by lowering ICP to normal values with medical or surgical measures (see Chapter 1), but at times, it may require support of the MAP with vasopressors, such as
   a. Phenylephrine 2 to 10 µg/kg/min
   b. Dopamine 2 to 10 µg/kg/min
   c. Norepinephrine beginning at 0.05 to 0.2 µg/kg/min and titrating to the desired effect

Subarachnoid Hemorrhage

General Care

1. Patients with SAH should have neurosurgical consultation for consideration of angiography and early aneurysm repair by open clipping or intra-arterial coiling. Abnormalities of coagulation and platelets should be corrected promptly as described earlier. Patients should be monitored in an intensive care unit with nurses skilled in neurologic assessment and management. Patients should be placed on bed rest in a quiet room with adequate sensory stimulation, such as reading, radio, or family visitors. Frequent neurologic examinations should be done looking for changes in level of consciousness and new focal signs.
2. Adequate analgesics should be given, including
   a. Acetaminophen 325 to 1,000 mg
   b. Oxycodone 5 to 10 mg every 4 hours
   c. Fentanyl 50 to 150 µg every 1 to 2 hours
   d. Morphine 1 to 20 mg every 2 to 3 hours

   Fentanyl and morphine may be given by continuous infusion by dividing the

total 24-hour dose needed by 24 to get the approximate infusion rate per hour. Mild sedation with benzodiazepines may be needed. Prophylactic anticonvulsants (e.g., levetiracetam 500 mg q12h) may be given because an early seizure may increase the risk of rebleeding. Stool softeners minimize straining that will transiently elevate ICP.

3. Adequate hydration should be given with normal saline. Serum sodium and urine volume should be monitored because patients may develop renal salt wasting, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), or diabetes insipidus. Hyponatremia is common. There is evidence of both SIADH with inadequate free water clearance as well as renal wasting of sodium, probably stimulated by atrial natriuretic factor or other plasma factors present in the setting of cerebral disease. Because it may be difficult to distinguish these two causes of hyponatremia clinically, because disordered antidiuretic hormone (ADH) regulation and renal salt wasting may occur simultaneously, and because volume contraction and dehydration may increase the risk of cerebral vasospasm, hyponatremia in the setting of SAH should be treated with adequate sodium replacement and volume replacement and maintenance, while free water should be restricted. Fludrocortisone 0.1 to 0.2 mg p.o. q12h may be helpful in maintaining eunatremia in some cases.

Surgical Therapy

1. The definitive therapy of aneurysmal SAH is obliteration of the ruptured aneurysm. As soon as the patient is stable, four-vessel angiography should be performed to define the ruptured aneurysm and any other aneurysms. Definitive control of the ruptured aneurysm may be achieved by surgical clipping, endovascular coiling, or novel hybrid approaches. Ideally, surgical and interventional neuroradiology teams collaborate to individualize the choice of therapy based on the characteristics of the patient and of the aneurysm. Unruptured aneurysms may be treated at the time of the initial surgery or at a later date on the basis of surgical principles.
2. Other complications of SAH for which surgical intervention is indicated are mass effect from large hematomas requiring early surgical decompression and hydrocephalus that requires ventricular drainage. In most cases, hydrocephalus will resolve after the acute phase of illness, although some

patients require ventriculoperitoneal shunting for long-term drainage.

Cerebral Vasospasm

1. Nimodipine 60 mg is given by mouth or by nasogastric tube every 4 hours for 21 days to improve outcome.
2. Adequate hydration should be given with normal saline.
3. TCD is a safe and reliable study to follow up patients for evidence of cerebral vasospasm. A baseline study of the circle of Willis vessels should be done shortly after admission. Then, serial studies can be done during the period of risk in the first 2 to 3 weeks after hemorrhage. Volume expansion with colloid solutions such as albumin may be given.
4. After surgical control of the aneurysm has been achieved, then induced HTN may minimize blood flow compromise in the setting of vasospasm. This may be achieved with volume expansion and vasopressor agents, such as phenylephrine (10 to 1,000 μg/min titrated to desired effect). Clinical response will determine the level of elevation needed, usually MAPs of 70 to 130 mm Hg adjusted to eliminate ischemic signs.
5. If patients have clinical and TCD evidence of persistent ischemia from vasospasm despite medical therapy, angiography should be done to confirm suspected vasospasm. Intra-arterial therapy of refractory vasospasm with balloon angioplasty and vasodilators, such as calcium channel blockers, should follow institutional protocols.

Intraparenchymal Hemorrhage

The major issues of therapy in patients with intracerebral hemorrhages are

1. Prevention of continued hemorrhage by early correction of coagulation and platelet abnormalities (see the section on General Principles)
2. Early control of elevated BP (see the section on General Principles)
3. Identification and control of urgent surgical issues such as threatening mass effect, intracranial HTN (see Chapter 1), and hydrocephalus
4. Definitive diagnosis of the cause of the hemorrhage and definitive treatment of the underlying cause

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*The volume of an ellipse equals $(4/3) \times \pi \times (d_1/2 \times d_2/2 \times d_3/2)$; hence, by simplification, approximately $(d_1 \times d_2 \times d_3)/2$.

14 Movement Disorders

Jordan D. Paulson and Lewis Sudarsky

PARKINSON DISEASE AND RELATED DISORDERS

Background

1. Parkinson disease (PD) was described in 1817 by James Parkinson, who observed the characteristic features of slowness, rigidity, rest tremor, and shuffling gait.
2. PD is the second most common neurodegenerative disorder after Alzheimer disease, affecting a half million people in the United States.
3. The incidence of the disease is age-related; it occurs infrequently before age 40. The prevalence worldwide is roughly 0.5% at ages 60 to 69 and 2% at ages above 80.
4. It is primarily a motor control disorder, although a variety of nonmotor symptoms also occur.
5. It is the most frequent reason for referral to a movement disorder specialist.

Pathophysiology

1. PD results in a gradual loss of the dopamine innervation of the basal ganglia, causing major disruptions of the output pathways of the basal ganglia that facilitate movement.
2. Pathology shows neuronal cell loss and depigmentation of cells in the pars compacta of the substantia nigra; these cells contain neuromelanin and produce the neurotransmitter dopamine that projects to the caudate and putamen.
3. When cell loss exceeds 60%, there is a critical deficiency of dopamine in

the forebrain, resulting in motor symptoms of PD.

4. The etiology of the disease is not known.
   a. Some degenerating nigral neurons contain inclusions (Lewy bodies), with aggregates of α-synuclein protein and ubiquitin.
   b. PD is considered a complex disorder where a product of a number of genetic and environmental factors eventually trigger necrosis and apoptosis of neurons.
   c. Although the majority of PD with onset after age 50 is sporadic, there are a number of single gene mutations that have been identified.
   d. Examples include point mutations, duplications, and triplications of the gene for α-synuclein (PARK 1 and PARK 4), mutations of the Parkin gene on chromosome 6 (PARK 2), and the LRRK-2 (PARK 8) mutation on chromosome 12. These genetic PD syndromes often have younger onset and an informative family history. Genetic testing for these disorders is increasingly available, although a role for gene testing in clinical practice has not yet been established.

5. Neuropathologist Heiko Braak suggested that changes of PD start in the medulla of the brainstem and in the olfactory bulb and then proceed to involve the substantia nigra and basal forebrain, where clinical evident motor symptoms of PD are seen.
   a. Braak staging mentions six stages where stages 1 to 2 involve premotor features of PD (anosmia, and rapid eye movement [REM] behavior sleep disorder), stages 3 to 4 clinical motor features of PD, and stages 5 to 6 end-stage PD symptoms involving the frontal and temporal lobes.

Prognosis

1. Dopamine cell loss in PD is progressive, beginning several years before clinical symptoms and continuing over 15 years or longer.
   a. The rate of progression is variable, and mobility can be supported with dopamine replacement therapy.
   b. Motor fluctuations develop in 40% to 50% of patients on levodopa at 5 years, 75% to 80% at 10 years. Most patients have accumulated significant disability at 15 years, whereas others retain a stable medication response, good balance, and preservation of cognitive function.

c. Dementia and falls emerge as treatment-limiting issues in patients with long-standing PD.

2. The progression of the disease can be followed using clinical measures, such as the Unified Parkinson's Disease Rating Scale (UPDRS, available at www.wemove.org). Although dopaminergic cell loss in the substantia nigra does not create a visible footprint on magnetic resonance imaging (MRI), other imaging modalities including single photon emission computed tomography (SPECT) and positron emission tomography (PET) are being applied to track progression of the disease.

Diagnosis

1. Diagnosis is made on clinical grounds; there are no laboratory tests. Onset is typically asymmetric. The cardinal clinical features are:
   a. Tremor at rest: Typically a pill-rolling tremor of the hands, sometimes affecting the lower limbs or jaw.
   b. Bradykinesia: Slowness of movement, or difficulty initiating movement. This is the major source of disability, sometimes described by the patient as weakness or heaviness.
   c. Rigidity with cogwheeling: A physical sign that is observed as the patient is passively moved. Cogwheeling is most easily appreciated at the wrist, ankle, and neck.
   d. Flexed posture/shuffling gait: A stooped posture is characteristic of PD. Shuffling gait is also typical but the least specific feature in differential diagnosis.

2. The typical case begins asymmetrically in the limbs with a rest tremor. A diagnosis of PD is also based on a number of more impressionistic findings: Loss of facial expression, hypophonic dysarthria, drooling, and micrographia.
   a. There are three clinically defined subtypes of PD: Tremor-dominant, akinetic-rigid, and postural instability and gait difficulty (PIGD).

3. Nonmotor symptoms like constipation, reduced sense of smell, and REM sleep behavior disorder can occur early, prior to the development of motor symptoms.

4. There is a degree of imprecision in clinical diagnosis. Ten percent to 15%

of patients in a PD clinic will turn out to have a related disorder. Early occurrence (within a year) of imbalance and falls should suggest an alternate diagnosis. Failure to respond to levodopa often indicates another diagnosis. The differential diagnosis of PD is reviewed in Table 14-1.

5. Several clues aid in the recognition of related neurodegenerative disorders:

a. Multiple-system atrophy (MSA)

1) MSA is a synucleinopathy, with pathology involving glial cytoplasmic inclusions of α-synuclein found in the striatum, the cerebellum, and the autonomic nervous system. It is a more aggressive disease with progression to death in 5 to 10 years, and a partial or waning response to dopaminergic treatment.

Table 14-1 Differential Diagnosis of Parkinson Disease

- Neurodegenerative disorders with atypical parkinsonism
  - Progressive supranuclear palsy
  - Multiple-system atrophy
    - Shy–Drager syndrome
    - Olivopontocerebellar atrophy (MSA-C)
  - Dementia with Lewy bodies
  - Corticobasal degeneration
  - Frontotemporal dementia with parkinsonism
  - Alzheimer–Parkinson overlap syndrome
  - Parkinson–amyotrophic lateral sclerosis–dementia of Guam
  - Huntington disease: Rigid variant
  - Hallervorden–Spatz disease
  - Pure akinesia syndrome
  - Primary progressive freezing gait
- Secondary parkinsonism
  - Toxic
    - MPTP (methyl-4-phenyl-tetrahydropyridine)
    - Manganese
    - Carbon monoxide
  - Drug-induced
    - Neuroleptic drugs
    - Metoclopramide, prochlorperazine
    - Reserpine
  - Vascular disease (arteriosclerotic parkinsonism)
    - Basal ganglia lacunes
    - Binswanger disease
  - Hydrocephalus
  - Trauma
  - Tumor
  - Chronic hepatocerebral degeneration

Wilson disease
Infectious
Postencephalitic parkinsonism
Creutzfeldt–Jakob disease
HIV/AIDS

MSA-C, multiple-system atrophy-cerebellar subtype.

Table 14-2 Consensus Criteria for Diagnosis of Probable Multiple-System Atrophy

Asporadic, progressive disease in adults (onset after 30 y of age) characterized by:
Autonomic failure involving urinary incontinence (inability to control the release of urine, with erectile dysfunction in males) or an orthostatic decrease of blood pressure within 3 min of standing by at least 30 mm Hg systolic or 15 mm Hg diastolic, plus one of the following:

1. Parkinsonism (bradykinesia, rigidity, tendency to fall) with poor response to levodopa multiple-system atrophy-parkinsonian subtype [MSA-P])
2. A cerebellar syndrome (wide-based gait, uncontrolled limb movements, action tremor and nystagmus; multiple-system atrophy-cerebellar subtype [MSA-C])

2) Manifestations: Consensus criteria for a diagnosis of MSA are reviewed in Table 14-2.
- **a)** Signs of autonomic failure (prominent orthostatic hypotension, urogenital dysfunction)
- **b)** Cerebellar and pyramidal features
- **c)** Parkinsonian features, often poorly responsive to levodopa
- **d)** "Red flags" supporting diagnosis: Sleep apnea, stridor, anterocollis, jerky, irregular postural or action tremor
- **e)** Not normally seen: "Pill-rolling" rest tremor, hallucination not induced by drugs, dementia
- **f)** Radiographically can sometimes see pons reduced in anteroposterior (AP) diameter, "hot cross bun sign," and putaminal rimming on MRI.

b. Dementia with Lewy bodies (DLB)

1) DLB is part of the PD spectrum, with more extensive pathology in the forebrain (also a synucleinopathy). It is the second most common form of degenerative dementia.

2) Manifestations
- **a)** Dementia, behavioral disorders, fluctuation of alertness and attention, and intermittent psychosis (typically visual

hallucinations) present within the first 2 years

b) Somnolence and REM sleep behavior disorder

c) Parkinsonism

3) Modified McKeith criteria for diagnosis of diffuse Lewy body disease (DLBD) are reviewed in Table 14-3.

c. Progressive supranuclear palsy (PSP)

1) In PSP, there is neurodegeneration of structures in the upper brainstem and diencephalon, with accumulation of globose neurofibrillary tau proteins.

2) Manifestations

a) Early imbalance or falls

b) Axial dystonia

c) Oculomotor abnormalities (particularly failure of conjugate downward gaze)

d) Radiographically, typically see generalized and brainstem atrophy, involving the midbrain but preserving the pons ("hummingbird sign") on MRI

Table 14-3 Modified McKeith Criteria for Diagnosis of Dementia with Lewy Bodies (DLB)

1. Central features (essential for diagnosis of diffuse Lewy body disease)
Dementia defined as progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function.
Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression.
Deficits on the tests of attention, executive function, and visuospatial ability may be especially prominent.

2. Core features (two core features are sufficient for a diagnosis of probable, on for possible DLB)
Fluctuating cognition with pronounced variations in attention and alertness
Recurrent visual hallucinations that are typically well formed and detailed
Spontaneous features of parkinsonism

3. Suggestive features (If one or more of these are present in the presence of one or more core features, a diagnosis of probable DLB can be made. In the absence of any core features, one or more suggestive features are sufficient for possible DLB. Probable DLB should not be diagnosed on the basis of suggestive features alone.)
REM sleep behavior disorder
Severe neuroleptic sensitivity
Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging

REM, rapid eye movement; SPECT, single photon emission computed tomography; PET, positron emission tomography.

d. Corticobasal degeneration

1) Corticobasal degeneration is also a "tauopathy," with progressive asymmetric onset.

2) Manifestations

a) Apraxia

b) Dystonia, rigidity, focal myoclonus

c) Cortical sensory loss

d) "Alien limb" movements

e) There is often focal cerebral volume loss (lobar atrophy) on imaging, later during the disease.

5. Occasionally, patients will have an axial parkinsonian syndrome and gait disorder ("lower body Parkinsonism") related to cerebrovascular small-vessel disease. Secondary parkinsonism from neuroleptic exposure (drug-induced parkinsonism) should always be considered because it is a treatable disorder. Drugs such as metoclopramide (Reglan), prochlorperazine (Compazine), and the atypical antipsychotics should not be overlooked. Neuroleptic drugs are highly tissue-bound, and motor signs can persist up to 12 weeks after these drugs have been discontinued. Toxin-induced PD related to manganese, carbon monoxide, or methyl-4-phenyl-tetrahydropyridine (MPTP) should be considered when environmental exposures have occurred.

Treatment Principles

1. Medical treatment for Parkinson disease can be divided into three parts:

a. Initiation of dopaminergic medication

b. Management of motor complications, including motor fluctuations and dyskinesias

c. Management of nonmotor symptoms and mental status changes

2. Exercise and physical therapy have been shown to provide benefit to motor symptoms during all stages of the illness and are imperative to address early and continually with patients.

3. Therapy should always be individualized with every patient, addressing lifestyle goals and functional disability versus side effects of medications at

each stage of the illness.

Initial Therapy of Parkinson Disease

1. After confirmation of diagnosis, consider whether the patient has disability sufficient to warrant some form of dopamine replacement. Although some advocate treatment at diagnosis, dopamine replacement therapy is generally provided for patients who have some difficulty in daily activities, difficulty with walking, or patients who are having difficulty with maintaining their occupation.
2. For patients with newly diagnosed PD, not yet requiring dopamine replacement, there is a range of therapeutic options:
   - **a.** Rasagiline (Azilect): This drug is a monoamine B inhibitor, with mild symptomatic benefits in early PD. In clinical trials, it delayed progression of motor disability in the first 2 years. The starting dose is 0.5 mg, which can be increased to 1.0 mg after a week. Because the monoamine oxidase inhibitor (MAO) inhibition is selective, the drug can be used together with levodopa, and tyramine reaction is quite rare in patients on a standard diet. Side effects include sleep disturbance and hyper- or hypotension. It should generally not be given with meperidine or selective serotonin reuptake inhibitor (SSRI) antidepressants because of the risk of serotonin syndrome.
   - **b.** Selegiline: Another monoamine oxidase B enzyme inhibitor, with some symptomatic benefits in early PD. It can elevate mood and help with fatigue. In one large clinical trial, selegiline delayed the introduction of levodopa by a year. Five milligrams are usually sufficient, given once a day in the morning. No special diet is required at doses under 15 mg. Infrequent side effects include insomnia, nausea, and hypotension. The drug is not well tolerated by confused patients. As with rasagiline, adverse interactions have been described with meperidine and SSRI antidepressants. An orally disintegrating, rapidly absorbed form of selegiline (Zelapar) avoids first pass hepatic metabolism. Dose is reduced accordingly (1.25 to 2.5 mg).
   - **c.** Amantadine: This older drug is a dopamine releaser and glutamate receptor antagonist. It is often helpful, particularly with tremor in early patients. In more advanced PD, it can help reduce dyskinesia. The dose is

100 to 300 mg/d; side effects include livedo reticularis and hallucinations.

d. Anticholinergic drugs: For younger patients with tremor as the major presenting symptom, trihexyphenidyl (Artane 2 mg three times a day [t.i.d.]), benztropine (Cogentin 0.5 mg twice a day [b.i.d.]), or ethopropazine (Parsitan 50 to 100 mg t.i.d.) can be helpful. These drugs can precipitate urinary retention or aggravate confusion and are poorly tolerated in older patients. Other side effects include dry mouth.

e. Neuroprotection options: There is presently no universally established evidence that any of the drugs delay dopamine cell loss in PD.

3. For patients whose PD has begun to affect their daily activities, and who have a degree of disability as a result, some form of dopamine replacement is indicated. The threshold for starting dopamine replacement therapy is somewhat subjective, as determined by the doctor and patient. The options include levodopa, or the use of a synthetic, direct-acting dopamine agonist. Half of the patients with new PD can be successfully treated with a dopamine agonist as monotherapy for 3 to 5 years. Motor complications (including dyskinesia) may be delayed, a particular advantage for younger patients. Levodopa remains the preferred initial therapy for older patients (older than 65 years), medically fragile patients, and those with cognitive and behavioral problems.

a. Dopamine agonists (ropinirole, pramipexole, rotigotine)

1) Advantages

a) Motor complications are delayed, particularly dyskinesias.

b) All three drugs have extended-release formulations, allowing once-a-day dosing.

2) Disadvantages

a) Greater cost

b) More adverse events

c) Somnolence, sudden sleep attacks, impulse control disorders

b. Levodopa preparations (Sinemet, Sinemet CR, Stalevo)

1) Advantages

a) Easier to use (may be titrated)

b) Superior efficacy

c) Better tolerated in frail, elderly patients and those with cognitive or behavioral changes

2) Disadvantage: treatment-emergent side effects (fluctuations, dyskinesias)

I. Medications used for dopamine replacement

a. Carbidopa/levodopa (Sinemet IR): Mainstay of therapy for most patients with PD, and the drug with the best therapeutic index. Sinemet is a combination of levodopa with carbidopa, a peripheral DOPA decarboxylase inhibitor. At doses above 75 mg, carbidopa reduces the peripheral decarboxylation of levodopa, increases fourfold the central nervous system (CNS) delivery, and reduces nausea and hypotension. Sinemet comes in 25/100, 10/100, and 25/250 tablets. The usual initial dosage of levodopa is 50 to 100 mg b.i.d. to t.i.d., increasing as required to 300 to 600 mg. Side effects include nausea, hypotension, constipation, confusion, and hallucinations. No intravenous (IV) preparation is available for surgical patients, but Sinemet tablets can be administered, crushed, by nasogastric (NG) tube or dissolved in carbonated water in a 1:1 dilution.

b. Sinemet CR (50/200 and 25/100): Carbidopa/levodopa in a polymer matrix designed to produce delayed enteric absorption and a 3- to 4-hour half-life. Absorption is incomplete, and onset of effect often takes 40 to 60 minutes. Many patients find this drug variable or unreliable. Sinemet CR also is only 75% of equivalent immediate release (IR) because of delayed gastric absorption.

c. Benserazide/levodopa (Madopar 50/100): An alternative to carbidopa/levodopa, using a different decarboxylase inhibitor. It is sold primarily in Europe.

d. Pramipexole (Mirapex, Mirapex ER): A D2 and D3 dopamine agonist. Used for initial monotherapy, or as adjunctive therapy of PD (with levodopa). Initial titration begins at 0.125 mg t.i.d. and proceeds slowly over 2 to 3 weeks to achieve 0.5 to 0.75 mg t.i.d.; 3 mg/d or above are often required for monotherapy after the first year. Adverse effects include nausea, somnolence, leg edema, confusion, and hallucinations. There are case reports of patients on pramipexole and ropinirole falling asleep while driving. Patients should not drive if somnolence is reported. There are also reports of impulse control difficulties like compulsive gambling. Mirapex ER is typically started at .375mg/day and increased every 5 to 7 days with maximum dose 4.5 mg/d.

e. Ropinirole (Requip, Requip XL): A D2 and D3 dopamine agonist. Used for initial monotherapy or as adjunctive therapy of PD (with levodopa). There is a very large dynamic range, with doses as high as 27 mg/d and above. Initial titration begins at 0.25 mg t.i.d. and proceeds slowly over 2 to 3 weeks to achieve 1 to 3 mg t.i.d.; 16 mg/d or above often required for monotherapy after the first year. Adverse effects include nausea, somnolence, leg edema, confusion, and hallucinations. This drug is metabolized by CYP1A2 enzymes in the liver, and can interact with other medications that share this pathway. Like pramipexole, there are case reports of patients on ropinirole falling asleep while driving. Patients should not drive if somnolence is reported. Ropinirole is now available in a sustained-release form (Requip XL), which has stable 24-hour kinetics, is easier to titrate, can be started at 2 mg/d, and advanced by 2 mg/d/wk. There is less nausea and sleep disturbance with the XL formulation, but it is more costly.

f. Rotigotine (Neupro): A transdermal patch formulation D2 and D3 dopamine agonist. It has a similar side effect profile to other dopamine agonists and rarely can precipitate skin reactions. Initial dosing is 2 mg/d and can be increased weakly to a goal of 6 mg/d.

g. Cabergoline: A newer ergot-derived dopamine agonist, which can be used as monotherapy for early PD, although not approved by the U.S. Food and Drug Administration (FDA) for this purpose in the United States. This drug has a long half-life and can be given twice a week. Side effects include nausea, hypotension, confusion, leg edema, rare pulmonary, or retroperitoneal fibrosis. Cardiac valve changes have also been reported, and annual monitoring using cardiac ultrasound is advised.

5. For anorexia and nausea in patients on Sinemet, an extra carbidopa (Lodosyn 25 mg) can help. Patients with nausea often tolerate Sinemet CR better because the drug peaks more gradually. Addition of an antiemetic such as trimethobenzamide (Tigan) 25 mg t.i.d., or ondansetron (Zofran) or domperidone (Motilium) 10 mg prior to each dose, may be necessary to counter gastrointestinal (GI) side effects of dopaminergic drugs.

Management of More Advanced Disease

1. As PD progresses over time, patients may have difficulty maintaining a

stable therapeutic response and independence in daily activities. It is important to describe the time and pattern of each complication because medication needs to be optimized individually.

2. Motor complications tend to involve three subtypes:
   a. Motor fluctuations: Wearing off, on–off fluctuations, dose failures, and sudden offs
   b. Dyskinesias: Chorea and dystonia associated with peak dose or a diphasic pattern
   c. Gait freezing and falls

3. With more advanced disease, motor fluctuations become more abrupt, erratic, and unpredictable. Levodopa is a medication with a half-life of 90 to 120 minutes. Many patients with long-standing or advanced PD experience a wearing off of drug effect at 2 to 3 hours, as the bioavailability of the drug declines. To extend the effect of levodopa, options include more frequent dosing, use of a longer acting levodopa preparation, or addition of a monoamine oxidase B or catechol-O-methyltransferase (COMT) enzyme inhibitor. Another option is to include the addition of longer acting dopamine agonists.
   a. Rasagiline/Selegiline: As mentioned earlier, these drugs are utilized for monotherapy, but both also can be used as well to stabilize motor fluctuations. They increase on time in fluctuating patients by 15%. Side effects include dizziness, blood pressure (BP) fluctuations, and increased dyskinesia.
   b. Entacapone (Comtan): Retards the enzymatic degradation of levodopa and dopamine by a peripheral mechanism. It increases the CNS delivery of levodopa and improves the kinetics. (It is ineffective without levodopa.) Dose is 200 mg, given with each dose of levodopa. No dose titration is required, although the dose can be reduced to 100 mg if necessary. It increases on time in clinical trials by 15%. Side effects include discoloration of the urine and infrequently diarrhea. It may increase dyskinesia.
   c. Levodopa/carbidopa/entacapone (Stalevo): Combination drug that provides levodopa/carbidopa with entacapone in a fixed dose combination: 50/12.5/200, 75/18.75/200, 100/25/200, 125/22.25/200, 150/37.5/200, and 200/50/200. It affords extra convenience for patients taking entacapone.

d. Tolcapone (Tasmar): COMT inhibitor that is more potent than entacapone in clinical trials and longer acting. The dosage is 100 to 200 mg t.i.d. Side effects include serious, occasionally fatal hepatotoxicity, and not infrequent diarrhea. Because of a small number of cases of sudden hepatic failure, an informed consent process is required, and liver function tests (LFTs) must be monitored every 2 weeks for the first year of therapy, every 4 weeks for the next 6 months, and every 8 weeks thereafter.

e. Dopamine agonists: As mentioned earlier, these agents are used for monotherapy but can also function to prolong the on time of levodopa.

f. Apomorphine (Apokyn): A unique, short-acting dopamine agonist that is indicated as a "rescue medication" for unpredictable off times or motor complications not controlled by other medications. It only comes in subcutaneous or intranasal formulations, and doses are variable and need to be titrated. It provides rapid symptom relief, but side effects include profound nausea that needs pretreatment with antiemetics, hypotension, and dyskinesias.

g. Rytary (IPX066): A novel carbidopa/levodopa formulation approved by the FDA in January 2015. It is a capsule composed of immediate-release and extended release beads that are absorbed at different rates in the GI tract. Studies have shown it improves wearing off between levodopa doses and improves the time between interval dosing. It can also be sprinkled on food for patients with dysphagia. Pitfalls include high cost and occasional trouble with titration from standard regimens. (Dose conversion table is available online from the manufacturer.)

h. Duopa (DuoDopa/LCIG): Carbidopa/levodopa enteral suspension approved in late 2015 for advanced PD with motor fluctuations. It is an intestinal gel that is infused through a percutaneous endoscopic gastrostomy with jejunostomy (PEG-J) tube continuously throughout the day via a portable infusion pump. Studies have shown that it improves "on" time without troublesome dyskinesias more than oral IR carbidopa/levodopa. Pitfalls include high costs, complications with device usage and PEG-J tube, and frequent visits and support from GI doctors, PD support team, and the drug manufacturer.

i. Dyskinesia most commonly occur with Sinemet therapy, particularly at larger doses and in young onset patients. Studies have shown that starting

therapy with a dopamine agonist may delay the onset of dyskinesias in PD patients. Patients with troublesome dyskinesias sometimes do better with a dopamine agonist as primary therapy, and a small dose of Sinemet as needed to enhance the effect. Supplemental use of amantadine can reduce dyskinesia in many patients.

5. Deep brain stimulation (DBS), a neurosurgical procedure, is an option for patients with more advanced PD when quality of life is impacted by motor complications and/or other adverse effects limiting the therapeutic response to medications. An ideal candidate for DBS surgery is someone who is responsive to carbidopa/levodopa for motor symptoms, suffering from dyskinesias and motor fluctuations, and cognitively intact. It typically does not help postural instability, freezing, gait and balance issues in older patients or nonmotor features of Parkinson disease. Surgical outcome is not good in patients with mental status changes, and surgery may exacerbate dysarthria.
6. Difficulty with gait initiation or freezing is a particularly challenging problem. Freezing is sometimes overcome by visual cues, and some patients can use an inverted cane to step over. (A variation in this technique is the use of a laser pointer to provide a visual target for step initiation.) The problem does not always yield to increasing doses of dopaminergic medication, although this should be attempted. Postural instability and recurrent falls may become a problem after 5 to 10 years of PD. Such patients have difficulty standing from a chair and are easily displaced backward. The unfortunate reality is that drug treatment does not always improve balance. As patients are mobilized by medication, they may be at increased risk for falls. Surgery does not reliably improve the "on" period gait freezing or prevent falls. The best treatment for this problem is a physical therapy–based intervention to improve axial mobility and balance. These programs typically utilize auditory and visual cueing to overcome freezing (in the United States, Lee Silverman Voice Training BIG and LOUD therapy).

Nonmotor Symptoms

Whereas motor complications can be managed with available medications and occasional use of functional neurosurgery (DBS), nonmotor symptoms are increasingly recognized as a contributing cause of disability in PD. Apathy and

depression are common, and mental status changes occur more often in advanced disease. A variety of autonomic nervous system problems, pain, and sleep disturbance can be major issues for some patients.

1. Postural hypotension occurs in PD because of autonomic involvement and the effects of medications. BP medications should be lowered. Decarboxylase inhibitors should be optimized, and MAO-B inhibitors should be discontinued. Some patients require supplemental mineralocorticoid (Florinef, 0.1 to 0.3 mg/d) and compression stockings. Midodrine (ProAmatine, 2.5 to 5 mg t.i.d.), and pyridostigmine (Mestinon, 30 to 60 mg t.i.d.) can also be helpful. L-dihydroxyphenylserine (Droxidopa) was recently approved for management of hypotension in PD and MSA.
2. Some patients require medication for bladder instability. Caution is advised because anticholinergic drugs can aggravate mental confusion.
3. GI motility is also a common problem in PD, and patients often require medication for constipation. Polyethylene glycol (MiraLAX) is often effective when used daily: 17 g dissolved in 8 oz water. Pyridostigmine (Mestinon) can also act as a prokinetic.
4. Drooling results from a reduced rate of swallowing, and not from increased production of secretions. Nonetheless, reducing saliva is sometimes helpful. Sublingual use of an ipratropium spray, oral glycopyrrolate, or transdermal scopolamine patch can be helpful. Injection of the parotid with botulinum toxin may be useful if other agents are not sufficient.

Management of Mental Status Changes

1. Cognitive difficulty, behavioral disturbance, and sleep disorder are not emphasized in classic descriptions of PD, but each poses a common therapeutic problem. Delirium in PD is generally transient and reversible, often related to medications or intercurrent illness. All antiparkinsonian medications have the potential to cause delirium, even transient psychosis. It is best to minimize the use of anticholinergic drugs, MAO-B inhibitors, and dopamine agonists in patients with mental status changes. The preferred strategy in such patients is to avoid polypharmacy and focus on the single drug with the best therapeutic index (carbidopa/levodopa). Use the lowest dose that provides adequate mobility.
   a. Clozapine (Clozaril): Clozapine in low dosage (12.5 to 75 mg at bedtime

[hs]) has been useful when hallucinations, paranoid thinking, and nocturnal agitation persist on minimal levodopa. It can cause daytime sleepiness, but it does not appear to exacerbate motor symptoms of PD (tremor may actually improve). Patients must be monitored with weekly complete blood counts (CBCs) for leukopenia and agranulocytosis. The manufacturer maintains a national registry.

b. Other atypical antipsychotics (quetiapine 25 to 150 mg; risperidone 0.5 to 3 mg) are sometimes used in this context because they do not require monitoring of blood counts. Again, low doses are recommended. With time, these drugs accumulate and motor symptoms may worsen. Sedation is the other major side effect. Older antipsychotics such as haloperidol and chlorpromazine should be avoided in PD because of stronger dopamine receptor blockade.

c. Black box warning: In elderly patients with dementia, the use of any of the atypical antipsychotics is associated with a slight increase in the risk of death from cardiovascular disease or pneumonia. These drugs should be used with caution and at low dose but can reduce hallucinations and agitation and help patients sleep at night.

d. Pimavanserin (Nuplazid) is a novel 5HT-2A inverse agonist that has been shown to reduce PD-related psychosis in a phase III trial in 2014 without worsening motor side effects.

2. Dementia occurs in 20% to 40% of patients with idiopathic PD by 10 to 15 years. Episodic confusion (even off medication), slowness, and frontal behavioral features are most often observed. Cholinesterase inhibitors (donepezil, galantamine, rivastigmine) have a beneficial effect on behavior in these patients and produce measurable (although modest) improvements in cognitive function.

3. Sleep disturbances are now recognized as an important issue in PD and are more frequent in patients with cognitive impairment. Some patients with PD awake rigid and uncomfortable, unable to turn in bed. These patients may require more nighttime medication. For other patients, disturbances in sleep state control may be aggravated by antiparkinsonian medications. Some patients experience daytime sleepiness, a frequent problem in patients on dopamine agonists; many have insomnia at night. Sleep is fragmented, and there may be reversal of the sleep–wake cycle. Judicious use of sleep

medications or sedating antidepressants can sometimes break the cycle. Stimulant drugs like modafinil (Provigil 100 to 200 mg), methylphenidate (Ritalin 5 to 10 mg), and caffeine supplements have been used to counteract daytime sleepiness. Driving should be restricted in patients with PD who experience daytime sleepiness. An REM sleep behavior disorder has been described in PD, with active nocturnal movements (talking, yelling, punching, kicking, or jumping out of bed) during dream sleep. This syndrome may be improved by clonazepam (Klonopin 0.5 to 1.0 mg hs) or high-dose melatonin.

HYPERKINETIC MOVEMENT DISORDERS

Hyperkinetic movement disorders are grouped into descriptive categories: Tremor, dystonia, chorea, athetosis, dyskinesia, myoclonus, and tic. In practical reality, the syndromes sometimes overlap. Tardive dyskinesia, for example, may take the form of a choreiform movement, dystonia, or a complex motor stereotypy resembling a tic. It is sometimes possible to move beyond descriptive recognition to pathophysiologic or molecular diagnosis.

Essential Tremor and Its Variants

1. Tremor is defined as a repetitive, involuntary, rhythmic, shaking movement across a fixed axis, often about a joint.
2. Tremor at rest, as occurs in PD, can usually be distinguished from tremor with movement (action tremor). Tremor with movement can further be classified as enhanced physiologic tremor (sometimes amplified by medication, anxiety or a metabolic disorder), essential tremor, and cerebellar tremor.
3. Task-specific tremors occur only with a particular movement and not at other times. Primary writing tremor is an example.

Background

Essential tremor is the most common movement disorder, with a prevalence of 350/100,000 population, three times greater than that of PD, with which it is sometimes confused.

Pathophysiology

Essential tremor has a central mechanism. Functional imaging studies show increased activity in cerebellar outflow to the brainstem and thalamus. In many cases, essential tremor has a genetic basis, with an autosomal dominant pattern of inheritance. More recent neuropathologic studies suggest that there may be changes in the cerebellar cortex

Prognosis

1. Onset varies widely from the teens to the 60s; it often runs a similar course within families.
2. Progression is slow over decades.

Diagnosis

1. Essential tremor is a 4 to 10/s action tremor, which may be large enough to interfere with activities of daily living.
   - **a.** It most typically involves the upper limbs symmetrically and may involve the head or voice.
   - **b.** There is both a postural and limb–kinetic tremor. Limb–kinetic tremor is multidirectional, and it does not increase in amplitude as the target is approached (in distinction to cerebellar tremor).
   - **c.** Some patients with long-standing essential tremor have a bit of rest tremor admixed, although no true bradykinesia. Soft cerebellar signs (oculomotor abnormalities, difficulty with tandem gait) are sometimes observed.
   - **d.** Essential head tremor can be confused with dystonic head tremor, which is directionally specific and is usually associated with a degree of torticollis.
   - **e.** There are no current diagnostic tests or genetic markers; thyroid function should be checked, and copper studies as appropriate.
   - **f.** Surface electromyogram (EMG) reveals a synchronous pattern of activation in antagonist muscles.

Treatment

1. Not every patient with essential tremor will require pharmacologic treatment.
   - **a.** Daily medication is usually reserved for patients with some degree of

disability: Difficulty with handwriting, drinking from a glass, managing eating, and self-care.

b. Patients who improve with alcohol will often respond to β-blockers.

c. In treating essential tremor, it is important to define the expected outcome. A 30% to 60% reduction of tremor amplitude is a good response.

d. To achieve better reductions of tremor amplitude, patients may require neurosurgical treatment.

2. First-line agents

a. Propranolol (Inderal) is effective across a dose range of 40 to 240 mg. Starting dosage is 10 to 20 mg t.i.d. or 60 mg of the long-acting preparation. Contraindications include asthma, heart failure, and insulin-dependent diabetes. Side effects include hypotension, fatigue, depression, and sexual dysfunction. Other β-blockers may be useful in particular patients but do not offer better tremor control.

b. Primidone (Mysoline) is the preferred therapy for patients with cardiovascular disease, and those with specific contraindications to β-blockers. It is easier to use, particularly for fragile older patients with multiple medical problems. The usual dosage is 50 mg given at night or b.i.d.; starting dose is 25 mg to avoid sedation and nausea. There is incremental benefit up to 250 mg and above; anticonvulsant doses are not required. Primidone is metabolized by the liver, and it induces hepatic microsomal enzymes.

3. Second-line agents include some of the newer anticonvulsants (topiramate, gabapentin), benzodiazepines (clonazepam), mirtazapine, and methazolamide.

a. Responses are less consistent, evidence for efficacy is difficult to establish, but each of these drugs has been helpful to some patients.

b. Alternative therapies include botulinum toxin and functional neurosurgery. Botox is particularly useful for head tremor; however, high doses are needed for limb tremors with weakness as a common side effect.

4. Functional neurosurgery

a. Stereotactic thalamotomy and DBS both target at the ventral intermediate nucleus, producing reductions in tremor amplitude of greater than 80% in PD and essential tremor.

b. Serious complications (intracranial hemorrhage, infection) occur in 2%.

c. MRI-guided focused high intensity ultrasound is under investigation for essential tremor. It is a less invasive technique producing a lesion in the ventral intermediate nucleus of the thalamus (VIM) similar to that resulting from stereotactic neurosurgical procedures.

Other Tremors

1. Enhanced physiologic tremor is usually rapid (8 to 12 per second) and does not often achieve disabling amplitude, unless there is a problem with thyroid function, medication, or significant anxiety.
2. Medications that cause tremor are listed in Table 14-4.
3. Lesions of the cerebellar outflow at a midbrain or thalamic level produce a combination of cerebellar postural tremor, resting tremor, and extrapyramidal rigidity (Holmes tremor), often large in amplitude. Mild weakness may be an associated sign. Although difficult to treat, this tremor sometimes responds to levodopa. Stereotactic thalamotomy has been used with benefit in some cases.
4. Orthostatic tremor is a variant of essential tremor.
   a. Patients report discomfort or unsteadiness in the legs activated by standing, generally improved as they begin to walk. The tremor in the legs is rapid (16 per second) and is not always visible, but it is palpable and can be demonstrated by surface EMG.
   b. Clonazepam is the drug of choice, but treatment of nonresponders is difficult.

Table 14-4 Medications Reported to Induce Tremor

Thyroid hormone, levothyroxine sodium (Synthroid)
Epinephrine
Amphetamine, phenylephrine, and other sympathomimetics
Caffeine, theophylline, and other xanthines
Nicotine
Lithium
Valproate
Phenothiazines and atypical antipsychotics
Tricyclic antidepressants
Methylbromide
Amiodarone
Cyclosporine, FK506
Monosodium glutamate

Corticosteroids (in high dose)
Insulin, oral hypoglycemic agents
Alcohol (withdrawal)
Metal intoxication (lead, arsenic, bismuth, mercury, manganese)

Dystonia

Background

1. Dystonia is defined as a syndrome of sustained or spasmodic muscle contraction, resulting in twisting/pulling movements and abnormal postures.
   - **a.** Involuntary muscle spasms are either slow (tonic) or rapid, but they tend to be repetitive, patterned, and can be discerned from other hyperkinetic movement disorders by directionality. Typically, the movements or tremors are more pronounced when they are positioned against the direction of the muscle pulling, and the movements are less in the direction of movement.
   - **b.** Dystonic tremor can be differentiated from other types of tremors based on irregular, jerky movements that are patterned.
   - **c.** Dystonia is traditionally classified as primary or secondary; secondary dystonia occurs as the product of another neurologic disease. Clinical expression can be focal, segmental, hemidystonic, multifocal, or general; recent 2013 guidelines now divide the dystonias by clinical features and etiology.
   - **d.** The prevalence of primary childhood-onset dystonia is 16/100,000 population. Focal dystonias are more common, probably exceeding 30/100,000, because these disorders are not always recognized and are underdiagnosed.

Pathophysiology

1. The pathophysiology of dystonia is not well understood. It is presumed to reflect a chemical and/or physiologic imbalance in the basal ganglia, upper brainstem, and possibly cerebellum. Primary dystonia is further divided into familial and sporadic forms, with presumed genetic contribution in both subsets.
2. The most well-known form of primary generalized dystonia is *DYT1*, or Oppenheim dystonia. This disorder is caused by a trinucleotide deletion in a

region coding for the protein torsin-A. Torsin-A is expressed in dopamine neurons, where it appears to function as a chaperone protein. Mutations in the genes for GTP cyclohydrolase 1 and tyrosine hydroxylase also produce a form of generalized dystonia. These proteins are involved in the metabolism or trafficking of monoamine neurotransmitters.

3. In recent years, there have been new genes discovered regarding the genetics of the primary dystonias; the most common are summarized in Table 14-5. The *DYT1* mutation is autosomal dominant, with variable penetrance; the disorder is expressed in 30% of gene carriers. *DYT1* dystonia is most often found in the Ashkenazi Jewish population. It typically causes severe generalized dystonia of childhood onset beginning in the limbs, but mutations are sometimes seen in adult patients with a more restricted disorder. Other associated genes are DYT5 and DYT7, dopamine-responsive dystonia, and adult-onset focal dystonia, respectively.
4. The secondary dystonias are a diverse group of structural, metabolic, and neurodegenerative disorders. Dystonia is often a secondary feature of well-characterized basal ganglia diseases, including PD and Wilson disease. Other examples include pantothenic kinase deficiency (Hallervorden–Spatz disease), juvenile striatal necrosis, and cerebral palsy. The common attribute appears to be damage to the basal ganglia.
5. Wilson disease is an autosomal recessive disorder that causes a defect in copper excretion, leading to copper deposition in the liver, brain, corneas, and other areas of the body. Common neurologic features include dystonia, dysarthria, "wing beating" tremor, chorea, and gait disturbances. All patients with liver disease and extrapyramidal symptoms should be tested for serum ceruloplasmin, 24-hour urine copper levels, and a slit-lamp examination to look for copper deposits in the cornea (Kayser–Fleischer rings). MRI findings include increased T2 signal in the striatum, thalamus, and brainstem as well as "face of giant panda" sign in the midbrain. It is imperative to diagnose early because treatment with copper chelating agents (penicillamine or trientine) will prevent worsening liver function and the neurologic manifestations.

Table 14-5 Genetics and Differential Diagnosis of Dystonia

Genetic	Protein

Mutation	Abnormality	Disease
Primary Dystonia		
DYT1	Torsin-A	Oppenheim dystonia (dystonia musculoram deformans)
DYT3		X-linked dystonia parkinsonism (Lubag)
DYT5	GTP cyclohydrolase-1	Dopa-responsive dystonia
DYT6	THAP-1	Mixed phenotype (Amish, Mennonite)
DYT7		Adult onset, cervical dystonia
DYT11	ε-Sarcoglycan	Myoclonus dystonia
DYT12	ATP1A3	Rapid-onset parkinsonism/dystonia

Disease	Protein Abnormality
Secondary/Acquired Dystonias	
Brain injury/stroke	Cerebral palsy
Wilson disease	Juvenile striatal necrosis
Pantothenic kinase deficiency	Mitochondrial encephalopathy (Leigh, Leber)
Neuroacanthocytosis	Sjögren syndrome
Lesch–Nyhan syndrome	Adult GM1 gangliosidosis
Familial calcification of the basal ganglia	Drug-induced (antipsychotics)
Parkinson and related disorders (MSA, PSP, CBD)	Encephalitis
Ceroid lipofuscinosis	Primary antiphospholipid syndrome

MSA, multiple-system atrophy; PSP, progressive supranuclear palsy; CBD, corticobasal degeneration.

5. Dystonia can also be pharmacologic. Drug-induced dystonias can be seen with antipsychotics or antiemetics as the most common culprits because they have dopamine receptor-blocking side effects; reactions can range from an acute dystonic reaction of stiffness, oculogyric crisis, or chronic tardive dystonia.

Prognosis

1. The prognosis in dystonia depends on etiology.
2. Adult-onset dystonias that begin focally usually do not generalize.

Recognition and Diagnosis

1. Recognition of dystonia first requires identification of the involuntary movements and abnormal postures as a neurologic disorder, as opposed to a musculoskeletal or psychologic problem.
2. In a large number of patients, dystonia is initially misdiagnosed as psychogenic. The distinction between psychogenic and organic dystonia is one of the more difficult problems in neurology because there are no laboratory tests. In contrast to a contracture, dystonia can usually be reduced, and the disorder will remit when the patient is asleep.
3. Many patients have "sensory tricks" also called *geste antagoniste* which can lessen the dystonic movements. These typically involve touching the face or the back of the neck in cervical dystonia.
4. Imaging (head and/or spine) is often done to exclude a secondary cause.
5. Genetic testing is usually reserved for patients with some suspicion of likelihood based on young onset or family history.

Treatment

Generalized Dystonia

1. Generalized dystonia is difficult to suppress with medication, although a variety of medications can produce partial symptomatic benefit.
   a. For most young-onset patients, a therapeutic trial of carbidopa/levodopa is warranted to exclude dopa-responsive dystonia. This disorder produces dystonia with diurnal variation and is exquisitely responsive to treatment. Lack of response to 400 to 600 mg of levodopa rules out the diagnosis.
2. Some patients benefit from a combination approach.
   a. Trihexyphenidyl (Artane): Begin at 2 mg b.i.d. (less for children); doses as high as 30 mg or above can be achieved in younger patients. Anticholinergic drugs (trihexyphenidyl, benztropine, benadryl) are also useful in acute dystonic reactions.
   b. Muscle relaxants (cyclobenzaprine, clonazepam, diazepam) can be helpful, although sedation is often a limiting issue.
   c. Carbamazepine (Tegretol) is sometimes helpful in generalized dystonias, particularly so in paroxysmal dystonias.
   d. Baclofen (Lioresal) is occasionally useful, particularly in cranial

dystonias. It can also be administered as an intrathecal preparation through an implanted programmable pump for patients with severe generalized dystonia affecting the trunk and lower limbs.

e. Tetrabenazine: This drug, a dopamine-depleting agent, is more frequently used for dyskinesias but does have benefit for dystonia. Beginning at 12.5 to 25 mg, the dosage can be advanced as needed to 50 mg t.i.d. or above but can cause a parkinsonian syndrome or depression.

3. In patients with severe dystonia who do not respond to these drugs alone or in combination, other options can be considered.

a. Pallidotomy or DBS targeted at the pallidal or thalamic site has produced dramatic results in appropriately selected patients with dystonia.

Focal Dystonia

1. Focal dystonia (torticollis, oromandibular dystonia, blepharospasm, writer cramp) can be treated with intramuscular injection of botulinum toxin. There are several botulinum toxin preparations.

a. Botulinum toxin A is a large protein which acts presynaptically at the neuromuscular junction. The SNAP-25 protein is inactivated, blocking the release of acetylcholine. Effects persist for 2 to 4 months.

b. Botulinum toxin B acts at the same synapse but targets the synaptobrevin protein.

c. There is a paradox in treating a disorder of CNS origin with a peripheral neuromuscular blocking agent, but the treatments are effective without systemic side effects.

d. Results depend on targeting the active muscles, and best results are obtained with EMG guidance for cervical and limb dystonias.

e. A degree of resistance to botulinum toxin develops in roughly 5% of long-term patients, characterized by dose escalation and diminishing response. Half of these patients have measurable antibodies to botulinum toxin. Switching to a different serotype is sometimes helpful.

2. Botulinum agents

a. Onabotulinum toxin (Botox) is a purified protein extract of botulinum toxin A. It is very potent but has a good safety margin when given by intramuscular injection. Systemic side effects are rare when the dose is under 500 units. Doses in the range of 60 to 300 units are generally used to

treat cervical dystonia. Twenty-five units per side is the usual dose for the orbital muscles in treating hemifacial spasm or blepharospasm.

b. Abobotulinum (Dysport) is another preparation of botulinum toxin A, widely used in Europe; 400 units of Dysport is roughly equivalent to 100 units of Botox.

c. Incobotulinum toxin (Xeomin) is a third type of botulinum toxin A. It comes in a ready-to-use form, without dilution with saline.

d. Myobloc is a botulinum toxin B serotype. It comes prediluted and ready to use; 5,000 units of Myobloc is the equivalent of 100 units of Botox. Side effects (dry mouth, dysphagia) are more frequent, and the duration of action slightly less.

Chorea, Athetosis, and Dyskinesia

Background

1. Chorea is characterized by irregular, brief, involuntary movements that range across the face, trunk, and limbs.

a. Chorea, from the Greek, means dance. The movements are dancelike, but the choreography appears random and the movements are unpredictable. The gait has a particular marionette quality.

b. Huntington disease (HD) is a hereditary neurodegenerative disease described in the 19th century. Average age of onset is 35. Cardinal features are chorea and cognitive and behavioral changes. The prevalence is 10/100,000 population.

c. Acute rheumatic chorea (Sydenham chorea) was described in the 19th century. An immunologic complication of streptococcal infection, it is less common in the antibiotic era.

d. Others genetic causes of progressive chorea include benign hereditary chorea, HD-like syndrome-2, neuroacanthocytosis, benign hereditary chorea, dentatorubral-pallidoluysian syndrome (DRPLA), Wilson disease, neuroferritinopathy, and pantothenate kinase-associated neurodegeneration (PKAN).

2. The spectrum of choreic movement disorders also includes hemiballismus, a large-amplitude, unilateral involuntary movement with flinging of the limbs on the affected side. It is caused by a small stroke in the region of the

subthalamic nucleus. Athetosis is a slower, writhing involuntary movement. The athetosis of cerebral palsy is a good example. The term "dyskinesia" encompasses a variety of choreic and dystonic movements, frequently a side effect of medication. Dyskinesias are usually repetitive and stereotyped and often involve the perioral area (lip smacking, tongue protrusion).

Pathophysiology

1. All the disorders mentioned earlier produce an imbalance in the basal ganglia circuit, with underactivation of the striatal indirect pathway. The net result is decreased activity in the subthalamic nucleus and internal globus pallidus, reducing the basal ganglia output.
2. In HD, the mutation on chromosome 4 is an expanded CAG trinucleotide repeat. The mutant protein has cumulative toxicity, resulting in neurodegeneration in mid-adult life. The spiny projection neurons of the putamen are most vulnerable. Ultimately a variety of neurotransmitters and intracellular messenger proteins are disturbed.

Prognosis

1. The prognosis depends on the etiology of the chorea.
2. In HD, typical age of onset is 35 with a large range (from younger than 10 to older than 60). There is an inverse correlation between number of CAG repeats and the age of onset.
3. Progression to loss of ambulation, dementia, and death extends over 20 or more years.
4. Comorbid depression is common, and there is an increased risk for suicide in HD.

Diagnosis

1. The differential diagnosis of choreic involuntary movements is broad and is summarized in Table 14-6. The common denominator in these diverse disorders is a disturbance and imbalance in basal ganglia output.
2. The first step after recognition is to ascertain the family history and pertinent medication exposures.
3. In the absence of a family history or neuroleptic drug exposure, workup should include imaging. In HD, and most other progressive chorea

syndromes, there is a loss of mass in the caudate head. Strokes in the pallidum and subthalamic area can produce chorea.

4. Laboratory tests include an antinuclear antibody (ANA), antistreptolysin O titer, ceruloplasmin and 24-hour urine copper level, and thick peripheral blood smear for acanthocytes.
5. If there is progressive chorea and a negative family history, consider HD genetic testing. In some patients with HD, the family history is not initially informative.

Treatment

1. For patients with chorea, treatment is best directed at the underlying disorder. Choreic movements can be severe and disabling, and suppression of involuntary movement with medication may be appropriate. Patients with HD often need, primarily, attention to depression, nutritional issues, their caregivers, and support system.
   a. Neuroleptics: Chorea can be decreased with conventional antipsychotic drugs such as haloperidol in low dose (0.5 to 2 mg). Larger doses are counterproductive because they quickly accumulate and produce motor side effects.

Table 14-6 Differential Diagnosis of Chorea

Huntington disease (HD)
Benign hereditary chorea, HD-like 2
Neuroacanthocytosis
Dentatorubral–pallidoluysian atrophy
Familial calcification of the basal ganglia
Paroxysmal kinesigenic choreoathetosis
Acquired hepatocerebral degeneration
Acute rheumatic chorea (Sydenham disease)
Systemic lupus erythematosus
Senile chorea
Encephalitis
HIV
Chorea gravidarum
Acute vascular hemichorea
Wilson disease
Drug-induced dyskinesia from:
- Neuroleptics
- Cocaine
- Anticholinergic drugs
- Antihistamines

b. Atypical antipsychotics: Quetiapine (25 to 150 mg) and clozapine (12.5 to 75 mg) are often useful for agitation and behavioral problems in more advanced HD.
c. Tetrabenazine: This drug is a dopamine-depleting agent, and it is approved by the FDA for treatment of HD. Beginning at 12.5 to 25 mg, the dosage can be advanced as needed to 50 mg t.i.d. or above. It is effective but can cause a parkinsonian syndrome or exacerbate depression.
d. Amantadine (100 to 300 mg): It is sometimes helpful to reduce chorea in HD, although the effects are modest.
e. Benzodiazepines: Diazepam and clonazepam are sometimes useful as adjuncts in HD.
f. CoQ10, creatine: These agents are well tolerated in patients with HD and improve cellular energetics. There is no strong evidence at present that they slow disease progression.
g. Anticonvulsants (phenytoin, carbamazepine): These drugs are effective for paroxysmal chorea.

Tardive Dyskinesia

Tardive means late. Tardive dyskinesia occurs with chronic exposure to neuroleptic drugs. A minimum of 3 months is generally required. Involuntary movements are a consequence of chronic blockade of the D2 dopamine receptor, with upregulation of receptor and its intracellular messengers. Through the D2 receptor, dopamine has an inhibitory effect on the striatal indirect pathway. The syndrome is less common with the newer atypical antipsychotics.

Prognosis

Tardive dyskinesia is sometimes reversible over a year if the onset is recent and the offending medication is promptly withdrawn. More often, it is persistent and nonprogressive.

Treatment

1. For tardive movement disorders, there is no ideal medication.

a. Always reevaluate the need for neuroleptic drugs. If these medications are eliminated, some patients will resolve, although the dyskinesia can intensify over the short run.
b. Suppressing the dyskinesia with increasing doses of neuroleptic drugs is not recommended because the long-term effect is to aggravate the underlying pathophysiology. Changing to a newer atypical antipsychotic may be helpful. Clozapine is sometimes successful when others fail.
c. Dopamine-depleting agents like tetrabenazine may be useful, although side effects include hypotension and significant risk of depression.
d. A common misconception is the use of anticholinergics in cases of dyskinesias and choreas. These medications make the movements worse and are helpful only for parkinsonism or dystonia syndromes.

Paroxysmal Dyskinesias

1. Paroxysmal dyskinesias are abnormal involuntary movements that are sudden, typically brief in duration. They are distinguished from startle syndromes, which are considered together with myoclonus. They often have a specific trigger.
2. These syndromes are divided into four groups: Paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED), and paroxysmal hypnogenic dyskinesia (PHD). A genetic locus has been identified for a number of these disorders.
3. Typical motor movements during attacks include chorea, ballism, or dystonia.
4. PKD is the most common and responds well to therapy with carbamazepine. It typically has sudden onset dystonia triggered my stress or sudden movements.

Myoclonus

Background

1. Myoclonus is a brief, shocklike muscle jerk, generally less than 150 ms in duration, originating in the CNS.

2. It may be restricted in extent (focal, segmental) or more widespread (multifocal, generalized).
3. Asterixis, defined as a brief lapse of tonic muscle activation, is a related phenomenon.
4. Myoclonus occurs in a variety of neurologic and metabolic disorders.

Diagnosis

1. Myoclonus can be classified by etiology or on the basis of its physiology.
2. The principal physiologic distinction is between epileptic and nonepileptic myoclonus. Electroencephalogram (EEG) is helpful to distinguish.
3. Neurodegenerative dementias and prion disorders often exhibit myoclonus.
4. In hospitalized patients, myoclonus is common as a manifestation of a metabolic encephalopathy, as in renal failure, liver failure, hyponatremia, or hypoglycemia. Evaluation should include glucose, electrolytes, calcium, magnesium, blood urea nitrogen, creatinine, and LFTs.
5. Medications and exogenous toxins can also produce myoclonus. Examples include bismuth, lithium, meperidine, levodopa, phenytoin, propofol, and the SSRI antidepressants.
6. A vexatious myoclonus is seen at times after cardiac arrest (postanoxic, or Lance–Adams, myoclonus).
7. Spinal myoclonus is typically regular (periodic) and restricted in expression. It reflects a disturbance of spinal segmental mechanisms and can be seen after contrast myelography or spinal anesthesia.

Treatment

1. Therapy should be directed at the underlying encephalopathy, where possible. With cortical myoclonus, valproate and anticonvulsants that enhance γ-aminobutyric acid (GABA) are particularly effective. For myoclonus unassociated with epilepsy or encephalopathy, clonazepam is usually the drug of choice. These agents should be tried empirically:
   a. Clonazepam: Effective in doses from 0.5 mg to 18 mg/d, in divided doses. Side effects include sedation, particularly at high dose, tolerance, and a withdrawal syndrome after chronic use.
   b. Valproate (Depakote): Particularly effective in epileptic myoclonus. Treat to achieve a therapeutic serum level (250 to 750 mg t.i.d.).
   c. Piracetam: This drug, not FDA-approved in the United States, is widely

used for treatment of myoclonus in Europe. Usual dose range is 1,200 to 16,000 mg/d; it is well tolerated at up to 24 g/d. Levetiracetam (Keppra) can sometimes be used in its place. Usual starting dose is 500 mg b.i.d.

Tics and Tourette Syndrome

Background

1. A tic is a repetitive, stereotyped movement, longer in duration than a myoclonic jerk and more complex. It may appear to be a caricature of a voluntary movement that has taken on a life of its own.
2. A tic has a subjective component: There is an urge to move and a feeling of release after. It can be suppressed for a time by force of will, but the subjective discomfort will build up.
3. Some tics are simple, involving an isolated muscle group, whereas others are complex.
4. Tics may involve vocalization.
5. Tourette syndrome (TS) was described in 1885 by George Gilles de la Tourette and appears to be genetic, with variable expression.

Diagnosis

1. Diagnostic criteria specify multiple motor tics, at least one vocal tic, and onset before age 18. Tics wax and wane over time; old ones remit, and new tics appear. Echolalia and coprolalia (profanity) occur in about 20%. Neurobehavioral disorders such as obsessive compulsive disorder (OCD) and attention deficit hyperactivity disorder (ADHD) occur in more than half of patients with TS.
2. Other related disorders include chronic tic disorder (multiple motor tics present for more than a year) and transient tic disorder. These tic disorders may be part of the Tourette spectrum. A family member may have just tics or just OCD.
3. Tics may also be a secondary phenomenon, occurring with another neurologic disease such as encephalitis, tardive dyskinesia, HD, or dystonia.

Treatment

1. The main principle of therapeutics is to identify first the source of the patient's distress.
2. Behavioral disorders such as OCD and ADHD may respond to appropriate medication (fluoxetine, clomipramine, methylphenidate). If tic suppression is the treatment goal, options include the following:
   a. Clonidine (Catapres): This is an α_2-adrenergic agonist. Begin at 0.1 mg/d and advance to 1 to 2 mg/d; several months may be needed to see improvement. Sedation, fatigue, and hypotension are side effects. The drug should not be withdrawn rapidly because rebound hypertension can occur.
   b. Guanfacine (Tenex): This drug is an α_2-adrenergic agonist, similar in mechanism to clonidine. Dose is 1 to 2 mg/d.
   c. Benzodiazepines such as clorazepate (Tranxene) 3.75 to 15 mg t.i.d. and clonazepam (Klonopin) 0.5 to 2 mg b.i.d. may reduce frequency of tics.
3. Neuroleptic drugs such as haloperidol and pimozide will ultimately work, but lower doses are preferred to minimize the risk of a tardive movement disorder.
   a. Risperidone (Risperdal): May be helpful (0.5 to 2 mg) for tic suppression and associated subjective distress. Once control is achieved, another agent such as clonidine or benzodiazepine may be more successful.
   b. Haloperidol (Haldol): Starting dosage is 0.5 mg once or b.i.d. Doses of 2 to 5 mg/d may be required. Higher doses should be avoided.
   c. Pimozide (Orap): This drug is a neuroleptic, marketed specifically for TS. Starting dose is 1 to 2 mg/d, doses of 6 to 16 mg/d may be needed.
   d. Tetrabenazine: May also be helpful for refractory tics. Starting dose of 12.5 mg with gradual increase to 25 mg t.i.d. There is no risk of tardive side effects, but higher doses can induce depression or parkinsonism. Liver enzymes should be monitored.
4. Cognitive behavior therapy: Specifically, habit reversal training has also shown evidence to assist treatment of tic disorders as either an alternative or adjunct to medications.

Restless Legs Syndrome

Background

1. Restless legs syndrome (RLS) was described by Ekbom in the 1940s. The subjective discomfort and urge to move are the primary disturbance, and symptoms are relieved by walking. Patients describe a "creepy crawly" sensation in the legs and an inability to sit still.
2. The disorder is worse in the evening; periodic leg movements of sleep are often associated.
3. RLS is now recognized as common, up to 5% to 10% of people over the age of 50 in primary care practice. In some cases, there may be a family history.
4. The patient should be screened for associated disorders such as iron deficiency and peripheral neuropathy. There has been a direct correlation to low levels of ferritin.

Treatment

1. Dopaminergic medication is the first line of treatment, provided the discomfort is sufficient to warrant it.
   a. The dose of 100 to 200 mg of Sinemet CR at bedtime may suppress symptoms.
   b. Dopamine agonists are quite effective at relatively low dosages: Pramipexole 0.25 to 0.5 mg, ropinirole 0.5 to 2 mg hs. A second dose may be needed during the daytime for some patients.
   c. Long-acting dopamine agonists (Requip XL, rotigotine patch) may be helpful in patients with symptoms into the daytime hours.
   d. Dopamine augmentation (daytime symptoms of RLS with increasing doses of dopamine agonists) can develop after many years of treatment with dopaminergic medication and typically require a change to another medication class.
2. Patients who are still uncomfortable despite dopaminergic drugs may improve if gabapentin (Neurontin), pregabalin (Lyrica), gabapentin enacarbil (Horizant), or low-dose opiates (tramadol 25 to 50 mg hs) are added on, although it is a chronic disorder, and opiates should be used only when absolutely necessary. Iron replacement therapy may be useful but should always be combined with a diagnostic evaluation aimed at uncovering the cause of the iron deficiency.

OTHER DISORDERS OF MOVEMENT

Ataxia

Background

1. *Ataxia*, from the ancient Greek, means irregularity or disorderliness. We use the term to describe an incoordination of movement of cerebellar origin. The patient exhibits dysmetria (past pointing) and difficulty with rapid alternating movements, and there may be intention tremor. There is usually a cerebellar dysarthria (irregular, poorly modulated speech) and an associated oculomotor disorder.
2. Gait ataxia is distinctive; the gait is wide-based with irregular stepping. The patient walks as if drunk.
3. Ataxia is easy to recognize, often difficult to diagnose, and nearly impossible to treat.

Prognosis

Prognosis in ataxia depends on the etiology of the disorder. Posterior fossa tumors, prion disease, and paraneoplastic degeneration are rapidly progressive (months to a few years), whereas some patients with pure cerebellar cortical degeneration of adult onset remain ambulatory 15 or 20 years after diagnosis.

Diagnosis

1. Ataxia can result from injury to the cerebellum through trauma, infection, or demyelinating or vascular disease. The neurodegenerative ataxias are divided in two large groups, hereditary and sporadic. As noted by Harding, older descriptive classifications have been problematic. These diseases are now classified on the basis of their genetic and molecular markers. A partial listing is included in Table 14-7. Hereditary ataxias have a combined prevalence of 5/100,000 population. A similar number of cases are sporadic. Full ascertainment of the family history is thus the most important initial step in evaluation.
2. The hereditary ataxias (see Table 14-7) are classified as autosomal dominant, autosomal recessive, and other inheritance (including mitochondrial). The dominantly inherited ataxias are difficult to diagnose

from their clinical features because there is a large overlap. Retinal pigmentary degeneration distinguishes SCA-7. SCA-3 (Machado–Joseph disease) patients can have significant dystonia or occasionally a parkinsonian syndrome. Some patients with SCA-6 have discrete episodes of vertigo, ataxia, or nausea, which is of interest as the mutation affects the *CACNA1A* calcium channel. (Point mutations in the same gene cause episodic ataxia type 2 and familial hemiplegic migraine.) DNA diagnostic testing is usually needed to diagnose any of these diseases, unless diagnosis has been confirmed in another family member.

Table 14-7 Causes of Ataxia

Hereditary ataxia

1. Autosomal dominant

SCA1	United States, Northern Europe
SCA2	Cuba, Caribbean
SCA3/Machado–Joseph disease	Portugal, Azores, worldwide
SCA6	A calcium channel disorder
SCA7	With retinal pigmentary degeneration
DRPLA	
Episodic ataxia, types 1 and 2	

2. Autosomal recessive

Friedreich ataxia

Ataxia with oculomotor apraxia

Ataxia with vitamin E deficiency

Ataxia telangiectasia

3. Mitochondrial, including POLG

Sporadic ataxia

1. Toxins: Alcohol, phenytoin, cytosine arabinoside

2. Hyperthermia

3. Trauma

4. Metabolic disorders

Hypothyroidism

Abetalipoproteinemia

	Urea cycle disorders
5.	Paraneoplastic cerebellar degeneration
6.	Neurodegenerative ataxia
	Cerebellar MSA (olivopontocerebellar atrophy)
	Pure cerebellar cortical degeneration

DRPLA, dentatorubral-pallidoluysian atrophy; MSA, multiple-system atrophy.

3. Friedreich ataxia was described in 1861. The typical form has onset between ages 8 and 25, with ataxia, dysarthria, and a spinal disorder (sensory loss, absent reflexes, extensor plantar response). Associated features include pes cavus, scoliosis, and a hypertrophic cardiomyopathy. The disorder is autosomal recessive, the product of an expanded GAA trinucleotide repeat on chromosome 9. The frataxin protein is involved in mitochondrial metabolism. Patients have deficiencies of mitochondrial energetics and are vulnerable to oxidant stress. Iron accumulates in the mitochondria of myocardial cells. Availability of genetic testing has resulted in the appreciation of a wider spectrum of illness, including patients with late onset, with retained spinal reflexes and a more restricted form of the disorder. Ataxia with vitamin E deficiency is similar to Friedreich ataxia in its clinical manifestations. This disorder is treatable, in that vitamin E replacement arrests the progression.
4. Fragile X–associated tremor/ataxia syndrome (FXTAS) occurs in older men who are premutation carriers of the FMR1 gene. The typical features of the disorder involve late-onset ataxia with postural tremors and, occasionally, cognitive decline, parkinsonism, and limb weakness.
5. In cases of progressive ataxia with a negative family history (sporadic ataxia), the workup is focused on looking for a toxic, paraneoplastic, or treatable metabolic disorder. Evaluation should include imaging (to characterize the topography of cerebellar degeneration and to look for evidence of MSA), thyroid-stimulating hormone (TSH), vitamin E level, lipoprotein electrophoresis, lactate and pyruvate (for mitochondrial disorder), and search for antineuronal antibodies (anti-Yo, in particular). Genetic testing should be considered as well. As with HD, many patients with hereditary ataxia present without a family history.
6. The cerebellar presentation of MSA is distinguished by the presence of extrapyramidal and autonomic signs. There may be brainstem atrophy,

increased signal in the putamen, or crossing fibers of the pons (hot crossed buns sign) on MRI. A pure cerebellar cortical degeneration is characterized by more restricted clinical expression and slower progression over decades.

Treatment

1. With Friedreich ataxia, therapy is focused on boosting mitochondrial function in an effort to improve cellular energetics and slow disease progression.
2. Mitochondrial supplements like coenzyme Q and idebenone have been used to retard progression, but current evidence of efficacy is lacking.
3. For all the other neurodegenerative ataxias, treatment is largely supportive. Pharmacotherapy of the ataxias has been disappointing. Rehabilitation-based therapies are generally more successful for ataxia.
4. Primidone (Mysoline): Dosages of 25 to 100 mg b.i.d. have been used for cerebellar tremor, with variable success. Cerebellar outflow tremor may be disabling and severe and is difficult to control with medications.
5. Thalamic DBS or thalamotomy has been shown to be beneficial in some cases of cerebellar or rubral tremors but does not alter the ataxia symptoms.

Spasticity

Background

Spasticity is characterized by increased tone, hyperreflexia, and velocity-dependent stiffness on passive movement. This is evident as “clasp knife” stiffness on examination of the limbs.

Pathophysiology

Spasticity occurs with a disorder of upper motor neurons. The result is disinhibition of spinal segmental mechanisms, with increased activity in the muscle spindle and overactivation of α-motor neurons.

Diagnosis

1. Spasticity can be a consequence of cerebral or spinal pathology.
   a. Cerebral spasticity is most common with stroke and birth injury (cerebral

palsy).

b. Spinal spasticity is usually the result of trauma, demyelinating disease, or cervical spondylosis.

2. There are a number of clinical problems that occur as a consequence of spasticity. Some patients experience uncomfortable flexor spasms in the legs. Ambulatory patients have difficulty with stiff-legged gait. Stiffness can restrict limb use in patients with partial function.

Treatment

1. Pharmacotherapy of spasticity is targeted at the intrusive positive symptoms (usually flexor spasm). These drugs will not help negative symptoms like muscle weakness, which is the principal functional limitation for many patients. At high dose, most spasticity drugs will increase weakness, so there is a therapeutic trade-off. These drugs can be used in combination.

a. Baclofen (Lioresal), a GABA-B agonist, promotes inhibition in the spinal cord. The starting dosage is 10 mg b.i.d., which can be increased as tolerated to 80 to 120 mg in divided doses. Common side effects include sedation, dizziness, nausea, and weakness. Baclofen should not be given to seizure patients. Ambulatory patients do not usually tolerate doses over 60 mg. LFTs should be checked in the first 6 weeks. Intrathecal baclofen can be given through a programmable pump in patients with spasticity refractory to oral agents. Surgical implantation is required. Complications include infection, and pump malfunctions can result in serious overdose.

b. Diazepam (Valium) acts at a benzodiazepine-binding site that promotes GABA-mediated spinal inhibition. Starting dosage is 2 mg b.i.d. or t.i.d. Some paraplegic patients benefit from doses as high as 40 to 60 mg/d, although sedation is often a limiting feature. Alcohol should be limited. Patients on long-term treatment with benzodiazepines develop dependence and can have a withdrawal syndrome.

c. Tizanidine (Zanaflex) is an α_2-agonist; it increases presynaptic inhibition of motor neurons. Starting dose is 2 mg/d; it is titrated up over weeks by 4-mg increments as high as 8 to 12 mg t.i.d. Side effects include weakness, hypotension, sedation, and dry mouth. LFTs should be checked in the first 6 weeks.

d. Dantrolene (Dantrium) acts directly on skeletal muscle, interfering with

the release of calcium from the sarcoplasmic reticulum. Initial dose is 25 mg/d, increased over 4 weeks to 200 to 400 mg. Weakness is a frequent and dose-related side effect. Dantrolene is most often used in nonambulatory patients with cerebral spasticity. It can cause serious hepatotoxicity and should not be given to patients with known liver disease. LFTs should be monitored.

2. Botulinum toxin (Botox) is increasingly finding use in patients with spasticity. The principal advantages are its ability to target a particular muscle and the lack of systemic side effects. Disadvantages include expense and the need for repeated procedures to administer Botox three to four times a year. Botox can be used for a variety of spastic disorders characterized by stiff-legged gait, although the physiology of stiff-legged gait is complex and the application needs to be tailored and targeted. It should be used in the context of rehabilitation therapy, preferably by a physician who can distinguish the various patterns and target muscles accordingly. Leg weakness and falls can result from overly vigorous application of Botox. Botox can sometimes help improve upper limb function, when stiffness constrains use of the arm in daily activities. It can also help with the bladder care of nonambulatory patients with adductor spasm.

Stiff Person Syndrome

Background

1. Described by Moersch and Woltman in 1956, stiff man syndrome is an autoimmune disorder with involuntary stiffness of axial muscles and painful muscle spasm. It is rare but is probably underdiagnosed.
2. Diagnostic criteria include slow progression of stiffness in the axial and proximal limb muscles, hyperlordosis and deformity of the spine, and episodic painful spasms precipitated by active or passive movement, sometimes triggered by sensory stimuli or emotional upset. Elemental neurologic exam is otherwise normal. Some patients have a peculiar stiff, wooden (Frankenstein) gait.
3. There is a therapeutic response to benzodiazepines, although large doses are often required to maintain benefit. Details of treatment are found in Chapter 10.

Pathophysiology

Stiff person syndrome is an autoimmune disorder, and many patients have a personal or family history of other autoimmune diseases (thyroiditis, pernicious anemia, diabetes, vitiligo). Eighty percent have measurable antibodies to glutamic acid decarboxylase, or anti-islet cell antibodies. There appears to be a disturbance of GABA-mediated inhibition in the CNS. A variant of stiff person syndrome has been described in association with breast cancer.

Treatment

1. Benzodiazepines are the first line of treatment, but large doses are needed to maintain benefit.
   - **a.** Diazepam may need to be given at 40 to 60 mg/d, and some patients require more than 100 mg/d.
   - **b.** Baclofen has also been used to treat muscle spasm and stiffness in this syndrome. It can be given orally at doses up to 80 to 120 mg or intrathecally through a surgically implanted catheter and pump.
2. Immunotherapy is required to obtain control of symptoms in more severely affected patients. Prednisone and azathioprine have been used.
3. Plasma exchange and IV immune globulin have also been effective as rescue therapy but are not suitable for long-term treatment.

PSYCHOGENIC MOVEMENT DISORDERS

Psychogenic movement disorders are common particularly at a tertiary care center. Although these patients' signs are sometimes confusing, the greater problem is their management once the problem is recognized. Management of such patients is resource intensive. Although dramatic cures and placebo responses still occur, a pattern of illness may go on over a period of years without satisfactory resolution. Several red flags suggest the possibility of a psychogenic disorder, but remember that *just because a movement disorder appears odd or unusual does not mean that it is psychogenic*.

1. Unexpected variability, fluctuations, and entrainment of motor symptoms from moment-to-moment in neurologic examinations.
2. Nonphysiologic pattern of weakness or sensory loss. Look for vibratory loss

that splits the midline, or lack of force development and posture compensation in the contralateral limbs (Hoover sign).
3. A gait pattern that requires athletic balance and skill for its execution (astasia-abasia).
4. A history of other multiple medical problems of unclear significance.
5. Secondary gain, unresolved litigation, or obvious malingering.

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15 Behavioral and Cognitive Neurology

Seth A. Gale and Kirk Daffner

DISORDERS OF ATTENTION AND EXECUTIVE FUNCTIONS

Background

Definitions

1. Attention involves a set of neural processes that allow a person to select which stimuli or thoughts will be the center of awareness while filtering out potential distractors.
   - **a.** Components of attention include arousal (a prerequisite for all), orienting (shifting of the direction of sensory organs), selectivity (focusing on certain stimuli), and the capacity to sustain processing (vigilance) and divide resources (during dual or multiple tasks).
   - **b.** Disruption of attention is likely to undermine most cognitive functions.
2. Executive functions are a set of complex cerebral processes that exert "top-down," volitional control over cognition and behavior.
   - **a.** Key executive functions include working memory, monitoring, inhibition, and initiation.
   - **b.** Executive functions facilitate context-appropriate behavioral responses while inhibiting inappropriate ones, maintaining and shifting cognitive sets, and monitoring and adjusting ongoing mental activity. They mediate insight, judgment, and problem-solving skills.
   - **c.** Executive functions are most closely linked to a person's capacity to remain independent.

Presenting Syndromes

1. Acute confusional state (ACS)
   - **a.** ACS is a disorder of higher cognitive function reflecting the loss of a normal, coherent stream of thought, which can also have features of illogical/abnormal behavior.
   - **b.** Its salient feature is a disruption of a patient's "attentional matrix."
   - **c.** "Delirium" is an alternative term for ACS that neurologists often reserve for confused and agitated patients who also frequently exhibit autonomic instability and hallucinations.
2. Attention deficit hyperactivity disorder (ADHD)
   - **a.** ADHD is defined by inappropriate levels of attention, impulsivity, or hyperactivity, any of which should be present before age 12 years, according to current criteria.
   - **b.** Forty percent to 60% of children with ADHD will continue to have symptoms in adulthood that can include inattention, easy distractibility, disorganization, impulsivity, affective lability, learning problems, and impairment of executive functions (i.e., dysexecutive syndromes), which disrupt daily activities.
3. Dysexecutive syndromes
   - **a.** Cognitive: Decreased planning and working memory, poor insight
   - **b.** Behavioral: Impulsivity, disinhibition, comportmental impairment, perseveration
   - **c.** Motivational: Apathy, abulia

Pathophysiology

Neuroanatomic Components

1. Frontal–subcortical circuits
   - **a.** Frontal lobes → basal ganglia (caudate) → globus pallidus/substantia nigra → thalamus (dorsal medial/ventral anterior) → frontal lobes.
   - **b.** Disruption anywhere along these circuits can lead to similar behavioral outcomes.
   - **c.** Topographically distinct circuits exist with key nodes in dorsolateral frontal cortex, medial frontal cortex, and orbital frontal cortex.

d. Most often, disruption of the dorsolateral frontal circuit is associated with cognitive signs, the medial frontal circuit with altered self-monitoring and motivation, and the orbital frontal circuit with lack of inhibition and affective lability.

2. Ascending neurotransmitter systems
   a. Norepinephrine (NE) from the locus ceruleus helps to mediate arousal and improves signal-to-noise ratio (i.e., reduces distractions).
   b. Dopamine (DA) from the ventral tegmental area is necessary for functioning of the prefrontal cortex and maintenance of appropriate behavioral engagement.
   c. Acetylcholine (ACh) from the basal forebrain and brainstem reticular systems may modulate activity of widespread regions of the thalamus and cortex and influence overall information processing capacity.

Disorders

1. Attention and executive functions can be undermined by a wide range of medical, neurologic, and psychiatric conditions.
2. Common causes include the following:
   a. Toxic–metabolic encephalopathy (including side effects of medications)
   b. Multifocal injury (including cerebrovascular disease [CVD], traumatic brain injury [TBI], multiple sclerosis)
   c. Developmental causes (e.g., ADHD, Tourette syndrome)
   d. Degenerative diseases (including behavioral variant frontotemporal dementia [bvFTD], Alzheimer disease [AD], and Parkinson disease [PD])
   e. Neuropsychiatric conditions (e.g., anxiety, depression, hypomania/mania, schizophrenia)
   f. Disorders of arousal and sleep (including sleep apnea and narcolepsy)

Prognosis

Prognosis is variable and depends on the underlying conditions.

Diagnosis

History (often very dependent on information derived from informants), mental status examination (MSE), including tests of complex attention/executive

functions (e.g., word-list generation, digit span in reverse, clock drawing, judgment questions, alternating sequencing tasks, and go–no go tasks), neuromedical assessment, and toxic–metabolic screen are used in diagnosis.

Treatment

General Principles

1. Review medications. Eliminate nonessential medications, being particularly mindful of those with anticholinergic, sedative, or extrapyramidal/parkinsonian side effects.
2. Review and treat systemic/medical conditions (e.g., cardiac, pulmonary, renal, endocrine, pain, and sleep).
3. Identify and treat neuropsychiatric conditions that may be contributing to impaired attention and executive functions (e.g., anxiety, depression, hypomania/mania, and psychosis).

Medications

Attentional Problems

1. Stimulant medications (Table 15-1): U.S. Food and Drug Administration (FDA) approval is limited to ADHD and narcolepsy. Side effects can include insomnia, anorexia, exacerbation of tics, agitation, anxiety, psychotic symptoms, mood lability, and lowering of seizure threshold. Serious cardiovascular adverse events (AEs), including sudden death, have occurred in patients with significant heart problems, and there are reports of cerebro- and cardiovascular events in adults. Potential risks should be reviewed with the patient (and with the patient's family, when appropriate). Monitor blood pressure, especially in patients with hypertension. Avoid concomitant use of monoamine oxidase inhibitors (MAOIs).
2. There are numerous medications currently available that vary in their pharmacokinetics, with short-acting, intermediate-acting, and longer acting preparations. Patients may respond better to one stimulant than another. Duration of action is one of the key considerations in choice of a stimulant medication.
3. Modafinil has a different mechanism of action than stimulants. It involves the activation of the orexinergic system; inhibition of DA and NE

transporters; elevation of extracellular catecholamines, glutamate, and serotonin; and diminution of γ-aminobutyric acid (GABA). It is approved for excessive daytime sleepiness related to narcolepsy, shift work sleep disorder, and as an adjunct treatment for obstructive sleep apnea. It may be efficacious in the treatment of ADHD in children and adults but does not have FDA approval for this. Potential side effects include insomnia, headache, nausea, nervousness, and hypertension. In addition, there is a risk of diminished appetite, weight loss, and significant dermatologic problems, especially in children and adolescents. The FDA has warned against its use in children. Start modafinil at 100 or 200 mg in the morning; it can be titrated to 400 mg/d (divided doses).

4. Armodafinil, the enantiopure of modafinil, reaches its peak serum concentration more slowly than modafinil. Thus, it may be able to promote wakefulness for a longer time in some patients. Starting dose may be 50 mg, but first benefit may not be apparent until 150 mg. Titration is to a lower maximum (250 mg) than that of modafinil (400 mg; see earlier).

5. Catecholamine "boosters"

   a. Atomoxetine is a selective norepinephrine reuptake inhibitor (NRI) that is approved in the United States for ADHD in children over 6 years, adolescents, and adults. Adult dose: Begin 40 mg/d; increase to 80 to 100 mg/d as single daily or twice-a-day (b.i.d.) dose. Potential side effects include gastrointestinal (GI) distress, increased blood pressure, sexual dysfunction, urinary retention, possible cardiac problems, and increased risk of suicidal thinking in children and adults. It is less likely than stimulants to cause insomnia and is contraindicated in patients on MAOIs or with narrow-angle glaucoma.

Table 15-1 Stimulant and Related Medications

Medication	Starting Dose	Dosing Range[a]
Short Acting (3–6 h)		
Methylphenidate	5 mg b.i.d.–t.i.d.	Up to 60 mg/d
Dextroamphetamine	5 mg q.d.–b.i.d.	Up to 40 mg/d
Dexmethylphenidate	5 mg b.i.d.	Up to 40 mg/d
Amphetamine-dextroamphetamine	5 mg q.d.–b.i.d.	Up to 60 mg/d

Intermediate Acting (4–8 h)		
Methylphenidate LA/SR	20 mg q AM	Up to 60 mg/d
Dextroamphetamine SR	5–10 mg q AM	Up to 60 mg/d
Amphetamine-dextroamphetamine ER	10 mg q am	Up to 30 mg/d
Longer Acting (8–12 h)		
Methylphenidate ER	18–20 mg q am	54–60 mg/d
Methylphenidate patch	30 mg (on for 9, off for 15 h)	Up to 60 mg/d
Dexmethylphenidate ER/XR	5 mg	Up to 40 mg/d
Lisdexamfetamine	30 mg q AM	Up to 70 mg/d
Other (Nonstimulants)[b]		
Modafinil	100 mg q.d.–b.i.d.	Up to 400 mg/d
Armodafinil	150 mg q.d.	Up to 250 mg/d
Atomoxetine	40 mg q.d.	Up to 100 mg/d

[a] Some clinicians increase these medications to even higher doses while carefully monitoring the clinical status of their patients.

[b] Modafinil and atomoxetine have different mechanisms of action from stimulants. b.i.d., twice a day; t.i.d., three times a day; q.d., every day; LA, long acting; SR, slow release; q, every; ER or XR, extended release.

b. Bupropion: Although the precise neurochemical mechanisms are not known, it probably affects both the NE and DA systems. There is increased risk of seizures, especially if more than 450 mg/d or more than 150 mg of immediate-acting formulation is given at one time, or the patient has bulimia. Start bupropion at 75 to 100 mg b.i.d. and increase up to 400 mg (in three divided doses); bupropion sustained release (SR) 150 mg every morning and increase to b.i.d. (with <8 hours between doses) up to 400 mg/d; or bupropion XL 150 mg every morning and increase to 300 mg/d (or rarely, 450 mg/d). Contraindications include use of MAOIs and seizure disorders. Bupropion may be particularly helpful for inattentive patients with concomitant symptoms of depression or nicotine dependence.

c. α_2-adrenergic agonists: There are abundant α_2-receptors in the prefrontal cortex, and studies have suggested that agonists may improve working memory, behavioral inhibition, and attentional focus. In adults, clonidine (0.1 mg/d, increase to b.i.d., up to 0.6 mg/d) and guanfacine (1

mg/d, increase up to 3 mg/d) have FDA approval only for hypertension, but guanfacine ER is approved for ADHD in children age 6 to 12 years (1 mg/d, increase up to 4 mg/d) and 13 to 17 years (up to 7 mg/d). These can be used as monotherapy or adjuncts to stimulants. Side effects include dry mouth, drowsiness, dizziness, constipation, and orthostatic hypotension. Guanfacine preferentially binds postsynaptic α_2A-adrenoreceptors in the prefrontal cortex and tends to be less sedating than clonidine.

5. Others (Table 15-2): Tricyclic antidepressants (TCAs) (e.g., nortriptyline, desipramine), selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., venlafaxine) can be considered primary or adjunctive therapies for inattention, especially when patients exhibit concurrent problems with anxiety, depression, pain, or sleep disturbance.

Executive Dysfunction

1. DA agonists/modulators (Table 15-3) may increase motivation, diminish apathy, and improve working memory or other executive functions. Evidence supports the notion that there is an optimal level of DA activity, with too little or too much leading to dysfunction. These medications predominantly affect dopaminergic neurons in the brainstem (e.g., substantia nigra, ventral tegmental area) and along cortical–subcortical pathways (e.g., nigrostriatal, tuberoinfundibular, mesocorticolimbic).
   a. Approval in the United States for most of these medications is limited to the treatment of PD or restless leg syndrome (RLS). Clinicians can consider "empiric" treatment of dysexecutive symptoms with these agents. In such circumstances, it is crucial to closely monitor whether symptoms are improving and assess the potential impact of negative side effects.
   b. Begin with the lowest dose possible and increase very slowly.
   c. Patient response and side effects should be followed on a regular basis using metrics that can be measured or counted (e.g., number of days patient dressed without assistance, number of emotional outbursts in the prior week, body weight, standing blood pressure). Potential side effects include sedation, postural hypotension, hallucinations, GI symptoms (e.g., nausea), and peripheral edema. Amantadine is also associated with anticholinergic-like side effects.

d. We have had some success with pramipexole and amantadine, especially with executive dysfunction in TBI and the degenerative dementias.

e. Often, the doses used are lower than what is typically prescribed for PD. However, in cases of profound abulia, very high doses of these medications can be tried, with caution.

2. Cholinesterase inhibitors (Table 15-4) may augment cholinergic tone from basal forebrain to frontal cortex, with the potential to improve attention and executive functions. They have been most studied in AD and dementia with Lewy bodies (DLB).

Table 15-2 Selected Antidepressant Medications

Medication	Starting Dose	Dosing Range
SSRIs		
Fluoxetine	10–20 mg/d	Up to 80 mg/d
Sertraline	25–50 mg/d	Up to 200 mg/d
Paroxetine	10–20 mg/d	Up to 60 mg/d
Citalopram	10–20 mg/d	Up to 60 mg/d[a]
Escitalopram	5–10 mg/d	Up to 20 mg/d
Fluvoxamine	50 mg/d	300 mg/d
5-HT2 antagonists		
Trazodone	25–50 mg qhs	Up to 400 mg/d (divided doses)
Nefazodone	50 mg qhs	Up to 600 mg/d
TCAs		
Nortriptyline	10 mg qhs	50–75 mg (therapeutic serum level: 50–150 ng/mL)
Desipramine	10 mg b.i.d.–t.i.d.	Up to 150 mg (therapeutic serum level: 150–300 ng/mL)
SNRIs		
Venlafaxine	25 mg b.i.d.–t.i.d.	Up to 375 mg/d
Venlafaxine ER	37.5 mg	Up to 225 mg/d
Duloxetine	20 mg q.d.–b.i.d.	Up to 120 mg/d
Milnacipran	12.5–25 mg	Up to 100 mg/b.i.d.

	b.i.d.	
Levomilnacipran	20 mg/d	120 mg/d
Other		
Bupropion	75–150 mg/d	Up to 450 mg/d
Bupropion SR	100–150 mg/d	Up to 300 mg/d
Bupropion ER/XL	150 mg/d	Up to 450 mg/d
Mirtazapine	7.5[b]–15 mg qhs	Up to 45 mg/d

For elderly patients, appropriate starting doses may be lower.

[a] Doses >20 mg for age >60 years, and doses >40 mg for all adults, are generally not recommended because of risk of QT prolongation.

[b] As a sleep aid, 7.5 or 15 mg may be most effective because the somnolence side effect is stronger at lower doses. SSRIs, selective serotonin reuptake inhibitors; qhs, every night; TCAs, tricyclic antidepressants; b.i.d., twice a day; t.i.d., three times a day; SSNRIs, selective serotonin norepinephrine reuptake inhibitors; ER or XL, extended release; SR, sustained release.

Table 15-3 Dopaminergic Agents

Medication	Starting Dose	Dosing Range
Pramipexole	0.125 mg q.d.–t.i.d.	0.375–4.5 mg/d
Bromocriptine	1.25 q.d.–b.i.d.	2.5–100 mg/d
Ropinirole	0.25 q.d.–t.i.d.	0.25–24 mg/d
Amantadine	100 mg	100–300 mg/d
Selegiline (MAO inhibitor)	5 mg	5–10 mg/d
Selegiline transdermal	6 mg/24 h	Up to 12 mg/24 h

q.d., every day; t.i.d., three times a day; b.i.d., twice a day; MAO, monoamine oxidase.

Table 15-4 Cholinesterase Inhibitors

Medication	Starting Dose	Dosing Objective	Comments
Donepezil	5 mg	Increase to 10 mg after 4–6 wk (can increase to 23 mg in selected patients)	Once per day dosing
Rivastigmine	1.5 mg	Increase by 3 mg q 2–	Possible impact of its butyl

	b.i.d.	4 wk (as tolerated) up to 6 mg b.i.d.	cholinesterase activity on ↓ AD progression
Rivastigmine patch	4.6 mg/d	9.5 mg/d (or 13.3 mg/d in selected patients)	Especially useful if GI intolerance with orals
Galantamine	4 mg b.i.d.	Increase by 8 mg/d approximately q 4 wk up to 12 mg b.i.d.	Possible impact of its modulation of nicotinic receptor on symptoms and ↓ AD disease progression
Galantamine ER	8 mg/d	Up to 24 mg/d	Once daily dosing may increase adherence.
Huperzine A	50 µg b.i.d.	Up to 400 µg/d	100 µg equals <5 mg of donepezil

Donepezil, rivastigmine, and galantamine are also available as oral solutions.

b.i.d., twice a day; AD, Alzheimer disease; GI, gastrointestinal.

Apathy

1. Apathy is defined as a disorder of motivation. It presents with a decrease in goal-directed behaviors that are appropriate to a patient's age and background. These include a loss of independence in one or more instrumental activities of daily living (IADLs), such as shopping, driving, using public transportation, or handling finances. Patients with apathy are emotionally unresponsive and disengaged from their environment. Apathy must be distinguished from depression, but these two disorders may be also be concurrent.
   - **a.** Abulia can be viewed as a more extreme presentation of apathy, with marked limitations in initiating purposeful behaviors.
   - **b.** Akinesia reflects a disorder of movement, manifesting as a disinclination to initiate movements.
2. DA agonists may be helpful (see Table 15-3).
3. Stimulant medications may also be used (see Table 15-1).

Behavioral/Environmental

Depends on the severity of the impairments.

1. General principles
   - **a.** Organizational strategies/time-management techniques and executive function skills training
   - **b.** External support/guidance

c. Increased structure (including cleaning and organizing the patient's living quarters)
d. Mindfulness-based meditation
e. Cognitive behavioral therapy (CBT)
f. Stable routines
g. Concrete rewards and consequences in response to the patient's actions
h. Planning for the patient's future
i. Education and support of caregivers

2. Referrals
   a. Occupational therapist, speech and language pathologist, or other rehabilitation specialist to work on behavioral strategies and organizational techniques.
   b. Social worker to help ensure adequate safety, planning for the future, and necessary caregiver support.

DISORDERS OF AROUSAL AND WAKEFULNESS

Background

An appropriate level of arousal is necessary, but not sufficient, for awareness and the performance of all cognitive tasks.

Pathophysiology

1. Neuroanatomic components: Reticular activating system, thalamus, hypothalamus, and bilateral cortical regions. Recent data also suggest that the mesopontine parabrachial nuclei may also be critical in modulating wakefulness.
2. Disorders: Primary sleep disorders, CVD, TBI, medication side effects

Prognosis

Prognosis is variable and depends on the underlying conditions.

Diagnosis

1. History, emphasizing sleep–wake cycle, symptoms of apnea, periodic limb movements, and narcolepsy; need to obtain information from patient's bed partner, including a history of snoring, apnea, jerky movements, sleep walking, or kicking off covers
2. Review of medications and systemic illnesses
3. Sleep diary
4. Consider formal sleep study.

Treatment

1. Medications: Stimulant medications, modafinil (see Table 15-1)
2. Improve sleep hygiene: Consistent bed and wake-up times; avoid caffeine, especially after 12 noon; limit alcohol intake; avoid stressful activities before bedtime; avoid daytime naps; consistent exercise routine
3. Simplify medication regimen if possible
4. A detailed discussion of the treatment of sleep disorders is found in Chapter 5.

DISORDERS OF MEMORY

Background

1. Although memory can be defined in terms of a variety of mental processes, the clinical focus is on explicit (declarative) memory. This involves the capacity to remember events that occurred within a specific temporal or spatial context (episodic memory/new learning) or to recall information in more permanent stores without reference to the specific learning context (semantic memory/facts).
2. Amnestic syndrome is characterized by recall deficits with relatively well-preserved attention, anterograde memory loss, and retrograde memory loss —events that occurred closest to the onset of memory loss are recalled least (Ribot law).

Pathophysiology

1. Neuroanatomic components: The limbic system and frontal lobes play a crucial role in episodic memory.
   - **a.** Limbic system: The neurotransmitter ACh, involved in pathways from the basal forebrain to limbic structures, facilitates the process. In general, a rapid rate of forgetting (with loss of stored data and reduced ability to even "recognize" previously learned information when tested by multiple-choice questions) strongly suggests impairment within the limbic system.
   - **b.** Frontal lobes: Activation–retrieval difficulties, marked by preserved recognition in the setting of poor recall, may indicate problems with frontal network functioning.

2. Disorders
   - **a.** Degenerative dementias (see "Dementia" section, below)
   - **b.** Transient global amnesia (TGA): A syndrome of reversible anterograde amnesia, etiology often unknown (possibly vascular, epileptic, or migrainous), with typical duration range of 6 to 24 hours and clinically characterized by profound disorientation, repetitive question asking, and inability for new memory formation.
   - **c.** Other damage to limbic system or frontal networks (e.g., TBI, anoxia, Korsakoff syndrome [see section on Vitamin Deficiency States/Toxins], limbic encephalitis [e.g., herpes simplex encephalitis, paraneoplastic encephalitis], temporal lobe epilepsy CVD).

Prognosis

Prognosis is variable and depends on the underlying conditions.

Diagnosis

History, MSE, and neurologic examination: To detect more subtle memory disorders, the MSE should include tests appropriate to the patient's educational level and premorbid level of functioning.

Treatment

Medications

l. Cholinesterase inhibitors (see Table 15-4)

a. Increase the availability of ACh.

b. Currently, approval in the United States includes the treatment of AD dementia and PD dementia (rivastigmine only for both AD and PD).

c. Cholinesterase inhibitors have been shown to result in a modest improvement in cognitive function relative to placebo in many trials. In addition to improved cognitive functioning, there is evidence of a beneficial impact on activities of daily living (ADLs) and reduction of behavioral/neuropsychiatric symptoms, especially apathy, and overall milder symptoms. Impact on delaying nursing home placement is conflicted.

d. There have been studies indicating the efficacy of cholinesterase inhibitors in treating patients with vascular dementia and mixed-type (neurodegenerative/vascular) dementia. Patients with DLB may show noticeable improvement in cognition and reduced visual hallucinations.

e. Clinicians can consider "empiric" treatment with cholinesterase inhibitors for non-dementia conditions with memory disturbance (e.g., TBI). It is always crucial to closely monitor whether symptoms are improving and be aware of the impact of potential negative side effects.

f. Donepezil is a reversible acetylcholinesterase inhibitor (AChEI) dosed once a day. Rivastigmine inhibits both acetylcholinesterase (neuronal) and butyl cholinesterase (plasma) activity, and a transdermal formulation may reduce the risk of GI-related side effects. Galantamine is an AChEI and also exhibits allosteric binding to nicotinic receptors; the clinical benefits of this additional mechanism have not been proven.

g. Rivastigmine and galantamine are given in b.i.d. dosing. Rivastigmine is also available as a once-a-day patch and galantamine has a long-acting, once-a-day tablet. There is no clear evidence that one agent is more efficacious than another. Patients vary in terms of which medication is better tolerated.

h. Potential side effects of cholinesterase inhibitors include GI distress (e.g., nausea, anorexia, diarrhea, vomiting, and weight loss), insomnia, vivid dreams, agitation, dizziness, and muscle cramps. Sometimes, initial side effects diminish or resolve after days/weeks. Some patients have intolerable side effects on one medication but tolerate another. Therefore, it is worth considering a switch to another agent prior to giving up on this

medication class.

i. Huperzine A, a herbal AChEI, offers an alternative for patients who prefer a "natural" treatment. It has shown modest efficacy in some trials for AD, with less clear benefit for vascular dementia, and ADHD. It is not approved in the United States for any indication. It comes in tablets of 50 μg. A typical dosage is one 100 μg/d (b.i.d. dosing). Up to 400 μg daily may be used if tolerated and necessary for optimal therapeutic benefit.

2. Herbal substances
   a. These have not been subject to the same scrutiny as medications that require FDA approval.
   b. Ginkgo biloba may have antioxidant properties, increase cerebral blood flow, inhibit platelet-activating factor, and have mild stimulating effects. Some combination of these actions may be relevant to their potential efficacy in the treatment of dementia. Doses range from 120 to 360 mg daily in divided doses. Several studies have shown that 240 mg/d can modestly improve cognitive performance and measures of global function over 22 to 26 weeks. Ginkgo appears to be safe for use, with no excess side effects compared with placebo. Ginkgo does not slow the rate of developing dementia in patients with mild cognitive impairment (MCI) and in normal older adults.

3. Memantine, a chemical relative of amantadine, is a moderate-affinity, uncompetitive *N*-methyl D-aspartate (NMDA) receptor antagonist and weak booster of DA. It has a greater NMDA antagonist effect at high levels of receptor activation than at low ones. The symptomatic improvement of cognition may result from improved "signal-to-noise" transmission across NMDA (and possibly AMPA) receptors and/or protection against glutamate-induced excitotoxicity. It comes in both 10-mg tablets and a long-acting, once-a-day (Namenda XR, patented) dose with 7, 14, 21, and 28 mg tablets. Typical doses are 20 or 28 mg daily (FDA-suggested), but doses up to 40 mg/d (divided doses) have been studied. It is approved in the United States for moderate to severe AD, but studies support potential efficacy in vascular dementia and mixed-type AD/vascular dementia. Combined treatment with cholinesterase inhibitors seems to be tolerated and may be more effective than using cholinesterase inhibitors alone.

Behavioral/Environmental Strategies for Memory Disorders

1. Mnemonic devices
2. Increasing depth of encoding
3. Rehearsal
4. External cueing to assist with retrieval
5. Use of written cues

BEHAVIORAL DYSREGULATION/OUTBURSTS

Background

Agitation, aggression, and outbursts of intense emotional behavior are among the most socially undesirable and dangerous manifestations of neuropsychiatric disorders.

Pathophysiology

1. Neuroanatomic components: Behavioral regulation is dependent on the appropriate functioning of limbic structures (e.g., hypothalamus, amygdala) and frontal networks (e.g., orbitofrontal cortex). Many neurochemicals, including serotonin, ACh, GABA, NE, DA, and androgens, play an important modulatory role.
2. Disorders: A wide range of disorders can be associated with behavioral dysregulation, including delirium/ACS, dementia, hyperthyroidism, CVD, TBI, developmental disorders, and psychiatric illnesses such as schizophrenia, mania, psychotic depression, and personality disorders.

Prognosis

Prognosis is variable and depends on the underlying conditions.

Diagnosis

History (including precipitating factors, medical and psychiatric history, baseline neurologic status), MSE, neuromedical evaluation, and a toxic–metabolic screen are used in diagnosis. A history of developmental delay and

intellectual disability, posttraumatic stress disorder (PTSD), antisocial or criminal behavior, TBI, and the patient's work and home environments are all important factors.

Treatment

General Principles

1. Evaluate and treat concurrent illnesses (e.g., toxic–metabolic state, infection, pain, constipation, endocrine disorders, sleep disturbance), especially in cognitively vulnerable patients (e.g., patients with dementia or intellectual disabilities).
2. Identify and treat neuropsychiatric symptoms and disorders that may be contributing (e.g., depression, anxiety, hypomania/mania, thought disorder).
3. Simplify medication regimen, if possible.
4. Medication treatment depends on the urgency/acuteness of the situation.
   - **a.** If a patient is wildly agitated and dangerous, haloperidol 5 mg intramuscularly (IM) or intravenously (IV) alone or in combination with lorazepam 1 to 2 mg IM/IV remains the mainstay of treatment. One can also consider droperidol 2.5 to 5.0 mg IM/IV alone or in combination with midazolam 2.5 to 5 mg IM/IV.
   - **b.** For most agitation, aggression, and emotional outbursts associated with cognitive/behavioral disorders, second-generation antipsychotics are recommended. Acutely, olanzapine (IM) 10 mg or oral disintegrating tablet (10 to 20 mg) may also be effective; onset of action is 15 to 45 minutes. Risperidone 0.5 to 4 mg oral or sublingual disintegrating tablets are an alternative.
   - **c.** Repeat as necessary until the behavior is under control. For older or cognitively disabled patients, much lower doses are appropriate, but the ratio of benzodiazepine to neuroleptic should be approximately the same.
   - **d.** Closely monitor the patient's vital signs and obtain an electrocardiogram (ECG) when feasible to check for QT prolongation because of neuroleptic medication use (especially IV haloperidol).
   - **e.** As with all treatments, the aim is to try to maximize efficacy and safety while minimizing untoward side effects. Behavioral strategies may reduce or eliminate the need for medication and so should be instituted initially

and then concurrently with medication.

5. Mood stabilizers
   a. Antiepileptic drugs (AEDs) (Table 15-5) have been used for over three decades for their mood-stabilizing and potentially behavior-stabilizing properties. Of note, no randomized controlled trials have demonstrated their efficacy in treating agitation and other neuropsychiatric symptoms associated with dementia.
      1) Valproic acid, usually given as divalproex sodium, has FDA approval for the treatment of acute mania in bipolar disorder and is commonly used in maintenance therapy. It should be used sparingly or avoided in agitation with neurodegenerative dementia because of general inefficacy and frequent side effects. We have had some benefit in patients with behavioral dysregulation associated with intellectual disabilities and seizure disorders.
      2) Gabapentin, between 300 and 900 mg/d (divided doses), may have some benefit for behavioral dysregulation, especially when there is concurrent anxiety disorder.
      3) Carbamazepine has a long history of use in the treatment of emotional outbursts and explosive behavior. Its extended-release formulation has FDA approval for the treatment of acute mania or mixed episodes associated with bipolar disorder. It has modest effects on agitation/aggression in dementia; drug–drug interactions and potential for anemia or agranulocytosis must be monitored.
      4) Oxcarbazepine probably has similar effects to carbamazepine and does not have the risk of hematologic derangement; periodic screening for syndrome of inappropriate antidiuretic hormone secretion (SIADH)/hyponatremia is needed.
      5) Lamotrigine has approval in United States for maintenance therapy in bipolar disorder.

Table 15-5 Antiepileptic Drugs and Others as Potential Mood/Behavior Stabilizers

Medication	Starting Dose	Therapeutic Range	Comments
Valproic acid	125–250 mg	750–1,250 mg/d,	Follow LFTs, CBC, platelets, weight gain,

	q.d.–b.i.d.	divided doses	sedation, GI distress, tremor; IV prep available
Carbamazepine	100 mg q.d.–b.i.d.	400–600 mg/d	Follow LFTs, CBC, Na, sedation, ataxia, dizziness
Carbamazepine ER	200 mg q.d.	400–600 mg/d	Time to peak is up to 12 h
Oxcarbazepine	300 mg b.i.d.	Up to 2,400 mg/d in divided doses	Follow Na
Lamotrigine	25–50 mg/d	300–500 mg/d in divided doses	Risk of Stevens–Johnsons syndrome/rash (reduced by very slow dose titration)
Gabapentin	100–300 mg qhs	Up to 1,200 mg t.i.d.	Sedation
Tiagabine	2–4 mg/d	Up to 32 mg in divided doses	Dizziness, sedation, may increase anxiety
Prazosin	1 mg qhs	3–15 mg qhs	Avoid with cardiac disease/arrhythmias, dysautonomia, or orthostatic intolerance.
Dextromethorphan/quinidine	20 mg/10 mg	Up to 40 mg/20 mg (divided doses)	Most studied in pseudobulbar affect but may have benefit for agitation in dementia.

q.d., every day; b.i.d., twice a day; LFTs, liver function tests; CBC, complete blood count; GI, gastrointestinal; IV, intravenous; Na, sodium; ER, extended release; qhs, at night; t.i.d., three times a day.

6) Other anticonvulsants have been studied using varying degrees of experimental control.

7). In general, aim for doses and therapeutic levels similar to those appropriate for the treatment of epilepsy.

b. Lithium should be used very cautiously in patients with overt brain disease (e.g., TBI, degenerative dementia). Begin with 300 mg daily or 150 mg b.i.d. Increase slowly, by increments of no more than 300 mg/d. Lithium has a very low therapeutic index: Levels of 1.0 are needed for the best outcomes in primary bipolar disorder, but a level of 2.0 will

cause neurotoxic symptoms in most patients. Common side effects of long-term lithium use include hypothyroidism and nephrogenic diabetes insipidus. Both conditions can aggravate neurologic impairment. Kidney function should be monitored as least weekly during dosage adjustment and at least quarterly thereafter. Thyrotropin and tetraiodothyronine (T_4) should be checked every 3 to 6 months and again if the patient develops new symptoms compatible with hypothyroidism.

5. Sympatholytics (catecholamine blockers)
   - **a.** Behavioral dysregulation and hyperresponsiveness may arise from some level of increased central nervous system (CNS) adrenergic activity, with increase postsynaptic release of NE.
   - **b.** Propranolol (β-blocker) 20 to 480 mg/d may be particularly effective for those with intellectual disabilities or autism spectrum disorder (ASD). Follow patient for signs of hypotension and bradycardia. Asthma is a relative contraindication. Improvement may not be noticeable for weeks.
   - **c.** Prazosin (α_1-blocker) is FDA-approved for hypertension but can also been used for nightmares, PTSD, and agitation/aggression in dementia. Start 1 mg/d and titrate 1 to 2 mg/wk to effect; maximum of 10 mg/d.

7. Dextromethorphan/quinidine is a sigma-1 agonist and weak NMDA-antagonist which is FDA-approved for the treatment of pseudobulbar affect (PBA). Some evidence has shown benefit for severe agitation in dementia and may be reasonable to try in order to avoid the need for antipsychotics. Consider one capsule (20 mg/10 mg) daily and increase to b.i.d., if warranted.

8. Atypical neuroleptics (Table 15-6)
   - **a.** These have FDA approval for the psychotic symptoms and agitation associated with schizophrenia. Many have FDA approval for acute mania or mixed episodes associated with bipolar disorder as well as for maintenance therapy.
   - **b.** Atypical neuroleptics also have been widely used to treat nonpsychotic patients whose behaviors are potentially dangerous to themselves and others. They also may have benefit for treating psychosis or agitation in dementia. Consider risperidone (up to 2 mg/d), quetiapine (up to 150 mg/d), or olanzapine (up to 5 mg/d).
   - **c.** All of the first-generation atypical neuroleptics block D_2 DA and 5-HT_2

serotonergic receptors as well as other DA and serotonin receptors to varying degrees. These medications have differing impacts on histaminic, γ-adrenergic, and cholinergic receptors. In general, potential side effects of neuroleptics include somnolence, dizziness, orthostatic hypotension, akathisia, extrapyramidal signs, dystonia, neuroleptic malignant syndrome, and tardive dyskinesia. Although the neurologic side effects are less frequent and less severe with the atypical rather than typical neuroleptics, all of them can occur, and patients with preexisting brain disorders are most vulnerable.

d. Extrapyramidal side effects can be addressed with low doses of amantadine, pramipexole, or bromocriptine (see Table 15-3) while monitoring for aggravation of the underlying behavioral problems. Dystonia can be managed by anticholinergic agents, either IV or by mouth (p.o.) (e.g., diphenhydramine 50 mg or benztropine 2 mg). Akathisia may be helped by propranolol 20 to 40 mg t.i.d.

e. Metabolic syndrome (obesity, hypertriglyceridemia, low high-density lipoprotein [HDL], hypertension, hyperglycemia) can be checked for by monitoring weight, waist circumference, fasting serum glucose, fasting lipid profile, and blood pressure.

Table 15-6 Atypical Neuroleptic Medications

Medication	Starting Dose	Dosing Range	Comments
Clozapine	6.25–25 mg/d	25–300 mg b.i.d.	Minimal extrapyramidal effects; risk of BM suppression (check frequent CBCs), seizures at higher doses; patients with PD and psychosis may respond to very low doses; disintegrating tablets and IM prep available
Olanzapine	1.25–5.0 mg qhs	2.5–20 mg/d	Weight gain; glucose intolerance; disintegrating tablets and IM prep available
Risperidone	0.25–1.0 mg q.d.–b.i.d.	0.5–3 mg b.i.d.	Of the atypicals may be most effective for agitation in dementia; most likely to cause extrapyramidal effects; disintegrating tablets and IM prep available
Quetiapine	12.5–25 mg	25–600 mg/d	Weight gain; sedation

	q.d.–b.i.d.		
Ziprasidone	20–40 mg q.d.–b.i.d.	20–160 mg/d	↑ QTc interval of unclear clinical significance; weight neutral; IM prep available
Aripiprazole	10–15 mg/d	15–30 mg/d	Weight neutral; akathisia common; adjunct to SSRIs for depression; IM prep available
Pimavanserin	17 mg/d	34 mg/d	Approved for PD psychosis; selective 5-HT2A receptor antagonism may limit extrapyramidal side effects

b.i.d., twice a day; BM, bone marrow; CBCs, complete blood counts; PD, Parkinson disease; IM, intramuscular; qhs, at night; q.d., every day; SSRIs, selective serotonin reuptake inhibitors.

f. There is some evidence that the use of typical and atypical neuroleptic medication is associated with an increased risk of death and cardiovascular events, especially in the elderly. The risk may increase at higher doses of the medication.

g. Randomized trials have suggested that atypical neuroleptics (e.g., olanzapine, risperidone) have some degree of efficacy in treating behavioral symptoms in elderly demented patients. However, the benefits may be outweighed by side effects.

h. We suggest avoiding this class of medication, when feasible, in treating elderly demented patients; discussing the risks/benefits/uncertainties with caregivers; using the lowest dose possible; and discontinuing the medication if ineffective.

). Benzodiazepines: An increase in GABA activity may reduce anxiety and have a calming effect. However, there is a risk of reducing inhibition, with a paradoxical increase in behavioral dysregulation.

). Buspirone, a 5-hydroxytryptamine 1A (5-HT_{1A}) agonist, is FDA-approved for generalized anxiety disorder and may also reduce aggressive behaviors. Begin 2.5 or 5 mg/d, up to t.i.d. Increase up to 60 mg/d in divided doses. Consider lower doses for those with any prior brain injury. The effects are often delayed. Side effects tend to be minor and include headaches and nausea. Buspirone does not suppress respiratory drive, so it can be used in patients with lung disease.

l. SSRIs (see Table 15-2) may reduce irritability and behavioral outbursts, especially in patients with concomitant anxiety and dysphoria. Some SSRIs

(e.g., sertraline and especially citalopram) have been shown to reduce behavioral problems in demented, elderly patients. For the behavioral problems associated with frontotemporal dementia (FTD), clinical experience and case series suggest that SSRIs are among the most effective. Low doses of the serotonin antagonist and reuptake inhibitor (SARI) trazodone (see in section below) may also be effective.

a. In general, we suggest that for neurologic patients, SSRIs be started at doses that are lower than usual (e.g., 5 mg of fluoxetine, citalopram, or paroxetine; 12.5 mg of sertraline).

b. Potential side effects of SSRIs include sexual dysfunction, increased apathy, RLS/periodic limb movements, akathisia, agitation, sleep disturbances, and the serotonin syndrome (a medical emergency involving a change in mental state, autonomic instability, and neuromuscular hyperactivity).

c. Clinicians have used a variety of treatments for SSRI-induced sexual dysfunction, including sildenafil (50 to 100 mg as needed), bupropion (75 to 150 mg/d), and buspirone (15 to 30 mg b.i.d.). Less well-studied options include cyproheptadine (4 to 12 mg as needed), amantadine (100 to 300 mg/d), or other dopaminergic agents (see Table 15-3).

2. Trazodone is a 5-HT_2 SARI; 25 to 300 mg/d has been used to help manage agitated patients. This medication can be sedating and cause headaches.
3. Cholinesterase inhibitors (see Table 15-4) have been shown to have beneficial effects on behavior and neuropsychiatric symptoms (usually of milder severity) in patients with probable AD.

Behavioral/Environmental

1. Safety: Protect the patient from self-harm. Protect the caregivers from potentially injurious behaviors.
2. Try to identify and avoid precipitating events.
3. Educate caregivers about management (e.g., gentle distraction).
4. Reduce excessive environmental stimulation and establish a calm and "predictable" environment and routine.
5. Ensure patients do not have access to firearms.
6. Improve sensory fidelity when feasible (e.g., glasses, hearing aids).
7. Improve sleep hygiene.

3. Ensure adequate fluid and nutritional intake.
4. Try to establish an exercise regimen.

OTHER NEUROPSYCHIATRIC DISORDERS

Neurologists often care for patients who suffer from a range of neuropsychiatric disorders. They should be aware of diagnostic issues and be prepared to provide initial treatment. However, complicated patients (i.e., those with significant psychiatric history, those at high risk for violence or self-injury, or those resistant to first-line treatments) usually should be referred to qualified psychiatrists with special expertise in this area.

Major Depression and Dysthymia

Background

Major Depression

1. Major depression is characterized by depressed mood and loss of interest or pleasure occurring for most of the time during at least a 2 week period.
2. Key symptoms include weight loss (without dieting), sleep disturbance, psychomotor retardation or agitation, fatigue, feelings of worthlessness/guilt, problems with concentration/decision making, and/or recurrent thoughts of death.
3. These symptoms should be associated with significant distress or impairment of daily functioning.
4. Cognitive problems tend to involve attention, executive function, and the activation–retrieval aspects of memory.
5. Clinically significant depression is common in neurologic patients, either as a direct consequence of brain dysfunction/injury or as a reaction to associated disabilities.

Persistent Depressive Disorder (Dysthymia)

Persistent depressive disorder reflects a chronically depressed mood that lasts more than 2 years and is associated with changes in appetite, alterations in sleep, fatigue, low self-esteem, diminished concentration, and hopelessness. It is closest to the prior disease entity known as dysthymia. In the *Diagnostic and*

Statistical Manual of Mental Disorders, *5th edition* (*DSM-5*), patients with chronic major depression are categorized as having persistent depressive disorder *with* a persistent major depressive episode.

Prognosis

Untreated depression is likely to further erode a patient's functional and cognitive status.

Diagnosis

1. History
2. MSE (including information about mood, energy level, libido, sleep, appetite, concentration, suicidal ideation/plans/attempts)
3. Formal scales of mood (e.g., Beck Depression Inventory) are useful but do not substitute for a sensitive clinical interview.

Treatment

Medications (see Table 15-2)

1. SSRIs (see information earlier)
   - **a.** SSRIs are often the first medication initiated because of their relatively good side effect profile/tolerability. They may also be helpful for patients suffering from persistent depressive disorder.
   - **b.** SSRIs can cause/exacerbate apathy, which sometimes is mistaken for depression.
   - **c.** Abrupt discontinuation, especially of the shorter acting SSRIs (paroxetine, sertraline, fluvoxamine), can lead to flulike symptoms (headache, nausea, malaise), paresthesias, dizziness, and rebound depression.
2. TCAs
   - **a.** Some would argue that TCAs are the most effective treatment for depressed patients who also have significant weight loss and sleep disturbance. They also may be particularly useful in depressed patients with pain and anxiety. TCAs are less likely to suppress libido and inhibit orgasm than SSRIs.
   - **b.** A major issue is anticholinergic side effects, including dry mouth, urinary retention, sedation, constipation, exacerbation of glaucoma, and confusion, especially in cognitively vulnerable individuals.

c. Cardiac conduction system disease should be ruled out by EKG before initiating therapy, especially in patients over 40 years old.

d. Secondary amine TCAs (e.g., desipramine, nortriptyline) have lower anticholinergic properties and cause less postural hypotension than tertiary amine TCAs (e.g., amitriptyline, imipramine).

e. If possible, TCAs should be tapered slowly to avoid symptoms of cholinergic rebound (e.g., GI distress, headache). Both TCAs and SSRIs increase the risk of falling in elderly patients. With TCAs, it is often caused by orthostatic hypotension, whereas with SSRIs the issue is one of mild motor impairment.

3. SNRIs (see Table 15-4): At low doses, venlafaxine blocks the reuptake of serotonin; at higher doses, it blocks the reuptake of both serotonin and NE. Potential side effects include insomnia, sedation, hypertension, sweating, and sexual dysfunction. Duloxetine is another SNRI that treats depression. It also has FDA approval for the management of diabetic neuropathy, chronic musculoskeletal pain, generalized anxiety disorder, and fibromyalgia. GI side effects are relatively common. Milnacipran and levomilnacipran may also be used, typically by depression specialists/psychiatrists. These should all be tapered slowly, over 2 to 4 weeks, to reduce serious symptoms of nausea, irritability, insomnia, and dizziness, part of a common, potentially debilitating SNRI discontinuation syndrome.
4. Bupropion (see Table 15-2)
5. MAOIs are effective antidepressants that also have anxiolytic properties. They tend to be used in treatment-refractory cases of depression and should be prescribed by clinicians who have experience with this class of medication.

a. Tranylcypromine: Initial dose is 10 mg b.i.d. to t.i.d.; increase up to 30 to 60 mg/d. This medication also has stimulant effects.

b. Phenelzine: Initial dose is 15 mg b.i.d. to t.i.d.; increase up to 60 to 90 mg/d.

c. Most serious side effects involve dangerous interaction with certain (tyramine-containing) foods (e.g., red wine, beer, aged cheeses, fava beans) and medications (e.g., certain cold remedies, meperidine, antidepressants) that can precipitate a hypertensive crisis, stroke, or serotonin syndrome (altered mental status, fever, tremor, myoclonus, and

autonomic dysregulation, possibly leading to death). Patients should check with their physician before taking any new medications and should be warned specifically about over-the-counter (OTC) sympathomimetic medications (e.g., pseudoephedrine). There should be a delay (usually 2 weeks) between stopping an MAOI and initiating treatment with a variety of medications (e.g., TCAs, many SSRIs). Precautions also need to be taken in terms of delaying treatment with an MAOI after a patient has been on a range of other medications.

Caution

1. Antidepressants can precipitate mania/hypomania in vulnerable individuals. A mood-stabilizing medication often needs to be added.
2. Hypomania because of antidepressants may present with irritability, agitation, intense anxiety, disinhibition, or poor judgment, without euphoria. The possibility of antidepressant-triggered hypomania should be considered when a patient's behavior deteriorates after an antidepressant has been started.

Psychotherapy

1. In combination with pharmacotherapy, psychotherapy (of various types) has strong evidence as an effective strategy. Some studied psychotherapy types include CBT, psychodynamic, and interpersonal psychotherapy.
2. It also provides neurologic patients with a much-needed avenue to work on adjusting to how their disease has impacted their lives.

Anxiety

Background

Anxiety is a common symptom in neurologic patients and has cognitive, somatic, affective, and behavioral components.

1. The cognitive experience is one of worry or fear.
2. The somatic component may include feelings of inner "shakiness" or discomfort, muscle tension, shortness of breath, chest pressure, diaphoresis, or nausea.
3. Behaviorally, patients may appear hyperactive and/or irritable, avoid exposure to certain stimuli, and repetitively seek reassurance.

4. Anxiety can undermine attention and executive functions.

Diagnosis

1. History, including family history of all psychiatric disorders.
2. MSE.
   a. In patients with concurrent cognitive impairment, behavioral observations (e.g., patient's demeanor, movements, and facial expression) and reports from caregivers are essential.
   b. Inquire specifically about trauma and PTSD, obsessions and compulsions, and phobias.
3. Workup should include the identification of underlying medical/endocrinologic conditions (e.g., hyperthyroidism, hypercortisolism, hyperparathyroidism, partial seizures) or medications/supplements that can cause or exacerbate anxiety (e.g., sympathomimetics; caffeine, alcohol, guarana).

Treatment

Medications

Medication should be considered for patients whose anxiety is associated with significant distress, irritability, sleep disturbance, and/or disruption of ADLs.

1. Benzodiazepines provide rapid relief of anxiety and are effective for the short-term management of these symptoms. Long-term use may increase the risk of incident dementia, and short-term use may lead to some cognitive and behavioral impairment, especially in patients with brain injury. They can also cause or exacerbate gait disturbance and falls. Begin treatment with low doses, preferably short-acting (triazolam, lorazepam, oxazepam) if cognitively impaired. Titrate until effective or untoward side effects develop. If patients need longer term treatment for anxiety, initiate an antidepressant (SSRI, SNRI, or buspirone), then taper off the benzodiazepine.
2. Antidepressants (see Table 15-2): SSRIs, SNRIs, and TCAs (e.g., nortriptyline) are efficacious in the treatment of anxiety. Contemporary first-line treatment is thought to be an SSRI. Therapeutic onset is slower than benzodiazepines. Treatment with antidepressants is particularly appropriate in patients who have a mixture of anxiety and depression. In general,

clinicians should initiate therapy with SSRIs at a lower dose than is used for depression as they can initially exacerbate anxiety.

3. Buspirone has the advantage of being associated with fewer side effects than benzodiazepines. However, efficacy is more variable with buspirone than benzodiazepines, and there can be a delay of up to several weeks before maximum response.
4. Mirtazapine, an α_2-antagonist, may be used as monotherapy or as an adjunct to SSRI/SNRIs, especially for refractory anxiety. Lower doses (7.5 mg to 15 mg) may be best for anxiety with insomnia, whereas higher doses (30 to 45 mg) can have an anxiolytic effect accompanied with increased alertness/arousal.
5. Atypical neuroleptics (see Table 15-6) tend to be reserved for extremely anxious patients who also exhibit paranoid or delusional thoughts. Given the potential risks of atypical neuroleptics, efforts should be made to prescribe other classes of medications.

Psychotherapy/Behavioral

1. Consider psychosocial interventions (e.g., psychotherapy, CBT, psychoeducational counseling by treating clinicians, support groups, relaxation and mindfulness training) that are aimed at helping patients cope with the stressors that they face.
2. For some patients, anxiety can be significantly reduced when clinicians are able to fully address their concerns.

Psychosis

Background

The cognitive aspect of psychosis is also known as thought disorder.

1. It can also present with hallucinations, delusions (including paranoia), bizarre and disorganized behavior or speech, or highly unusual movements (e.g., posturing, immobility) not explained by an identifiable movement disorder.
2. More subtle manifestations of a thought disorder may include odd associations, vague speech, unusual beliefs that are intensely held, or inappropriate suspiciousness.

3. Thought disorder can be seen in patients suffering from delirium, toxic encephalopathy (e.g., secondary to drugs like amphetamines, phencyclidine [PCP], lysergic acid diethylamide [LSD]), temporolimbic seizure disorder (often with relatively preserved social and interpersonal behavior), dementia (more common in genetic FTD-motor neuron disease [MND] and early-onset, genetic FTD), mood disorder (severe depression or mania), overwhelming stress (i.e., brief psychotic disorders), or schizophrenia-spectrum illnesses.

Diagnosis

1. History (baseline psychiatric and cognitive status, precipitating events, illicit drug history).
2. MSE, neuromedical examination, toxic–metabolic screen, and often neuroimaging and electroencephalogram (EEG).

Treatment

1. Atypical neuroleptics (see Table 15-6) are the mainstay of treatment.
2. These medications have their most immediate impact on agitation, irritability, and behavioral outbursts. Hallucinations, disorganized thinking, and delusions often take longer to resolve. Persistent delusions associated with schizophrenia tend to be more resistant to treatment.
3. Pimavanserin was approved for use in April 2016 in the United States for the treatment of hallucinations and delusions in patients with PD psychosis. Although considered an atypical neuroleptic, pimavanserin is a highly selective 5-HT_2A inverse agonist, which differentiates it from the multireceptor impact of other neuroleptics, perhaps reducing EPS.
4. Patients with PD who exhibit disabling psychotic symptoms (e.g., hallucinations, delusions) may also benefit from clozapine (at low doses), which also does not tend to exacerbate motor symptoms:
   a. Clozapine should be monitored closely because it can cause severe neutropenia, sedation, orthostatic hypotension, seizures, and cardiomyopathy. Given these possible side effects, it is reasonable to begin treatment with another atypical neuroleptic (e.g., quetiapine, olanzapine).
   b. If titrating other atypicals worsens existing parkinsonian symptoms, then

switch to clozapine.

5. Delusions associated with DLB and AD may have modest improvement with cholinesterase inhibitors.
6. Psychotic patients with concomitant mood disorders need additional treatment of their mania or depression (see Tables 15-2 and 15-5).

DEMENTIA (OR MAJOR NEUROCOGNITIVE DISORDER)

Diagnosis

1. The *DSM-5* replaced the long-used term "dementia" with "major neurocognitive disorder (NCD)."
2. Clinicians can further specify the disease causing the NCD (e.g., "major neurocognitive disorder due to . . . [Alzheimer disease] or [Parkinson disease] or [multiple etiologies]").
3. The following *DSM-5* diagnostic criteria are common to dementia of any etiology:
   - **a.** Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on
     - **1)** Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function
     - **2)** A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
     - **3)** Cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex IADLs such as paying bills or managing medications).
     - **4)** The cognitive deficits do not occur exclusively in the context of a delirium. See Table 15-7 for differences between delirium and dementia.
     - **5)** The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

4. Mild NCD is reserved for disorders that meet all criteria for major NCD (aforementioned), except (b): In mild NCD, cognitive deficits do *not* interfere with independence in daily activities.

Table 15-7 Characteristics of Dementia Versus Delirium

	Dementia	Delirium
Onset	Months to years	Hours to days
Course	Steady	Fluctuating
Duration	Years	Days
Attention	Intact in mild/moderate stages	Altered (hypo- or hypervigilant)
Level of arousal	Normal	Fluctuating
Sleep–wake cycle	Usually normal	Often disturbed
Visual hallucinations	Infrequent	Frequent
Myoclonus	Infrequent	Frequent
Seizures	Uncommon	More common

5. This distinction between major and mild NCD is analogous to that between MCI and dementia in the neurology literature. Clinicians should be aware that not all dementias present with prominent memory deficits.
6. Several clinical characteristics may help to differentiate delirium from dementia (Table 15-8). Delirium has a multitude of etiologies but is often a result of toxic–metabolic derangements or infections. Patients with dementia are particularly likely to develop delirium as a result of these perturbations.
7. Table 15.8 lists many causes of dementia. This chapter will explore a select group of these causes.

MILD COGNITIVE IMPAIRMENT (OR MILD NEUROCOGNITIVE DISORDER)

Background

1. MCI is thought to represent a transitional state from normal aging to dementia. When an underlying neurodegenerative disease is suspected, many

consider MCI to be an early stage of that disease. Accepted formulations divide MCI into amnestic and nonamnestic subtypes. In the latter, the cognitive impairment is of a nonmemory domain.

2. Amnestic MCI is more likely to transition to AD, whereas nonamnestic MCI is more likely to transition to vascular dementia, frontotemporal lobar degeneration (FTLD), or DLB. MCI subtypes are not able to predict the development of a particular, pathologic disease with high certainty, nor can they clearly distinguish between any existing pathologic process. For example, neuropathologic studies suggest that up to half of nonamnestic MCI patients actually have underlying AD.
3. Nonamnestic MCI patients have consistently shown decreased frontal lobe metabolism with functional imaging compared to amnestic MCI patients. Patients convert from MCI to AD at a rate of 10% to 15% per year compared to a 1% to 2% conversion of age-matched controls, in studies involving specialty memory clinics.
4. In some epidemiologic studies, the rates of conversion are lower, and 15% to 30% of patients eventually "revert to normal" on subsequent evaluations (i.e., they no longer qualify for the MCI designation), suggesting that MCI does not always reflect an underlying neurodegenerative process. The epidemiology of MCI is uncertain given the heterogeneity of the definition used in various studies.

Table 15-8 Causes of Dementia

Neurodegenerative
Alzheimer disease
Frontotemporal lobar degeneration
Dementia with Lewy bodies
Huntington disease
Multisystem atrophy
Argyrophilic grain disease
Wilson disease
Pantothenate kinase–associated neurodegeneration (PKAN)
Mitochondrial diseases
Kufs disease (neuronal ceroid lipofuscinosis)
Metachromatic leukodystrophy
Adrenoleukodystrophy
Inflammatory/infectious
Multiple sclerosis
Syphilis

	Lyme disease
	HIV
	Creutzfeldt–Jakob disease
	Primary CNS vasculitis
	Vasculitis secondary to other autoimmune disorders (i.e., lupus)
	Sarcoid
	Chronic meningitis (i.e., tuberculosis, *Cryptococcus*)
	Viral encephalitis (i.e., HSV)
	Whipple disease
	Systemic lupus erythematosus
	Sjögren syndrome
Vascular	
	Vascular dementia
	Hypoxic/ischemic injury
	Post-CABG
	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)
Metabolic/toxins	
	Hypothyroidism
	Vitamin B_{12} deficiency
	Thiamine deficiency (Wernicke–Korsakoff)
	Niacin deficiency (pellagra)
	Vitamin E deficiency
	Uremia/dialysis dementia
	Addison/Cushing disease
	Chronic hepatic encephalopathy
	Heavy metal exposure
	Alcohol exposure
Neoplastic/immune-mediated	
	Tumor (depends on location)
	Paraneoplastic limbic encephalitis (anti-Hu)
	NMDA-receptor (and other autoimmune) encephalitides
	Stiff person spectrum disorders
	Acute and chronic sequelae of brain radiation (acute and subacute encephalopathy, radiation necrosis, diffuse late brain injury)
	Chemotherapy
	Lymphomatoid granulomatosis

This list is not exhaustive because any brain injury can result in dementia depending on location. Some diseases could be under multiple categories.

CNS, central nervous system; HSV, herpes simplex virus; CABG, coronary artery bypass graft; NMDA, *N*-methyl D-aspartate.

Pathophysiology

1. Many patients with amnestic MCI who have come to autopsy have the pathologic hallmarks of AD.
2. Amnestic MCI patients often have cerebrospinal fluid (CSF) biomarkers of

AD (high total tau, low β-amyloid 42) as well as indications of amyloid plaques in the cortex (see section on Alzheimer Disease)

3. Meta-analyses of studies using Aβ-specific imaging tracers, which allow for in vivo detection of amyloid plaques, show that between 45% and 60% of MCI patients demonstrate Aβ-related AD pathology. This proportion is consistent with the autopsy and longitudinal data.

Prognosis

1. Rate of conversion to AD is described earlier.
2. A number of factors appear to modify the rate of MCI conversion to AD dementia. The factors are all generally characteristics of patients who have AD dementia. Poor episodic memory, greater hippocampal atrophy, hypometabolism in posterior temporal and parietal regions on fluorodeoxyglucose-positron emission tomography (FDG-PET), lower CSF Aβ-42, and the presence of an apolipoprotein E (APOE) ε4 allele are all associated with a higher rate of conversion to AD dementia.

Diagnosis

1. The diagnosis is made on a clinical basis. Patients must present with cognitive complaints and have objective evidence of impairment in one or more domains, relative to age- and education-matched norms.
2. They must perform well on other tests of general, cognitive function and, by definition, have *no* significant difficulty with ADLs.
3. As earlier, depending on whether memory is affected (amnestic MCI), and on the number of cognitive domains involved (single domain vs. multi-domain), one can classify MCI into subtypes.

Treatment

1. Several clinical trials have examined the role of cholinesterase inhibitors in MCI. The results have been largely mixed with, at best, a small delay in time to conversion to dementia, or modest benefit in other measures, like neuropsychological testing. Despite a lack of efficacy as a whole, many clinicians believe a trial is reasonable in some patients.
2. Further research is needed to determine appropriate management. These

patients may eventually benefit from the novel, disease-modifying interventions being developed for all patients along the AD spectrum (i.e., "preclinical" AD [still a research term], MCI, and AD dementia).

3. Exercise programs in RCTs, some up to 1 year in duration, have been associated with mild improvement in some cognitive measures in MCI.
4. Adherence to either a Mediterranean-style or DASH (Dietary Approaches to Stop Hypertension) diet has shown promise; each diet has been associated with a decreased incidence of both AD dementia and PD as well as a delay in cognitive decline or progression to dementia in cognitively normal individuals and MCI.

NEURODEGENERATIVE DEMENTIAS

Alzheimer Disease

Background

1. AD is the most common degenerative dementia and causes a progressive decline in cognitive function.
2. In most cases, an episodic memory deficit is the predominant, initial complaint, with milder deficits in attention, visuospatial processing, naming/language, and executive functions also sometimes present. The memory deficit is one of impaired memory storage, as opposed to the encoding and retrieval difficulties that characterize patients with frontal network impairment.
3. Atypical AD presentations like posterior cortical atrophy (PCA) (with predominantly visuospatial symptoms) or logopenic progressive aphasia (with predominantly language symptoms) may have more focal/segmental brain region pathology.
4. Over time, multiple cognitive domains become progressively more impaired, and most AD patients reach the point where they are no longer able to perform any ADLs or recognize family members.
5. Neuropsychiatric symptoms, such as depression, apathy, anxiety, agitation, and delusions are common.
6. An estimated 45 million people worldwide, and 5.3 million in the United

States, are living with AD. About 1 in 9 people age 65 years and older (11%) and 1 in 3 people age 85 years and older (32%) have dementia due to AD.

Pathophysiology

Genetics

1. In 2% to 3% of cases, the disease is transmitted in an autosomal dominant fashion.
   - **a.** Three known genetic mutations result in this mode of inheritance:
     - **1)** Mutations of the amyloid precursor protein (APP) on chromosome 21 (hence the nearly invariable association of AD with trisomy 21/Down syndrome)
     - **2)** Presenilin 1 protein on chromosome 14
     - **3)** Presenilin 2 protein on chromosome 1
     - **4)** These mutations seem to result in increased cerebral accumulation of β-amyloid (Aβ)-42, a neurotoxic form of the Aβ peptide.
     - **5)** Patients with autosomal dominant forms of AD often have an earlier age of onset, usually before age 60 years, and even as early as their 30s or 40s.
2. The remaining <97% of cases are considered "sporadic," with the exception of a few described nondominant familial cases.
   - **a.** These patients usually become symptomatic in their 60s or later.
   - **b.** Multiple genetic and environmental factors likely play a role in the development and symptom onset of sporadic AD. The following factors may increase the risk of AD:
     - **1)** Having a first-degree relative with AD
     - **2)** Having a history of moderate to severe TBI
     - **3)** Being female (there is a 2:1 female predominance)
     - **4)** Presence of the ε4 allele of the APOE gene on chromosome 19, which codes for a cholesterol-transporting protein that may be involved in the clearance of Aβ
     - **5)** Having at least one ε4 allele confers a threefold increased risk of AD
     - **6)** Having only minimal years of formal education
     - **7)** Having several cardiovascular-impacting conditions from midlife onward, including smoking, obesity, and diabetes, and also likely hypertension and hyperlipidemia

Pathology

1. The main pathologic findings of AD are amyloid and neuritic plaques, neurofibrillary tangles, and loss of neurons and synapses.
2. Amyloid plaques are spherical, extracellular accumulations of Aβ deposits.
3. Neuritic plaques are amyloid plaques surrounded by dystrophic neuritic processes, tau-paired helical filaments, and often reactive astrocytes and microglia. There is only modest correlation between plaque burden and symptom severity.
4. Neurofibrillary tangles are intracellular, paired helical structures composed of hyperphosphorylated tau proteins. Tangles seem to correlate well with disease severity and neuronal death. They are present in the hippocampus, amygdala, nucleus basalis of Meynert, locus ceruleus, dorsal raphe nucleus, and the neocortex (most prominently the posterior parietal and temporal association cortices).

Neurochemistry

1. There is reduction in the content of ACh and the activity of choline acetyltransferase as a result of basal forebrain degeneration.
2. This loss of ACh is associated with memory and other cognitive impairment, making it a target for pharmacotherapy.
3. The effectiveness of cholinesterase inhibitor medications supports the role of ACh depletion in the clinical phenomenology.
4. Other neurotransmitter systems are also impaired.

Prognosis

1. The range of the course of this progressive illness until death is from ~5 to 15 years after the onset of symptoms.
2. Most patients with AD die from other more proximate medical causes, including pneumonia or cardiac disease.

Diagnosis

1. According to National Institute on Aging-Alzheimer Association (NIA-AA) criteria, dementia because of probable AD requires a history of insidious onset of “clear-cut” observed/reported cognitive decline, over months to years, with either an amnestic or nonamnestic (executive, visuospatial,

language) presentation. There also must be an absence of substantial, concomitant CVD, core features of DLB or FTLD, and other active neurologic disease or nonneurologic medical comorbidity that could have a substantial effect on cognition.

2. Probable AD dementia with an "increased level of certainty" requires biomarker evidence of the AD pathophysiologic process, which includes magnetic resonance imaging (MRI) or CSF-based evidence of neurodegeneration and/or positive amyloid-PET imaging.
3. Except for "pathophysiologic proven AD," which can be made only with the pathologic examination of brain tissue using defined pathologic criteria, the diagnosis of AD remains a "clinical diagnosis" supported by emerging biomarkers.
4. The NIA-AA criteria have been shown to have a good high specificity for probable AD (70% to 85%), with less impressive sensitivity (from 50% to 70%).
5. MRI or computed tomography (CT) should be performed to rule out structural lesions or significant CVD. Medial temporal and posterior temporal and parietal atrophy often may be seen.
6. Single photon emission computed tomography (SPECT) and FDG-PET may modestly increase sensitivity and specificity for the diagnosis of AD; bilateral hypoperfusion (SPECT) or hypometabolism (PET) of the posterior temporal and parietal lobes is consistent with the diagnosis.
7. Detection of the ε4 allele is not diagnostic but may increase specificity in patients who meet clinical criteria.
8. Current guidelines suggest the selective use of CSF biomarkers and molecular imaging (e.g., amyloid-PET). These should be reserved for patients who have either early-onset or atypical clinical presentations, when there is diverging data between their neuropsychological profile, MRI/CT, and clinical history or when the diagnosis is equivocal for other reasons.

Treatment

Potential Disease-Modifying Agents

1. Several therapeutics with promise to modify the course of AD target either the removal of or decrease the production of Aβ deposits. These deposits may exist within amyloid plaques or as soluble oligomers.

2. Two major mechanisms of action include immunotherapy (i.e., active Aβ immunization or passive anti-amyloid antibodies) and protease inhibition of APP processing (i.e., β-secretase or γ-secretase inhibitors). Several novel drugs with these mechanisms are currently in late-stage clinical trials.
3. Other potential mechanisms of action for novel drugs include promotion of neurotrophic factors, inhibition of tau (fibrillary tangle) accumulation, shifting of brain energy metabolism, and augmenting intrinsic cerebral anti-inflammatory mechanisms.
4. α-Tocopherol (vitamin E) is an antioxidant that inhibits free-radical formation and lipid peroxidation. In a recent, large 2-year study, 2,000 IU/d was safe and demonstrated a delay in clinical progression (equivalent of 6 months of daily functioning) compared with placebo. There was no evidence of an increased risk of mortality.
5. Nonsteroidal anti-inflammatory drugs (NSAIDs), statins, ginkgo biloba, and high-dose vitamin B (B_{12}, B_6, and folic acid supplementation) have all been studied as potential disease-modifying interventions; they have some epidemiologic support, but randomized controlled trials have been disappointing.

Symptomatic Treatment

1. Cholinesterase inhibitors (see earlier parts of this chapter and Table 15-4) have been shown to result in a modest improvement in cognitive function and performance of ADLs relative to placebo in many trials. In addition to improved cognition, there is some evidence for reduced behavioral and neuropsychiatric symptoms.
2. Memantine (see section on Disorders of Memory) has demonstrated improved cognition over placebo in the treatment of moderate to severe AD in one large 28-week trial. A pooled analysis of six studies for the same population showed benefit of 20 mg/d in treating or preventing behavioral/neuropsychiatric symptoms (e.g., agitation, delusions) in AD.
3. In moderate to severe AD, treatment with memantine in combination with cholinesterase inhibitors appears more efficacious than cholinesterase inhibitors alone. Data supporting benefits of memantine in mild AD have had mixed results.
4. Symptomatic treatment for neuropsychiatric symptoms (e.g., depression, apathy) and specific cognitive deficits should be pursued as outlined earlier.

Citalopram and risperidone have been the most studied, showing modest to moderate benefit for the neuropsychiatric symptoms of AD.

5. Treat concurrent medical illnesses and chronic conditions (e.g., diabetes, hypertension) because patients with AD have diminished cognitive reserve.

Frontotemporal Lobar Degeneration

Background

1. FTLD is a large group of mainly language-, behavior-, and/or motor-based degenerative diseases, the third most common after AD and DLB. FTLD is a pathology-based term that encompasses many different clinical syndromes, united by their predilection for frontal and/or temporal lobe degeneration. These clinical syndromes can have many different underlying, molecular subtypes/histopathologies. Three of the major clinical syndromes to highlight are:

   a. bvFTD

   This is marked primarily by progressive changes in personality and behavior.

   1) Clinical criteria for possible bvFTD include three or more of early behavioral disinhibition (loss of manners/decorum; rash/careless actions), early apathy or inertia, early loss of sympathy or empathy, early perseverative, stereotyped or compulsive/ritualistic behavior, hyperorality and/or dietary changes (sweet tooth; oral exploration), and a neuropsychological profile of executive deficits.

   2) Lack of insight into changes, brushes with law enforcement, breakdown of family dynamics, and "utilization" behavior are also common.

   3) Neuropsychological tests of frontal lobe–mediated functions are often abnormal, especially attention and executive functions, with relative sparing of memory storage and visuospatial function.

   4) Difficulties with sustained attention, verbal fluency, and higher order reasoning are common, especially in cases with preferential injury of the dorsolateral frontal lobes. When right > left atrophy is observed, patients are more likely to exhibit associated prosopagnosia, topographagnosia, and comprehension difficulties.

   5) Differential diagnosis includes "frontotemporal brain sagging

syndrome" (FBSS), where spontaneous intracranial hypotension (SIH) can cause a bvFTD-like syndrome, and the bvFTD "phenocopy" syndrome (see "Prognosis" section below).

b. Primary progressive aphasia (PPA)

PPA is a syndrome marked by initial, selective impairment of language function, whether verbal fluency, repetition, comprehension, or grammar/syntax. Even as other domains (memory, executive function) become affected with disease progression, language deficits remain dominant.

1) Recent formulations divide PPA into three broad variants: agrammatic/nonfluent, semantic, and logopenic. Patients often have numerous symptoms that span these different variants.

2) Early on, PPA-agrammatic patients have predominant agrammatism and/or apraxia of speech (distorted speech sounds; impaired rhythm/prosody).

3) PPA-logopenic patients tend to have impaired single-word retrieval in conversation and impaired sentence repetition. The logopenic variant is also commonly associated with AD pathology on autopsy.

4) PPA-semantic patients tend to have impaired comprehension on a single-word level and markedly impaired confrontation naming (e.g., difficulty naming animals or objects when shown pictures and identifying objects that are named).

5) PPA-semantic patients also often have problems with category fluency (e.g., "Name as many animals as you can in 1 minute.") and the reading and writing of irregular words (e.g., "surface dyslexia"). They tend to make semantic paraphasic errors, often only being able to produce the supraordinate category for an item (e.g., "animal" instead of "giraffe").

6) A right temporal variant of PPA-semantic, often associated with co-dominant behavioral changes, has also been described.

c. Corticobasal syndrome (CBS)

CBS is a progressive, asymmetric extrapyramidal motor disorder, with parietal lobe symptoms and cognitive decline.

1) An asymmetric, rigid–akinetic parkinsonism or dystonia (usually of the upper limbs) is prominent.

2) Severe apraxia (ideomotor, limb kinetic, and eye-opening), cortical sensory loss, and the "alien limb" phenomenon (the limb "has a mind

of its own"; in 30% of patients over disease course) are other common features.

3) Orofacial apraxia, dysarthria, reflex myoclonus, horizontal supranuclear gaze palsy, and postural instability may also be seen.
4) Cognitive impairment (predominantly executive dysfunction) is present in up to half of patients at onset, close to 70% through disease course.
5) Slow speech production, nonfluent aphasia, and anarthria can all occur, sharing overlap with the PPA syndromes (earlier).
6) A "frontal behavioral-spatial syndrome" variant (executive dysfunction, personality/behavior changes, visuospatial deficits), without extrapyramidal features, is less common.
7) CBS is a syndrome, defined by a cluster of signs/symptoms, and it can have different underlying pathologic subtypes (see "Pathophysiology" section below). The most common is termed "corticobasal ganglionic degeneration" (CBD), an FTLD pathologic subtype, but CBS can also be caused by the AD pathologic type as well. Prominent memory impairment and left posterior superior temporal cortex atrophy increase the likelihood that CBS is due to AD.
8) SPECT/FDG-PET demonstrates decreased cerebral blood flow/glucose metabolism in left frontal and parietal lobes, perirolandic region, and sometimes thalamus and caudate head.

d. With disease progression, it is common for patients to exhibit features of both bvFTD and PPA as well as parkinsonism that are seen in CBS and progressive supranuclear palsy syndrome (PSPS); this progression reflects multifocal cortical spread.

e. FTLD often presents in the fifth and sixth decades. Some cases are associated with MND, referred to as FTD-MND. These cases are more likely to be hereditary, as in they are driven by an identifiable genetic mutation.

Pathophysiology

l. The events inciting the FTLD pathophysiologic cascade remain unknown. Preferential atrophy of the frontal and (often anterior) temporal lobes, with relative sparing of occipital and posterior parietal cortices, is a gross biomarker on CT/MRI. Like in AD, cerebral volume loss often occurs years

after the onset of pathophysiologic change at the cellular level.

2. The basal ganglia and substantia nigra also may be involved. The hippocampus is often less involved than more anterior limbic structures (i.e., amygdala).
3. FTLD has over 15 different pathologic subtypes. Close to 90% of all cases, though, have one of two subtypes: FTLD-tau and FTLD-TDP. Some clinicopathologic correlation is possible during life, but precision is difficult. Many subtypes give rise to different clinical syndromes. Patterns do emerge. For example, the majority of PPA-agrammatic cases have an FTLD-tau subtype.
4. Clinicopathologic correlation may become increasingly important in the upcoming era of pathology-targeted drug therapy.
5. FTLD-tau cases are characterized by accumulations of the microtubule-associated protein tau. These cases include the corticobasal degeneration (CBD) and PSP subtypes. As earlier (section on Background), CBS, the clinical syndrome itself, usually has either a CBD or AD pathologic subtype.
6. FTLD is frequently sporadic, although a significant minority (up to one-third) may have some family history. This history may include other members with recognized FTLD or, commonly, others who had some neuropsychiatric disorder which was never diagnosed as FTLD.
7. Seven gene mutations have been identified to have a monogenic causality for the development of FTLD.
   a. A repeat expansion mutation on an open-reading frame of chromosome 9 (called C9orf72) is the most common cause of hereditary FTLD, responsible for up to 30% of cases. This mutation can also cause FTD/MND and MND (amyotrophic lateral sclerosis [ALS]) alone. Patients with C9orf72 mutations have a higher rate of prodromal and disease-stage psychosis (delusions, hallucinations) than FTLD noncarriers.
   b. Two genes on chromosome 17, GRN (progranulin) and microtubule-associated protein tau (MAPT), can give rise to bvFTD or PPA. When these mutations are associated with parkinsonism, the syndrome has been called frontotemporal dementia with parkinsonism (FTDP-17).

Prognosis

1. The estimated life span following diagnosis ranges widely from 5 to 12 years.
2. Concomitant motor neuron (MND) or extrapyramidal symptoms may be factor that indicates more rapid decline.
3. There are rare cases where patients fulfill clinical criteria for bvFTD, with either minimal or no executive dysfunction, and then either show no decline or have a slow, minimally progressive decline over years. This has been called the bvFTD "phenocopy" syndrome, and underlying neurodegeneration is questionable.

Diagnosis

1. The diagnosis is primarily clinical, with characteristic focal/segmental volume loss on imaging sometimes helpful.
2. The mean age of symptom onset ranges from late 50s/early 60s (typical for bvFTD, PPA) to slightly older (mid-60s/early 70s) for CBS and other FTLD-parkinsonian syndromes.
3. Relatively spared memory storage and hippocampal volume may help differentiate FTLD from AD.
4. Amyloid PET is very useful in distinguishing FTLD (negative) from AD (positive).
5. FDG-PET/SPECT can also be useful. bvFTD and PPA patterns typically show frontal and temporal hypoperfusion/hypometabolism (may be asymmetric), and CBS can show lateralized perirolandic, thalamic/midbrain, or bilateral caudate hypoperfusion/hypometabolism.

Treatment

1. There is some evidence that serotonin levels may be low in FTLD and that treatment with SSRIs may improve behavioral symptoms (see Table 15-2).
2. Atypical neuroleptic agents may also be necessary for more severe behavioral problems (see Table 15-6).
3. Sparing of the cholinergic system in FTLD may be the reason for the lack of clear utility of AChEIs. In some studies, these medications lead to worse symptoms.
4. As with other dementias, cognitive symptoms should be targeted and trials with various agents may be pursued. Despite the common use of memantine,

recent studies have shown no benefit for neuropsychiatric symptoms or daily functioning.

5. Treatment of motor dysfunction (CBS, PSPS) is difficult. Few patients show improvement with carbidopa/levodopa. Myoclonus may respond to clonazepam. Botulinum toxin for painful dystonia (CBS, others).
6. Nonpharmacologic interventions, like regular sleep schedules, speech and occupational therapy, and caregiver education can be beneficial.

Dementia with Lewy Bodies (see also Chapter 14)

Background

1. DLB may be the second most common form of neurodegenerative dementia after AD. Lewy body pathology is found in up to 35% of all dementia cases. Median age of onset may be between 75 and 78 years.
2. It is characterized by fluctuations in cognition, visual hallucinations, and mild extrapyramidal features. The hallucinations tend to be well-formed and are often of people or animals. They are usually nonthreatening or disturbing to patients.
3. Cognition tends to be mostly impaired in the realms of executive function, attention, speed of processing, and visuospatial abilities.
4. Memory is impaired at the levels of encoding and retrieval, but dysfunction of memory tends to be less severe than in AD.
5. Depression and rapid eye movement (REM) sleep behavior disorder (RBD) are relatively common, sometimes occurring decades prior to cognitive or extrapyramidal symptoms.
6. The clinical overlap with PD-associated dementia (PDD) is substantial, and distinguishing one from the other can be difficult (see section on Diagnosis below).

Pathophysiology

1. Cortical Lewy bodies (spheric, intracytoplasmic, eosinophilic, neuronal inclusions containing α-synuclein, and ubiquitin proteins) and Lewy neurites (α-synuclein inclusions in neural processes) are found on autopsy and likely contribute to the dementia. Involvement outside of the brainstem is particularly prominent in the temporal cortex and limbic structures.
2. Lewy body pathology in the substantia nigra, locus ceruleus, and nucleus basalis also may contribute to the subcortical, cognitive symptoms (apathy, slowed processing) in DLB.
3. AD pathology is common in these patients (diffuse Aβ-42 staining), with 60% or more meeting pathologic criteria for AD as well as DLB. The

proportion of neuritic plaques and neurofibrillary tangles appears to be lower in these patients.

4. The presence of an APOE ε4 allele is a risk factor for DLB. It is also increased in prevalence in patients with PD and dementia, as opposed to PD patients without dementia.

Prognosis

The course is similar, if not more rapid, than in AD, with survival from 3 to 12 years.

Diagnosis

1. A "prodromal" stage likely exists, up to 20 years prior to overt cognitive, visual, or parkinsonian symptoms. This stage can include RBD, hyposmia, constipation, and depression or anxiety. A diagnosis is not made until the core clinical symptoms emerge.
2. A diagnosis of "probable" DLB requires (a) cognitive impairment enough to cause loss of ADLs, combined with two of the three "core" features (fluctuations of attention/alertness, parkinsonism, or visual hallucinations) or (b) dementia, associated with one "core" feature and one or more supportive features, which include RBD, severe sensitivity to neuroleptics, or low-DA transporter uptake in the basal ganglia by SPECT or PET.
3. The parkinsonism is often mild, bilateral, and symmetric, with characteristics of bradykinesia, mild gait changes, and truncal/limb stiffness.
4. By definition, parkinsonian features should *not* precede the onset of the dementia by more than 12 months. If this occurs, it is important to consider that the condition might be PD, with its associated dementia (PDD).
5. Fluctuations are notoriously difficult to quantify, and inter-rater reliability is generally poor. Having three or more of the following has reasonable supportive sensitivity and specificity for a DLB diagnosis: (a) excessive daytime sleepiness; (b) daytime sleep of 2 or more hours; (c) staring into space for prolonged periods; and (d) periods of disorganized, illogical, or incoherent speech.
6. A cognitive profile of impaired visuospatial abilities, executive function, and attention, in the setting of relatively preserved memory and naming, distinguishes patients with DLB from AD with reasonable accuracy.

7. A structural imaging study should be performed to rule out other potential contributing processes, such as strokes.
8. SPECT and FDG-PET imaging may reveal occipital hypoperfusion/hypometabolism. 123-I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy demonstrates low uptake in DLB, representing reduced postganglionic sympathetic cardiac innervation.

Treatment

DLB is difficult to treat, requiring a delicate balance of trying to improve motor symptoms without exacerbating confusion and hallucinations.

1. Cognition: AChEIs often improve attention and processing speed and can also decrease hallucinations and behavioral symptoms (see Table 15-4). Rivastigmine and donepezil have been studied the most rigorously. Consistent with the greater cholinergic deficit in DLB than AD, AChEI often have a greater therapeutic benefit in the former.
2. Motor symptoms: A trial with L-dopa or dopaminergic agonists (see Table 15-3) is reasonable, although it may result in increased hallucinations and confusion. Anticholinergics (benztropine, trihexyphenidyl) and antiemetics (metoclopramide, others) can worsen motor symptoms.
3. Depression/anxiety: Treatment with SSRIs/SNRIs or bupropion (see Table 15-2) may be effective. TCAs may also be tried and often have good benefit, but optimization is usually limited by anticholinergic side effects (often cognitive).
4. Psychosis/behavioral symptoms: The hallucinations are usually nonthreatening or disturbing and thus do not have to be specific treatment targets. Atypical neuroleptics, such as quetiapine, olanzapine, or clozapine (see Table 15-6), should be used cautiously. Neuroleptic hypersensitivity reactions in DLB (incidence up to 50%) can manifest as severe rigidity, dysautonomia, confusion, increased parkinsonism, or even prolonged periods of decreased responsiveness. Atypical neuroleptics are less likely than typical neuroleptics to exacerbate. Clozapine or pimavanserin usually do not exacerbate extrapyramidal symptoms. All antipsychotic medications may worsen fatigue and confusion.
5. Sleep disorders: Stimulants may be beneficial for excessive daytime sleepiness. Melatonin, up to 12 to 15 mg, is often effective in improving symptoms of RBD. Clonazepam may also treat RBD.

5. Autonomic dysfunction: Postural hypotension, which can manifest as presyncope episodes, general weakness, and fatigue, may be treated with increased salt and water intake, thigh-high compression stockings, and fludrocortisone and midodrine (in some patients). Oral trospium may be effective for urinary frequency, which may arise from autonomic detrusor instability.

Huntington Disease

Background

1. Huntington disease (HD) is an autosomal dominantly inherited, neurodegenerative disorder that causes progressive cognitive decline, marked extrapyramidal motor abnormalities, and neuropsychiatric symptoms.
2. HD is rare, occurring in 5 to 10/100,000. Cognitive symptoms may precede the motor symptoms. Impairment of executive functioning and attention is common. Visuospatial deficits are also frequently seen.
3. Loss of voluntary motor control and the development of chorea (rapid involuntary movements around multiple joints), arrhythmic fine motor movements, and other extrapyramidal symptoms are the hallmarks of the disease.
4. Depression is the most common psychiatric manifestation, but apathy, mania, psychosis, anxiety, and delusional thinking can occur.
5. Patients tend to become symptomatic by midlife, but onset has been reported from early childhood to late life.

Pathophysiology

1. HD arises from a mutation in a gene (HTT) on chromosome 4, which codes for the huntingtin protein.
2. The mutation manifests as a CAG trinucleotide repeat expansion with a variable number of repeats. Less than 40 repeats yields variable penetrance, whereas 40 or more usually amounts to full disease penetrance.
3. Larger numbers of repeats are associated with an earlier age of onset.
4. Proteolytic products of the huntingtin protein, containing polyglutamine repeats, are sequestered in cell nuclei and interfere with cell regulation.

5. Degeneration occurs most prominently in the striatum, but there is also neuronal loss in the cortex and other deep gray nuclei.

Prognosis

1. HD inevitably leads to death, usually 15 to 25 years after initial presentation.
2. Death is usually caused by medical complications.
3. The suicide rate has been as high as 5% in some larger cohort studies.

Diagnosis

1. The diagnosis should be considered in any patient presenting with chorea, particularly with any concomitant cognitive or psychiatric symptoms.
2. A family history is clearly helpful, and genetic testing is confirmatory. The differential diagnosis includes dentatorubral–pallidoluysian atrophy (DRPLA) and hereditary neuroferritinopathy, among others; these are also autosomal dominant disorders with chorea.
3. If the HTT gene is negative, C9orf72 mutations can be looked for because these seem to be the most frequent cause of HD-like syndromes. Presymptomatic genetic testing is controversial and should involve genetic counseling.
4. MRI often reveals significant caudate atrophy later in the course of disease.

Treatment

1. There is currently no treatment to slow the course of the illness.
2. Psychiatric and cognitive complaints should be treated symptomatically.
3. Chorea may respond to tetrabenazine (FDA-approved) or neuroleptic agents.

NONNEURODEGENERATIVE DEMENTIA

Vascular Cognitive Impairment

Background

1. Vascular cognitive impairment (VCI) encompasses the range of mild to

severe cognitive impairment (including vascular dementia; VaD) that is associated with CVD.

2. Etiologies of CVD include accumulated, subcortical ischemic vascular disease (SIVD, previously "Binswanger disease"); strategically located large-vessel strokes ("multi-infarct dementia" [MID]); multiple, often distributed, small-vessel and/or "lacunar" infarcts; and the vasculitides (e.g., primary CNS angiitis) and arteriopathies (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]).
3. VaD is probably the second most common form of dementia after AD. Prevalence studies are difficult because of the high coincidence of AD and vascular pathology in autopsy studies.
4. Given the varying vascular etiologies, VCI has broad heterogeneity in signs and symptoms. SIVD and multiple small-vessel/lacunar strokes often present, slowly over time, with apathy, frontal-attention based cognitive impairment, and psychomotor slowing. Patients may have corticospinal signs (extensor plantar responses, mild limb spasticity) and subtle speech difficulties. MID from large-vessel strokes often cause symptoms referable to the site of the lesion(s), such as aphasia, alexia, or agnosia.

Pathophysiology

1. Risk factors for VCI include poorly controlled hypertension, diabetes, hypercholesterolemia, cardiac arrhythmias, and smoking.
2. Coronary and carotid arteriosclerosis, and a history of TIA, are also independent risk factors in the development of VCI.
3. Aging, hypertension, diabetes, and arteriosclerosis produce narrowing and tortuosity of deep white matter vessels (most notable in SIVD). This narrowing likely results in arteriole lipohyalinosis, poor vascular reserve, and chronic inflammation, leading to hypoperfusion of tissue. The end result is a functional disconnection between white and gray matter nuclei, causing the cognitive impairment.
4. SIVD is marked by white matter signal changes on MRI or CT and is associated pathologically with axon loss and demyelination. Ischemia of deep gray structures also can contribute to cognitive dysfunction.
5. Cortical infarcts cause direct impairment of the cognitive function(s)

subserved by those areas of cortex.

Prognosis

1. The course is variable. The average time to death after diagnosis ranges from 4 to 20 years.
2. The causes of death include complications of dementia, stroke, and myocardial infarctions.

Diagnosis

1. Consensus by the American Heart Association and American Stroke Association suggests a diagnosis of VCI based on two factors: (a) demonstration of the presence of a cognitive disorder and (b) a history of clinical stroke or CVD on neuroimaging that suggests a link between the cognitive disorder and the CVD.
2. As a guideline, cognitive symptoms that occur either abruptly or within 3 months after a clinically evident stroke are suggestive. Otherwise, either a "stepwise" or slowly progressive decline, with characteristic clinical symptoms (see section on Background earlier), *along with* MRI/CT evidence, is also suggestive.
3. Neuroimaging often will support the clinical/cognitive syndrome or neurologic exam, with evidence of cortical strokes, subcortical strokes, or extensive SIVD ("white matter disease").
4. Use of the Hachinski Ischemic Score (HIS) can increase sensitivity, but it is less helpful in differentiating VaD from "mixed-type" (neurodegenerative/vascular) dementias.

Treatment

1. Aerobic exercise from one's early 60s (and probably throughout early/middle adulthood) reduces the incident rates of VCI and all-cause dementia in observational studies. Lowering blood pressure from age 55 years and older, and likely from an earlier age, probably decreases the risk of VCI and all-cause dementia.
2. Lifestyle interventions (healthy eating, aerobic exercise) may play an important role in reducing further declines in VCI. However, no studies, to date, have shown intervention with specific, disease-ameliorating benefit in

VaD.

3. Other stroke risk factors, including smoking, hyperlipidemia, and diabetes, should be aggressively addressed and managed because they are modifiable risks for VCI.
4. The importance of stroke risk reduction is made even more salient by the finding that stroke may hasten the onset of clinical AD.
5. Cholinesterase inhibitors (see Table 15-4) in patients with VCI and those with "mixed-type" (neurodegenerative/VCI) have been demonstrated to have a mild cognitive benefit in many studies.
6. A similar benefit has been seen with memantine (see section on Treatment of Disorders of Memory).
7. Given the high association of depression after stroke, a trial with an antidepressant (see Table 15-2) is reasonable if there is any suspicion of a mood component.

Normal Pressure Hydrocephalus

Background

1. Normal pressure hydrocephalus (NPH) is characterized by the clinical triad of dementia, impairment of gait, and urinary incontinence.
2. Gait and cognitive findings generally occur early in the course, whereas incontinence tends to occur later.
3. The dementia is characterized by impaired attention, concentration, executive functioning, and sometimes psychomotor slowing.
4. Apathy can be a major feature.
5. NPH is most prevalent in the sixth and seventh decades but can be seen at any age.
6. Overall prevalence is not well established but may represent 1% of all dementia patients.

Pathophysiology

1. NPH results from greater production than absorption of CSF. This is most commonly thought to be caused by insufficient absorption through the arachnoid granulations and villi.
2. Most cases are idiopathic, but some are secondary to such disorders as a

prior subarachnoid hemorrhage, meningitis, trauma, or very elevated CSF protein.

3. The pathology in these secondary cases likely leads to inflammation and subsequent fibrosis of the arachnoid granulations, leading to impaired CSF resorption.
4. Although intracranial pressure is "normal" by definition, transient elevations in pressure are thought to occur that result in ventricular enlargement. The frontal horns are often disproportionately enlarged, resulting in stretching of motor fibers to the legs and sphincters. Compression of the frontal cortex, originating from periventricular white matter tracts, likely accounts for the cognitive impairment.

Prognosis

1. If untreated, there is a risk of progression to an abulic/akinetic state.
2. Response to ventricular shunting (VS) is variable, but those with isolated gait difficulty, a shorter duration of dementia, and elevated CSF R_0 (or conductance; not commonly measured) have a higher likelihood of a good outcome in idiopathic NPH. Also, demonstrated symptom relief with external lumbar drainage (ELD) or with repeated, high-volume LPs ("tap test" [TT]; 30 to 50 mL) increases the likelihood of success with VS, regardless of a patient's age.
3. More than 2 years of dementia, the presence of significant CVD and cortically based cognitive impairment (apraxia, aphasia) predict poorer outcome with VS for idiopathic NPH.

Diagnosis

1. Diagnosis can be difficult. Establishment of the appropriate clinical setting and evidence of hydrocephalus on CT or MRI are necessary.
2. The gait disorder is often early, associated with imbalance, and appears as "magnetic" (patient's feet seem to be glued to the ground). The urinary symptoms may start as urgency and progress to frank incontinence.
3. Differentiation of NPH from hydrocephalus ex vacuo (i.e., ventriculomegaly from adjacent, parenchymal volume loss; common in AD, for example) is not easy. Certain radiographic clues are helpful: less prominent cortical atrophy with NPH, disproportionate enlargement of the frontal and inferior

horns compared to sulci, and prominent aqueductal flow or transependymal edema on MRI/magnetic resonance angiogram (MRA).

4. Removal of CSF through TT or ELD, with symptom relief, and possibly measurement of CSF pulsatility in response to arterial pressure, all seem to have high sensitivity, but variable and incomplete specificity. Patients may show transient improvement in gait and cognition.
5. Measurement of CSF compliance (R_0) by repeated lumbar injections (e.g., normal saline, lactated ringers) in patients selected on the basis of only clinical history and neuroimaging can add sensitivity and specificity but still produces many false negative results.
6. Radioisotope cisternography has also been used but is relatively insensitive and nonspecific.

Treatment

1. Surgical placement of a ventricular shunt (usually ventriculoperitoneal) is a treatment for patients with idiopathic NPH with most benefit often in gait and subjective cognitive symptoms. Because of significant AE risk, risks and benefits should be carefully weighed.
2. Difficulties with attention, apathy, and executive functioning can be treated symptomatically, as outlined earlier.

DEMENTIA CAUSED BY INFECTIOUS PROCESSES
(SEE ALSO CHAPTER 19)

HIV-Associated Neurocognitive Disorder

Background

1. HIV-associated neurocognitive disorder (HAND) includes a spectrum of disorders associated with HIV infection, ranging from asymptomatic neurocognitive impairment (ANI), to mild neurocognitive disorder (MND), to HIV-associated dementia (HAD), when there is clear loss of autonomy in IADLs/ADLs. Neuropsychological testing is necessary if one uses these classifications clinically.
2. HAND is caused by the primary HIV infection and the brain's response and should be distinguished from cognitive impairment that results from opportunistic infections.
3. The cognitive decline is noted to occur over 6 months or longer.
4. The cognitive impairment is of the "subcortical type," which typically involves impaired attention/concentration, executive function, psychomotor slowing, and memory problems at the level of encoding and retrieval.
5. Depression and/or apathy may be prominent.
6. Since the introduction of combination antiretroviral therapy (ART), the percentage of HIV-positive patients with HAD has dramatically declined to about 1%. HAD now occurs almost exclusively in untreated HIV-positive patients, particularly when the CD4 cell count is <200 cells/μL.
7. About 30% of ART-adherent patients have ANI, and about 10% to 12% have MND.

Pathophysiology

1. HIV passes in to the CNS during the initial days of systemic infection and can be detected early on in the CSF.
2. Multinucleated macrophages and leukoencephalopathy (more advanced

stages) are pathologic findings.

3. Macrophages that sustain compartmentalized brain infection may be the primary source of the toxic signaling pathway that underlies neuronal dysfunction.
4. Subcortical gray structures are also prominently involved.
5. Cortical atrophy in the frontal and temporal lobes can occur with progression.
6. A major source of neuronal dysfunction or death may be caused by local, cerebral inflammatory effects rather than direct infection of neurons.
7. Many patients continue to show biomarker evidence of mild immune activation in the CNS even after years of viral suppression; this may be driven by low levels of persistent brain infection (even with ART).
8. Neuronal apoptosis may be accelerated in HAD.

Prognosis

1. ART status impacts the presentation of HAND. If they are on ART, many patients live with chronic HIV infection and have minimal or no neurocognitive deficits. Without ART, patient have a high risk of either MND or HAD.
2. Cognitive deficits from HAND are worsened with comorbidities, such as major depression, other infections, or even early neurodegenerative disease.

Diagnosis

1. The diagnosis is made on the basis of clinical findings and neurocognitive/neuropsychological evaluation in patients with HIV infection.
2. Testing for HIV should be pursued in patients with the appropriate cognitive profile, particularly young patients or those with risk factors for HIV infection.
3. Differential diagnoses include opportunistic CNS infections, CNS malignancies, nutritional deficiencies, and other dementias. Focal neurologic findings suggest an opportunistic CNS infection.
4. MRI is important to help rule out opportunistic infections, such as toxoplasmosis and progressive multifocal leukoencephalopathy (PML), as well as primary CNS lymphoma.

5. In patients with advanced HIV infection and HAD, MRI may show ill-defined, increased white matter hyperintensities on T2-weighted images and/or diffuse cerebral atrophy.
6. In the rare "CNS viral escape syndrome," patients on ART have clear, serologic viral suppression yet develop subacute, progressive cognitive deficits. These patients often have detectable CSF HIV RNA levels, which could be obtained in appropriate cases.
7. CSF biomarkers, including viral load, can generally be useful, even if there seems to be a poor association between neurocognitive/neurologic deficits and CSF HIV levels.
8. CSF can also be helpful to rule out cryptococcal meningitis, cytomegalovirus (CMV), and neurosyphilis.

Treatment

1. Symptomatic treatment of cognitive dysfunction (stimulants, cholinesterase inhibitors) should be pursued, despite lack of evidence from RCTs.
2. Treatment using combination ART is aimed at reducing the plasma viral load. The use of ART in the treatment of the milder forms of HAND has less clear benefit than it has for the prevention/treatment of HAD.
3. CSF HIV RNA detection can help to establish that there is a CNS target for some specific ART agents.
4. The specific resistance profile of the plasma virus to certain ART agents is now a regular consideration in treatment. It is unclear which particular combinations of ART are most effective in the treatment of HAND. Some protease inhibitors (darunavir) and integrase inhibitors (dolutegravir) seem to have excellent blood–brain barrier penetration, a more important consideration with HAD than with milder forms of HAND. Efavirenz seems to have the most risk of neuropsychiatric side effects and thus might be avoided or discontinued in vulnerable or symptomatic patients.

Neurosyphilis

Background

1. Syphilis is a sexually transmitted disease caused by *Treponema pallidum*.
2. Tertiary syphilis, which occurs in 30% of untreated patients, may produce

dementia.

3. In the common era of widespread antibiotic use, neurosyphilis is most frequently seen in HIV-positive patients.
4. General paresis, the term used to describe the chronic, low-grade encephalitis thought to cause the dementia of tertiary syphilis, often occurs 15 to 30 years after initial infection.
5. Meningovascular syphilis (usually occurring 2 to 10 years after infection) can produce both dementia and strokes by causing arteritic occlusion of blood vessels.
6. Almost any neuropsychiatric symptom may be present, including psychosis, grandiosity, mania, and depression.
7. A significant minority (20% to 40%) have only dementia. Poor attention and memory (on the basis of encoding and retrieval difficulty) are common features.
8. Reduced speech output and anomia may be present.
9. PBA and intention tremors of the face, tongue, and hands may be other prominent features.
10. Signs and symptoms of other manifestations of tertiary syphilis are often present, including tabes dorsalis, Argyll–Robertson pupils, and optic atrophy.

Pathophysiology

1. General paresis is thought to be caused by direct parenchymal infection, arising years after presumed, asymptomatic meningitis.
2. The majority of patients with antibodies to *T. pallidum* in the CSF do *not* develop clinical signs of neurosyphilis for unknown reasons.
3. Atrophy is most pronounced in the frontal and temporal cortices.
4. Cortical organization is disturbed with neuronal loss and astrocytic and microglial proliferation.
5. The disease tends to be more aggressive in patients with HIV presumably because of their impaired immune system.

Prognosis

1. About half of all patients will demonstrate improvement with treatment.
2. Arrest of further progression in those who do not improve is another

potential outcome.

Diagnosis

1. Any patient with signs or symptoms suspicious for the diagnosis should have serologic testing.
2. The rapid plasma reagin (RPR) serology provides an initial screen but is associated with false-positive results (false negatives are less common).
3. A positive test should be followed by a treponemal serologic test, such as the fluorescent treponemal antibody (FTA), to confirm the diagnosis. If tertiary syphilis is suspected, CSF should be obtained. An elevated protein level, pleocytosis, and a positive venereal disease research laboratory (VDRL) test are expected.
4. If CSF VDRL is nonreactive, and neurosyphilis is still suspected, then CSF FTA-antibody absorption (ABS) can be ordered (highly sensitive).
5. If at least one CSF abnormality is present in suspected cases, treatment should be pursued.

Treatment

1. The treatment of choice is penicillin G at 4 million units IV every 4 hours for 10 days.
2. For patients who have a penicillin allergy, amoxicillin, doxycycline, and ceftriaxone are alternatives but of less-known efficacy.
3. CSF should be examined every 3 to 6 months for gradual return to normal protein and cell count as well as disappearance of or stable reduction in titer of the VDRL.
4. Because of an increased treatment failure rate in patients with HIV, some have recommended additional treatment with weekly IM benzathine penicillin for 3 weeks or doxycycline 200 mg b.i.d. for 30 days after initial treatment.
5. Prophylactic measures in HIV-positive patients need further study. These patients should be carefully monitored for relapse for up to 2 years after treatment.

Prion Diseases

Background

1. These are a collection of rare, neurodegenerative diseases caused by abnormal accumulation of prion proteins.
2. They can occur sporadically, as in Creutzfeldt–Jakob disease (sporadic CJD; 85% of CJD), or in families, as in fatal familial insomnia (FFI), Gerstmann–Straüssler–Scheinker syndrome (GSSS), and familial CJD (15% of CJD).
3. A small percentage of CJD cases (called variant Creutzfeldt–Jakob disease [vCJD]; section below) have been acquired iatrogenically from pooled human growth hormone, corneal and dural transplants, and incompletely sterilized surgical equipment.

Sporadic Creutzfeldt–Jakob Disease

1. This disease usually presents in the fifth through seventh decades, with an annual incidence of less than 1 per million.
2. The classic clinical triad is rapidly progressive dementia, myoclonus, and ataxia.
3. Often, the dementia precedes the onset of progressive pyramidal, extrapyramidal, and cerebellar abnormalities.
4. Variants with more focal brain region involvement can present with more dominant visuospatial abnormalities (Heidenhain variant) or ataxia (Brownell–Oppenheimer variant).

Variant Creutzfeldt–Jakob Disease

1. Evidence suggests it may represent the bovine-to-human transmitted form of bovine spongiform encephalopathy (“mad cow” disease). It has been seen primarily in the United Kingdom, with scattered other cases globally.
2. It has an average age of onset in the second decade, with the youngest reported case in an 11-year-old.
3. The course is more indolent than sporadic CJD and marked by more prominent, early neuropsychiatric and sensory symptoms; upgaze paresis occurs in up to 50% of cases.

Gerstmann–Straüssler–Scheinker Syndrome

1. GSSS is a familial disease with an autosomal dominant pattern, characterized by prominent spinocerebellar ataxia and progressive

hyporeflexia.
2. Dementia of variable severity, MND signs, and extrapyramidal signs are variably present.
3. Patients usually present in their 30s or later.

Fatal Familial Insomnia

1. FFI is marked by progressively severe dyssomnia, with hypersomnolence, dreamlike intrusion in wakefulness and hallucinations most common.
2. Dysautonomia and ataxia are also well-described.
3. Extrapyramidal and pyramidal signs may occur, with dementia being less prominent.

Pathophysiology

1. Disease-causing prions are abnormal isoforms of the normally present, human prion protein which cause the normal form to fold into abnormal isoforms. The process leads to aggregation of the isoforms into pathologic deposits which cause brain injury. In the case of vCJD, the prion protein is likely introduced exogenously, either by ingestion (e.g., consumption of contaminated beef) or through transfusion.
2. Prion proteins are transcribed from the *PRNP* gene (chromosome 20), which is also the locus of various mutations that cause familial CJD, GSSS, and FFI.
3. These different clinical syndromes are a reflection of differences in the brain region and structure of the histopathology.
4. Sporadic CJD demonstrates spongiform changes, gliosis, and neuronal loss in the gray matter. GSSS is unique in its histopathology of diffuse amyloid plaques (kuru plaques).
5. Dense prion protein plaques surrounded by a halo of spongiform changes (florid plaques) are unique to vCJD. FFI has few spongiform changes but is marked by gliosis of the thalamus, inferior olives, and cerebellum.

Prognosis

1. The median and mean survival for CJD is 4 and 7 months, respectively, with up to 90% mortality within the first year.
2. vCJD has a somewhat longer course, with a median survival of 14.5 months.
3. The course for GSSS can be up to 10 years.

Diagnosis

1. Sporadic CJD
   - **a.** Diagnosis is made on the basis of clinical findings but often supported by MRI and sometimes EEG. Criteria are progressive dementia plus two of these four: myoclonus, visual or cerebellar signs, pyramidal/extrapyramidal signs, and akinetic mutism.
   - **b.** EEG finding of 1- to 2-Hz generalized, triphasic periodic sharp waves are present in about two-thirds or more, at some point throughout the disease (EEG ≤ clinical criteria have specificity >95%).
   - **c.** MRI has also proven useful, with fluid-attenuated inversion recovery (FLAIR) and, especially, diffusion-weighted imaging (DWI) (sensitivity/specificity from 85% to 95%) lesions in caudate, putamen, and cortical ribbon.
   - **d.** Hyperintensities in the cortex, basal ganglia, thalamus, and cerebellum have been described.
   - **e.** In some contexts, the 14-3-3 protein detected in the CSF has a high sensitivity/specificity for CJD but is often considered adjunctive in diagnosis.
   - **f.** Brain biopsy or autopsy is definitive.

2. vCJD
   - **a.** Clinical features may be the most helpful: At least 6 months of a progressive, psychiatric disorder, closely followed by ataxia, dementia, extrapyramidal movement disorder, persistent dysesthesias, and dysarthria.
   - **b.** MRI (FLAIR and DWI sequences) may have equal utility in suspected cases, with increased signal in the pulvinar and/or dorsomedial thalamic nuclei (sensitivity around 80%, specificity close to 100%).
   - **c.** EEGs are abnormal, with a slow-wave pattern, and do not have the classic, periodic sharp waves seen in sporadic CJD.
   - **d.** Tonsil biopsy holds promise for detecting abnormal prions of vCJD, in certain clinical contexts.

3. GSSS and FFI
   - **a.** GSSS and FFI may be diagnosed clinically with attention to family history.

b. MRI findings are often normal in FFI, but PET may show thalamic and cingulate hypometabolism.
c. Genotyping can also be pursued.

Treatment

1. There is currently no treatment available.
2. Symptomatic treatment for neuropsychiatric symptoms, seizures, and myoclonus are encouraged, especially if appropriate in palliative care. There is little data to support any particular regimen.

VITAMIN DEFICIENCY STATES/TOXINS

Vitamin B_{12} Deficiency

Background

1. Deficiency of vitamin B_{12} can result in cognitive and psychiatric disorders. These can range from mild memory impairment to severe dementia and neuropsychiatric symptoms.
2. When severe, it can also cause myelopathy (subacute combined degeneration of the spinal cord) and large-fiber peripheral neuropathy manifestations.
3. The hematologic manifestation of vitamin B_{12} deficiency, macrocytic anemia with hypersegmented neutrophil nuclei, is not always present in the setting of neurologic symptoms.
4. The epidemiology is not well established, but some studies have shown that as many as 10% to 20% of the elderly have some level of vitamin B_{12} deficiency, usually mild and subclinical.
5. Patients with HIV and AIDS, as well as malnourished populations, alcoholics, and vegans, have a higher prevalence.

Pathophysiology

1. The most common cause of vitamin B_{12} deficiency is pernicious anemia.
2. Other potential etiologies include dietary deficiency, gastric resection or severe gastritis (loss of intrinsic factor), *Helicobacter pylori* infection, or

diseases of the ileum (portion of the bowel in which absorption takes place).

3. Vitamin B_{12} is a cofactor in two essential enzymatic reactions: The conversion of homocysteine to methionine and the conversion of methyl malonyl-coenzyme A (CoA) to succinyl-CoA.
4. The cause of CNS dysfunction in vitamin B_{12} deficiency is unclear, but it is thought to be caused by impaired myelin synthesis.
5. However, in the spinal cord, there is evidence of the degeneration of both myelin and axons.
6. Demyelination is seen in the cerebral white matter.

Prognosis

1. If untreated, low vitamin B_{12} levels can produce progressive myelopathy, encephalopathy, anemia, and osteoporosis.
2. At least partial resolution of cognitive deficits and perhaps white matter changes are possible.

Diagnosis

1. Diagnosis is based on detection of a low-serum vitamin B_{12} level.
2. However, low-normal values do not preclude a de facto deficiency state, with attendant symptoms. Vitamin B_{12} metabolic intermediates, homocysteine and methylmalonic acid, may be obtained in these cases because they are elevated throughout the whole vitamin B_{12} deficiency spectrum.
3. MRI of the spine may reveal posterior column T2-weighted signal hyperintensities.
4. Cerebral white matter may also show T2-weighted hyperintensities.
5. Although rare, folate deficiency can co-occur with, or mimic, vitamin B_{12} deficiency, causing megaloblastic anemia; folate is easily tested for and deficiency is treatable.

Treatment

1. Treatment is usually IM (or parenteral) at 1,000 μg for 5 to 7 days, until serum levels normalize.
2. If the cause of deficiency cannot be corrected (e.g., status-post ileal

resection), monthly injections or high oral doses (1 mg/d) are necessary.
3. Various associated cognitive deficits can be treated symptomatically.

Wernicke Encephalopathy/Korsakoff Syndrome

Background

1. Korsakoff syndrome most often arises as a late manifestation of Wernicke encephalopathy (WE) (see also Chapter 18 on Toxic and Metabolic Disorders), most commonly associated with chronic alcohol use. It can occur without a clear history of WE.
2. WE is marked by relatively acute onset of a confusional state, often with the presence of ataxia, ophthalmoplegia, and nystagmus.
3. The syndrome is most notable for anterograde and retrograde memory deficits out of proportion to impairment of other cognitive domains.
4. However, frontal executive impairment, apathy, and confabulation are often present.

Pathophysiology

1. Thiamine (vitamin B_1) deficiency is thought to underlie the disorder.
2. Thiamine is thought to be important in glucose metabolism and energy production.
3. Alcoholics are particularly predisposed to the syndrome because of poor dietary intake and impaired absorption of thiamine.
4. Other forms of malnutrition or malabsorption can also cause the disorder.
5. The memory deficits of the Korsakoff syndrome are thought to relate to damage to the anterior thalamic nucleus (ATN) and/or the mammillary bodies. Many WE patients, who have sparing of the ATN, do not develop Korsakoff syndrome.
6. Periventricular lesions with petechial hemorrhage are found in the regions of the third and fourth ventricles.
7. The higher energy demands of the lesioned periventricular structures may make them susceptible to thiamine deficiency.
8. Midbrain and cerebellar lesions explain some of the clinical manifestations

of WE. Dorsomedial thalamus injury may contribute to executive function impairment.

Prognosis

1. Most patients do not improve or recover over time.
2. They seem to have a normal life expectancy, assuming abstinence from alcohol.

Diagnosis

1. The diagnosis is largely clinical.
2. A history of alcohol abuse, malnutrition, and WE strongly suggest the diagnosis in a patient with predominant memory findings.
3. MRI may reveal periventricular lesions or mammillary body atrophy.

Treatment

1. Thiamine replacement with 100 mg/d IV or IM may reverse signs and symptoms of WE and prevent further deterioration.
2. Cholinesterase inhibitors have had mixed results but should probably be tried (see Table 15-4).

Exposure to Heavy Metals

Background

1. Exposure to several metallic agents can result in dementia, often with associated peripheral nervous system and systemic illness.
2. Lead, mercury, manganese, arsenic, thallium, aluminum, gold, tin, bismuth, nickel, and cadmium have been associated with impairment of intellectual function.
3. Chronic, lower level lead exposure in adults, resulting in elevated serum levels, can lead to both multi-domain cognitive deficits and endorsement of depression and anxiety.
4. These toxins also tend to produce extrapyramidal and cerebellar signs and symptoms.

Pathophysiology

These agents likely interfere with cellular metabolism and produce structural brain damage.

Prognosis

Once structural injury has occurred, recovery is unlikely, but progression can be halted.

Diagnosis

1. Diagnosis is based on the clinical features and potential for exposure.
2. Several of these exposures have specific findings that are highly suggestive of the diagnosis; for example, Mees lines in arsenic poisoning, basophilic stippling with lead exposure, and alopecia with thallium poisoning.
3. Serum or urine tests for heavy metals provide more definitive diagnosis.

Treatment

1. Removal of the exposure is crucial.
2. Treatment with chelation, usually with ethylenediaminetetraacetic acid (EDTA) or penicillamine, may also be helpful and result in some recovery.
3. Symptomatic treatment of cognitive deficits is warranted.

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16 Management of Neurologic Disorders in Resource-Limited Settings

Aaron L. Berkowitz

BACKGROUND

The Global Burden of Neurologic Disease

1. Neurologic diseases are estimated to account for approximately 15% of the global burden of mortality. Approximately 70% of this burden—11% of the total global burden of mortality—is because of stroke.
2. The global burden of neurologic disease disproportionately affects low- and middle-income countries (LMIC) as compared to high-income countries (HIC).

The Global Distribution of Neurologists and Neurodiagnostic Tests

1. There are on average 3 neurologists per 100,000 citizens of HIC, whereas there are on average only 0.03 neurologists per 100,000 citizens in low-income countries.
2. There are approximately 42 computed tomography (CT) scanners per 1 million population in HIC compared to approximately 0.32 per 1 million population in low-income countries. Even where neurodiagnostic tests are available in certain resource-limited settings, they are commonly inaccessible and/or unaffordable for many patients.

Where diagnostic resources are extremely limited, management of

neurologic disease requires judicious empiric treatment of potential etiologies of common presentations based on local epidemiology.

STROKE

Global Epidemiology

1. In 2010, there were an estimated approximately 17 million strokes, 6 million deaths caused by stroke, and 100 million disability-adjusted life years (DALYs) lost due to stroke, making stroke the second leading cause of death and third leading cause of disability worldwide.
2. Approximately 70% of strokes and stroke-related mortality and nearly 80% of stroke-related disability occur in LMIC. This is not simply because of a greater proportion of the world's population living in LMIC: Incidence rate, mortality rate, and mortality-to-incidence ratio for stroke are all higher in LMIC compared to HIC.
3. Approximately 70% of strokes worldwide are ischemic strokes, and 30% are because of intracerebral hemorrhage (ICH). However, this ratio differs depending on world region, ranging from 10% of strokes caused by ICH in HIC to 34% of strokes caused by ICH in parts of sub-Saharan Africa.
   a. Approximately 60% of ischemic stroke incidence, mortality, and DALYs lost occur in LMIC.
   b. Approximately 80% of ICH incidence, 84% of mortality, and 86% of DALYs lost occur in LMIC.
4. Higher incidence of stroke, mortality because of stroke, DALYs lost because of stroke, and proportion of ICH as a cause of stroke are correlated with lower per capita income even after adjustment for cardiovascular risk factors, suggesting that limitations in resources to screen for and modify stroke risk factors and treat stroke contribute to greater burden of stroke, stroke-related mortality, and stroke-related disability in LMIC.

Diagnosis in Resource-Limited Settings

1. A key branch point in the acute management of stroke is determining whether the stroke is caused by an ischemic infarct or an ICH. However, CT is

unavailable in many resource-limited regions.

2. Clinical signs at stroke onset such as coma, neck stiffness, seizures, diastolic pressure >110 mm Hg, vomiting, and headache suggest ICH as the underlying etiology of acute stroke. However, strategies for acute stroke management in resource-limited settings must account for the fact that it is often unknown whether a stroke is ischemic or hemorrhagic.

Acute Management of Stroke of Unknown Etiology

1. Many elements of acute supportive management of acute ischemic stroke and acute ICH are shared, including maintenance of euglycemia and euthermia, prevention of aspiration and deep venous thrombosis, and treatment of seizures if they occur (see Chapter 13). If CT is unavailable to distinguish ischemic stroke from ICH, prophylactic anticoagulation to prevent deep venous thrombosis should be deferred until 1 to 2 days following stroke.
2. Blood pressure is generally allowed to autoregulate in patients with acute ischemic stroke, whereas it should be reduced in ICH (see Chapter 13). Where CT is unavailable to distinguish between ischemic stroke and ICH, one can consider lowering systolic blood pressure to just below 180 mm Hg in the acute setting. This would provide benefit in ICH, and because blood pressure lowering to this degree is indicated when patients with ischemic stroke receive intravenous tissue plasminogen activator (IV-tPA), this is likely also safe if the stroke is ischemic. In rare cases in which patients clinically worsen when blood pressure is reduced, blood pressure could be raised with a bolus of IV normal saline and subsequently allowed to autoregulate.
3. Thrombolysis or aspirin is administered to a patient with acute ischemic stroke, whereas such therapies could worsen ICH. Thrombolysis is unavailable in most LMIC, so the question with respect to antithrombotic therapy in acute stroke in resource-limited settings is whether it is safe to administer aspirin when it is unknown whether stroke is because of ischemia or ICH. Aspirin is beneficial to patients with acute ischemic stroke when administered within 48 hours but could lead to hematoma expansion in patients with acute ICH. Because the period of highest risk of hematoma expansion is in the first 24 hours after ICH and because the International

Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) trials demonstrated that the benefit of aspirin for acute ischemic stroke requires it to be given in the first 48 hours, I recommend considering aspirin administration to patients with stroke of unknown etiology between 25 and 48 hours after stroke onset unless clinical signs point convincingly toward ICH. Decision analysis modeling suggests this strategy has less risk than is commonly perceived.

Determination of Etiology

In addition to screening for vascular risk factors, infectious causes of stroke must be considered in resource-limited settings including syphilis, tuberculosis meningitis, and cryptococcal meningitis.

Secondary Prevention

Risk factor modification for secondary prevention of ischemic stroke and ICH is similar (most importantly, control of hypertension), but whether or not to administer aspirin after stroke of unknown etiology is debated. Decision analysis suggests that the secondary prevention benefits of administering low-dose aspirin to all patients after stroke of unknown etiology likely outweigh the risks of recurrent hemorrhage in patients whose initial stroke was because of ICH.

EPILEPSY

Epidemiology

1. Approximately 90% of the world's patients with epilepsy live in LMIC, where yearly incidence rate of epilepsy is nearly twice as high as that of HIC.
2. Epilepsy rates are likely higher in LMIC because of three factors:
   a. Higher burden of head trauma because of poor road safety and limited use of motorcycle helmets
   b. Higher incidence of intracranial infections, especially neurocysticercosis, which is estimated to cause up to 30% of cases of epilepsy in endemic

regions

c. Inadequate access to prenatal, perinatal, and postnatal care

3. All of these risk factors for epilepsy are potentially modifiable through improved road safety and increased use of motorcycle helmets, expanding access to vaccination against pathogens that cause bacterial meningitis, improved hygiene and animal husbandry to reduce transmission of cysticercosis, and improvement in access to prenatal and perinatal care.
4. The treatment gap for epilepsy is defined as the percentage of patients with epilepsy who require treatment but remain untreated. The treatment gap is 75% or greater in low-income countries as compared to less than 10% in HIC.

Diagnosis

1. Community-based programs that include community health workers for case finding, referral, and subsequent follow-up of patients with epilepsy can reduce the treatment gap by identifying patients; assuring follow-up; and improving patient, family, and community education about epilepsy.
2. Although electroencephalogram (EEG) is often unavailable, inaccessible, or unaffordable for patients in resource-limited settings, there are numerous examples of programs in such settings that have been highly successful in the diagnosis and management of epilepsy without the use of EEG.

Management

1. Principles of medication choice and drug titration using available medications are the same as in other settings (see Chapter 2). In HIV-positive patients, drug–drug interactions that may alter antiretroviral or antiepileptic drug concentrations should be considered, highlighted in a 2012 American Academy of Neurology (AAN) guideline statement: Phenytoin may decrease lopinavir and ritonavir levels, requiring dose augmentation of the latter; valproate may increase zidovudine levels, requiring dose reduction of the latter; and atazanavir and ritonavir may decrease lamotrigine levels requiring augmentation of the latter.
2. If seizures do not respond to antiepileptic therapy and CT is unavailable, I recommend considering an empiric course of treatment for

neurocysticercosis with steroids and antiparasitics (see Chapter 19), which causes up to 30% of cases of epilepsy in endemic regions.

3. In addition to increased morbidity and mortality because of epilepsy, patients with seizures in LMIC often face enormous stigma and marginalization, which must be addressed at both the individual and community levels.

MENINGITIS (SEE ALSO CHAPTER 19)

1. Cerebrospinal fluid (CSF) diagnostics are often limited in LMIC, requiring empiric treatment of meningitis based on clinical context.
2. If a patient with meningitis does not respond to treatment for bacterial meningitis, empiric treatment for tuberculosis meningitis should be considered. If the patient has a CD4 count <200 cells/mm^3, empiric treatment for cryptococcal meningitis should be considered (see Chapter 19).
3. For patients with presumed bacterial meningitis in LMIC, steroids may not have the benefit that has been demonstrated in HIC, according to data from Vietnam and Malawi.
   a. In the Vietnam study, there was benefit of steroids in patients with confirmed bacterial meningitis but increased risk of death at 1 month in patients with probable bacterial meningitis who received steroids. This latter finding was attributed to some of the patients in the "probable bacterial meningitis" group actually having had tuberculous meningitis.
   b. In the Malawi study, only 70% of the patients had confirmed bacterial meningitis (8% ultimately had alternate confirmed etiologies of meningitis including *Cryptococcus* and tuberculosis), 90% of patients in the study were HIV positive, and median duration of symptoms was 72 hours at presentation, all factors that may have contributed to the lack of benefit of steroids in this setting.

MYELOPATHY

Epidemiology

1. Nontraumatic progressive paraparesis/paraplegia is a common presentation in LMIC. Without access to MRI, if there are no bony abnormalities on x-ray (or CT where available), many cases remain cryptogenic.
2. Compared to HIC where degenerative conditions and neoplasm are the leading causes of nontraumatic spinal cord disease, infections (most commonly tuberculosis and HIV) are the most common etiology of

myelopathy in LMIC.

3. Because access to surgery for degenerative diseases of the spine, oncologic care for primary or metastatic tumors, and immunomodulatory therapies for potential demyelinating diseases are often unavailable in LMIC, the main potentially treatable etiologies of myelopathy to consider are nutritional and infectious.

Diagnosis and Treatment

Nutritional Myelopathies

1. Vitamin B_{12} deficiency–associated myelopathy selectively affects the corticospinal tracts and dorsal columns and may also cause a concurrent peripheral neuropathy. Therefore, sensory ataxia and mixed upper motor neuron and lower motor neuron findings are characteristic (see Chapter 18). Elevated red blood cell mean corpuscular volume (MCV) is a helpful laboratory marker when present but may be normal (e.g., if there is concurrent iron deficiency causing an "averaging" of microcytic and macrocytic red cell populations, which yields a normal MCV). Treatment is discussed in Chapter 18.
2. Lathyrism and konzo refer to myelopathy caused by grass pea flour (genus *Lathyrus*) and inadequately prepared cassava, respectively. These conditions occur in settings of famine and/or drought, predominantly in Africa. There is no known effective treatment for either, and therefore, prevention is paramount.

Infectious Myelopathies

1. Bacterial epidural abscess should be suspected and empirically treated in patients with acute myelopathy and fever (see Chapter 19).
2. Tuberculosis can affect the spine in several ways: Disease of the vertebrae (Pott disease), tuberculoma of the spinal cord, and spinal meningitis/arachnoiditis. Many patients with spinal tuberculosis have no clinical or radiographic evidence of pulmonary tuberculosis. Pott disease can generally be diagnosed on x-ray (demonstrating vertebral collapse), but tuberculoma and meningitis/arachnoiditis are more challenging to diagnose in resource-limited settings. Treatment of spinal tuberculosis requires

prolonged multidrug therapy (see Chapter 19). Judicious use of empiric therapy in patients with no other apparent cause of myelopathy, risk factors for tuberculosis (e.g., close contact with known case of tuberculosis, HIV infection), and positive purified protein derivative (PPD) may be considered.

3. Schistosomiasis can cause an acute, rapidly progressive painful myelopathy after swimming in fresh water. Schistosomiasis is endemic in Africa, the Middle East, Southeast Asia, the Caribbean, and South America. Treatment is with praziquantel 60 mg/kg/d in divided doses for 3 days with concurrent corticosteroids. Steroids are generally initiated several days before initiation of praziquantel and maintained for several months following praziquantel treatment. Empiric treatment for spinal schistosomiasis should be considered if a rapidly progressive myelopathy occurs in a patient with exposure to fresh water in an endemic region.

4. Although neurocysticercosis most commonly affects the brain, the cysts may occur in the subarachnoid space surrounding the spinal cord (causing a polyradiculitis, commonly of the roots of the cauda equina) or more rarely in the spinal cord itself (causing a myelitis). Spinal neurocysticercosis most commonly occurs in combination with cerebral neurocysticercosis but may rarely occur in isolation. Optimal management often involves surgical removal, although this is often unavailable in resource-limited settings (where a definitive diagnosis is also often not feasible because of lack of advanced neuroimaging). Empiric treatment with antiparasitics (albendazole and/or praziquantel) and corticosteroids (see Chapter 19) can be considered in patients with cryptogenic myelopathy or cauda equina syndrome in endemic regions (Africa, Central/South America, the Caribbean, India, Southeast Asia).

5. Human T-lymphotropic virus type 1 (HTLV-1) and HIV can both cause chronic myelopathies of insidious onset and evolution.
   - **a.** HTLV-1 myelopathy (tropical spastic paraparesis) affects only a very small percentage of patients infected with the virus, which is endemic in East and Southeast Asia, the South Pacific islands, the Middle East, South America, the Caribbean, and sub-Saharan Africa. There is no known effective treatment, although some practitioners use antiretroviral therapy.
   - **b.** HIV vacuolar myelopathy occurs in patients with advanced AIDS and may be seen concurrently in patients with HIV dementia.

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17 Neuroophthalmology

Robert M. Mallery and Sashank Prasad

VISUAL LOSS SEEN BY THE NEUROLOGIST

Retinal Causes

Amaurosis Fugax

Background

Amaurosis fugax refers to transient monocular blindness. A common and worrisome cause is emboli to the central retinal artery or its branches. The symptom typically lasts seconds to minutes. The classic description is of a dark shade progressing downward, although other variations may occur.

Pathophysiology

Emboli to the retinal circulation may be of three major types: cholesterol (which has a yellow, shiny appearance), calcium (which appears chalky white), and platelet fibrin. If the embolus has lysed spontaneously, then the visual loss is transient and no retinal abnormalities will be apparent on examination. If not, then either a central retinal artery occlusion (CRAO) or branch retinal artery occlusion (BRAO) will occur, with edema and pallor of the affected territory in the acute phase.

Some forms of transient monocular blindness are not caused by emboli. These include retinal migraine and vasospasm, which presents with recurrent, self-limited bouts of decreased perfusion to the retinal arterioles.

Prognosis

Transient monocular blindness owing to embolic disease carries a risk of subsequent retinal occlusion, parenchymal ischemic stroke, or transient ischemic attack.

Diagnosis

To direct the evaluation, careful attention must be paid to the duration of the attacks, associated symptoms at the time of the attacks, frequency of the attacks, extent of visual loss, and precipitating factors. In most cases, an ophthalmologist should also be involved in the patient's care because a dilated fundus examination is essential to look for signs of retinal ischemia or emboli in the retinal arterioles. Diagnostic evaluation should include carotid imaging, echocardiogram, long-term telemetry monitoring, and a lipid panel. In young patients, a search for causes of hypercoagulability may be warranted. In some cases, the appearance of the retinal emboli may direct the workup (i.e., cholesterol emboli tend to come from the carotid arteries, whereas calcific ones typically travel from the heart valves or aorta).

Treatment

1. If symptomatic severe carotid stenosis is found, then either endarterectomy or stenting may be considered.
2. If atrial fibrillation, a cardiac thrombus, or a hypercoagulable state is revealed, anticoagulation is indicated. Elevated cholesterol may be managed with statin therapy.
3. Retinal migraine, relating to recurrent attacks of vasospasm, may respond to the use of calcium channel blockers.
4. When no clear cause is identified but the patient has other vascular risk factors such as hypertension or diabetes, the treating physician may recommend antiplatelet therapy such as aspirin or clopidogrel.

Optic Neuropathies

Optic nerve injury often presents with impaired acuity and color vision because of the high metabolic needs of the maculopapillary fibers. Such a presentation will be accompanied by either a central or cecocentral (stretching from the physiologic blind spot to fixation) scotoma. Other patterns of peripheral field loss are also suggestive of optic nerve injury, including arcuate scotomas (following the arc-like trajectory of retinal nerve fibers) or altitudinal defects (although the latter may occur with superior or inferior BRAO as well). An optic neuropathy is suggested by a relative afferent pupillary defect, which manifests as a dilation of both pupils when a light source is swung from the intact eye to the one with the optic neuropathy (the

swinging flashlight test), although this sign may also occur with severe retinal disease such as a CRAO.

Anterior Ischemic Optic Neuropathy

Anterior ischemic optic neuropathy (AION) may be divided into two forms: arteritic and nonarteritic. The first results from giant cell arteritis (GCA), and rarely from other vasculitides, whereas the second tends to occur in isolation.

Giant Cell Arteritis

Background

The incidence of this condition correlates with age, and it is exceedingly rare for it to occur prior to 50 years of age. Patients with polymyalgia rheumatica carry an increased risk. Headache, especially scalp tenderness, is a regular feature, and other symptoms include jaw claudication, myalgias, fever, and weight loss.

Pathophysiology

Inflammation of the media of extracranial medium-sized arteries narrows the lumen and leads to ischemia. The cause of this inflammation remains unclear. It may cause AION, with optic disc swelling, as well as CRAO and BRAO. It may even affect the circulation of the posterior nerve, producing an ischemic optic neuropathy with no changes in the appearance of the optic nerve head (posterior ischemic optic neuropathy [PION]).

Prognosis

This is an acute illness and neuroophthalmic emergency. Early clinical diagnosis and treatment are required to mitigate the risk of severe bilateral visual loss. In rare cases, GCA may be complicated by posterior circulation stroke, myocardial infarction, or aortic dissection.

Diagnosis

1. Arteritic AION presents with sudden vision loss in one eye, sometimes preceded by amaurosis fugax. Pallid optic disc swelling is characteristic, often with peripapillary splinter hemorrhages.

2. If untreated most patients with unilateral arteritic AION would develop fellow eye involvement within weeks. Bilateral simultaneous arteritic ION is rare.
3. The finding of AION with cilioretinal artery occlusion is virtually pathognomonic of GCA.
4. Associated symptoms result from involvement of branches of the external carotid artery and include headache, scalp tenderness, and jaw claudication. Systemic symptoms that often accompany the disease include fatigue, fever, and myalgias. Important signs include a distended and tender temporal artery.
5. Approximately 15% of cases of arteritic ION have no associated systemic features, so-called "occult GCA."
6. When suspected, GCA should prompt an immediate search for associated laboratory abnormalities including an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and thrombocytosis. Treatment with steroids should not be delayed until these results are back. ESR elevation is 95% sensitive, and CRP elevation is 97% sensitive.
7. A definitive diagnosis may be made with a temporal artery biopsy revealing a lymphocytic infiltrate with or without giant cells.

Treatment

1. High doses of oral or intravenous (IV) corticosteroids are indicated when the patient with suspected GCA is experiencing transient or persistent visual loss.
   a. A typical regimen is 3 days of 1 g/d of methylprednisolone followed by high doses (about 1 mg/kg) of oral prednisone.
2. In cases without imminent threat of visual loss or stroke, oral prednisone can be started. There are no good data to definitively establish an appropriate dosage, but 1 mg/kg of body weight of prednisone per day is usually adequate.
   a. A biopsy should always be done to establish the diagnosis. The window for obtaining the biopsy is within 7 days after starting the prednisone, although it should be performed as soon after starting therapy as possible.
   b. Despite having many side effects, prednisone therapy must be prolonged for most patients with GCA. After high doses are used for approximately 2

months, the dose can be slowly weaned. As a rule of thumb, the typical course may extend between 9 and 12 months, but individual cases will vary.

c. It can be challenging to decide how fast to taper the dose of prednisone. If symptoms recur, the dose should be elevated. It is less clear whether to increase the dose on the basis of a rising ESR or CRP levels. Trying to achieve and maintain a normal ESR or CRP may prolong high doses of therapy beyond what is necessary.

3. The addition of other immune-modulating drugs, such as methotrexate or tocilizumab (IL-6 inhibitor), can help taper steroids to lower doses in some patients.

Nonarteritic Anterior Ischemic Optic Neuropathy

Background

Nonarteritic anterior ischemic optic neuropathy (NAION) is typically seen in older patients with vascular risk factors, especially hypertension and diabetes. Most patients will have a "crowded" optic disc, with a congenitally small or absent optic nerve cup. Severe blood loss, coronary bypass surgery, and prolonged surgical procedures with the patient prone are other causes.

Pathophysiology

The best evidence at this time suggests that there is an occlusion or reduction of blood flow in the posterior ciliary arteries, which supply the optic nerve head. The ensuing ischemia seems to start a pathologic cascade of edema that further compromises perfusion and leads to additional ischemia and swelling. Associations have been made with diabetes, hypertension, smoking, obstructive sleep apnea, hyperlipidemia, and nocturnal hypotension.

Prognosis

1. The visual loss in the affected eye usually remains static, but a minority of patients have a partial recovery.
2. The lifetime incidence of involvement of the other eye is approximately 30%.

Diagnosis

1. NAION can mimic arteritic ION except that the amount of vision loss may

be less and the associated symptoms and signs of GCA are not present.

2. In the acute stage, the disc in NAION appears swollen and hyperemic, typically with splinter hemorrhages. The swelling may be sectoral, sparing a segment of the optic disc and corresponding with the area of visual field loss.
3. A finding of a small cup-to-disc ratio in the fellow eye aids the diagnosis.
4. Fluorescein angiogram will show normal filling of the choroidal circulation as fluorescein transits the retinal arterioles, and mid to late frames will demonstrate leakage at the disc.
5. Occasionally, patients with risk factors present with sectoral optic disc swelling without visual field loss.
6. The phosphodiesterase inhibitor sildenafil has in some cases appeared to be associated with NAION. The same population of patients using this medication also have typical vascular risk factors for NAION, and it has been difficult to ascertain the exact proportion of case that can be definitively attributed to use of the medication.

Treatment

1. There is no convincing evidence that any therapy alters the natural history of this condition.
2. It is reasonable to recommend that patients avoid taking antihypertensive medications at bedtime because nocturnal hypotension is considered to be a possible provoking factor.
3. If the patient has an elevated intraocular pressure, topical medications that normalize the pressure may be indicated.
4. A large randomized trial showed that optic nerve sheath decompression is not helpful.
5. Untreated obstructive sleep apnea may be a risk factor for AION, possibly because of nocturnal hypoxia. Patients with symptoms suggestive of OSA should be referred for a sleep study and treatment if confirmed.
6. Treatment with prednisone until the optic disc swelling resolves is occasionally offered in monocular patients or patients with involvement of the second eye, although the efficacy is uncertain and appropriate dosing is based on limited evidence.

Diabetic Papillitis

Background

Diabetic patients may present with optic disc swelling with no or minimal visual loss.

Pathophysiology

The pathophysiology is not entirely clear, but diabetic papillopathy may represent impending NAION or a mild form of NAION.

Prognosis

Some patients with diabetic papillopathy progress to develop significant vision loss related to NAION, but in others, the optic disc swelling remits without visual loss.

Diagnosis

Although this entity is similar to NAION, the patient is more likely a type 1 diabetic whose diabetes is under good control.

Treatment

There is no specific treatment for this disorder, but good glycemic control and avoidance of nocturnal hypotension are advised.

Idiopathic Demyelinating Optic Neuritis

Background

This is a common cause of monocular loss of vision in a young person, especially females, and often occurs in association with multiple sclerosis (MS).

Pathophysiology

Optic neuritis is an inflammatory demyelination of the optic nerve. It may occur in the context of MS or in isolation. Visual loss progresses for 2 to 4 weeks and then begins to improve at approximately a month.

Prognosis

According to the Optic Neuritis Treatment Trial, 95% of patients will recover to 20/40 or better by a year. In fact, most of the improvement occurs by 6 months. Although most cases will improve without treatment, baseline vision may not return. Permanent impairment of low contrast visual acuity and color vision is common.

Diagnosis

1. A clinical diagnosis of optic neuritis can be made in a patient presenting with typical symptoms of subacute vision loss, a relative APD, pain with eye movement, and fundus exam showing either mild optic disc edema or normal optic nerve head in the case of retrobulbar optic neuritis.
2. Contrast-enhanced magnetic resonance imaging (MRI) of the orbits and brain supports the diagnosis, which usually reveals enhancement of the optic nerve. The finding of asymptomatic T2 hyperintensities or enhancing T1 lesions may contribute to an early diagnosis of MS.

Treatment

1. Based upon the Optic Neuritis Treatment Trial (ONTT), optic neuritis treated first with 3 days of IV methylprednisolone at a dose of 1 g/d, followed by oral steroids at a dose of 1 mg/kg for 11 days with a 4-day taper (20, 10, 0, and 10 mg), will resolve more rapidly than when not treated. However, there will be no significant effect on visual acuity at a year. The use of IV steroids for optic neuritis is not absolutely indicated unless it is bilateral or the patient has poor vision in the unaffected eye.
2. Patients treated with IV steroids are less likely to be diagnosed with clinically definite MS within the next 2 years. After 2 years, however, the incidence of MS in the treated and nontreated groups becomes equivalent.
3. In patients with optic neuritis and evidence of subclinical demyelination on brain MRI, disease-modifying treatment can be considered.

Neuromyelitis Optica (NMO)

Background

NMO was described by Devic as a concomitant optic neuritis with transverse myelitis. It is now understood that years may separate one event from the other and that episodes may recur.

Pathophysiology

In contrast to the cell-mediated basis of MS, neuromyelitis optica (NMO) is considered to result from an antibody-mediated autoimmune response triggering complement-dependent mechanisms. Although NMO was originally thought to spare the brain, it is now known to affect regions of high aquaporin-4 expression, including the area postrema and hypothalamus. Pathology may

show necrosis, perivascular complement deposition, and axonal loss in addition to inflammatory demyelination.

Prognosis

Visual loss in NMO tends to be of greater severity than that of MS-related optic neuritis, with less recovery.

Diagnosis

The 2015 criteria outline the diagnosis of NMO spectrum disorders, stratified according to the presence or absence of the aquaporin-4 antibody. Seronegative patients must have either optic neuritis, longitudinally extensive myelitis, or the area postrema syndrome. For seropositive patients, the criteria are more relaxed, and the clinical syndrome may include any of those listed earlier, or a diencephalic syndrome, other brainstem syndrome, or other cerebral syndrome. The revised criteria reflect growing recognition of the high specificity of the aquaporin 4-IgG test using evolving methods such as the cell-based assay.

Treatment

The optic neuritis of NMO may be treated with high-dose IV steroids, but in cases with severe deficits, strong consideration should be given to treatment with plasmapheresis. Among maintenance therapies, rituximab has been particularly promising. Other treatment options include mycophenolate mofetil and azathioprine. Accurate diagnosis is critical because agents used to treat MS, such as interferon β, natalizumab, and fingolimod, have been shown to worsen the disease course in patients with NMO spectrum disorder.

Papilledema

Background

Papilledema refers to swollen, elevated optic discs resulting from increased intracranial pressure (ICP). Unlike other optic neuropathies, early papilledema tends to spare visual acuity, color vision, and the central field because the maculopapillary bundle is relatively spared. Instead, papilledema commonly manifests with blinds spot enlargement and peripheral visual field loss, often of the inferior nasal quadrant. Left untreated, however, acuity can eventually be severely affected.

Pathophysiology

Increased ICP is transferred to the perineural cerebrospinal fluid (CSF) and compresses the anterior optic nerve, thus reducing axoplasmic flow of cellular waste products, leading to edema. Venous congestion also results, leading to papillary hemorrhages. Some patients have asymmetric communication of CSF to the perineural space and thus papilledema may be asymmetric or even manifest only in one eye.

Prognosis

1. This depends on duration and the severity of the papilledema itself.
2. Certain associated findings indicate a poor prognosis for vision loss in cases of papilledema. The major one is systemic hypertension. Others are high-grade disc edema, peripapillary subretinal hemorrhages, visual acuity loss at presentation, old age, myopia, retinochoroidal collateral vessels, and glaucoma.

Diagnosis

1. Imaging with a contrast MRI or computed tomography (CT) should be the first diagnostic step in the evaluation of papilledema in order to evaluate for a mass lesion as the cause.
2. MR or CT venogram (MRV or CTV) should also be acquired to rule out a cerebral venous sinus thrombosis (VST).
3. Lumbar puncture (LP) confirms elevated pressure but should only be performed once imaging has ruled out a mass lesion that could result in herniation. The opening pressure should be evaluated with the patient in the lateral decubitus position, as relaxed as possible with his or her legs extended.
4. LP is required to detect inflammatory, infectious, or neoplastic infiltration of the CSF that has caused elevated ICP.
5. In the face of a negative MRI/MRV, elevated ICP, and normal CSF constituents, a diagnosis of idiopathic intracranial hypertension (IIH, pseudotumor cerebri) is confirmed. This typically occurs in young, obese women who present with headache, pulsatile tinnitus, and papilledema. Horizontal diplopia from sixth nerve dysfunction may be present. The condition may remit after a year or two but in some patients appears to be a chronic condition.
6. A common but often overlooked cause of bilateral optic disc swelling is

malignant hypertension. Blood pressure should be measured, and the fundus should be examined for signs of retinal damage.

Treatment

1. Mass lesions responsible for elevated ICP should be treated appropriately.
2. If the occurrence of raised ICP can be attributed a medication such as tetracycline, vitamin A, nalidixic acid, nitrofurantoin, or lithium, these drugs should be discontinued.
3. Inflammatory causes such as sarcoidosis may be treated with steroids.
4. Infectious causes should be treated with the appropriate antibiotics.
5. The treatment of leptomeningeal neoplasm depends on the type of tumor but may involve radiation and/or high-dose systemic or intrathecal methotrexate.
6. Acetazolamide may be used to lower ICP and is the first-line treatment for patients with IIH. Some physicians use up to 4 g/d. Topiramate is another treatment option. Both acetazolamide and topiramate may precipitate renal stones. Some patients may respond to furosemide.
7. Weight reduction is a critical aspect of the management of patients with IIH.
8. If medical therapy is not effective and visual deficits are progressing, then ICP may be lowered with either a ventriculoperitoneal or lumboperitoneal shunt.
9. Optic nerve sheath decompression is an alternative method, particularly for patients with progressive visual loss in the absence of refractory headache. Surgical treatments for IIH are reviewed in Table 17-1.
10. A single LP does not have lasting benefit, but repeated LP can be effective, although impractical.
11. Placement of a stent in the transverse sinus is an investigational therapy to be considered in the setting of venous sinus stenosis with an abnormal trans-stenosis pressure gradient.
12. In cases in which there is coexistent systemic hypertension and raised ICP, caution must be used in lowering the systemic blood pressure, as a sudden drop in blood pressure may precipitate further vision loss.

Table 17-1 Surgical Treatments of Refractory Idiopathic Intracranial Hypertension

Ventriculoperitoneal	Lumboperitoneal	Optic Nerve	Venous Stenting

Shunt (VPS)	Shunt (LPS)	Sheath Fenestration	
• Revisions less often required than LPS • Requires craniotomy and associated risks of hemorrhage, infection, and seizure • Low-pressure headaches, treatable with programmable shunt	• Requires more revisions than VPS • Increased risk of shunt obstruction compared with VPS • Abdominal pain • Migration of shunt • Acquired Chiari malformation	• Late failures may occur • May not control headaches • Ocular motility disorders (often temporary) • Conjunctival blebs • Orbital hemorrhage • Optic nerve trauma • Orbital apex syndrome • Intraoperative angle closure glaucoma • Deterioration of visual function, transient blindness • Central or branch retinal artery occlusion	• Only potentially helpful in cases with transverse sinus stenosis. Not well studied.

Compressive and Intrinsic Optic Neuropathies

Pathophysiology

Most of the visual deficits caused by these entities are because of direct compression of axons, but in some cases, interruption of blood supply plays a part. The unifying feature is that visual loss tends to be progressive. Tumors that tend to compress the optic nerve include meningiomas of the sphenoid wing, optic nerve sheath meningiomas, pituitary tumors with anterior extension, and metastases to the orbit. Aneurysms of the ophthalmic segment of the internal carotid artery (ICA) may also compress the optic nerve. Gliomas may arise within the optic nerve during childhood, in which case the pathology is that of a benign pilocytic astrocytoma. These tumors typically arise in association with neurofibromatosis type 1. Optic nerve gliomas in adults are

exceedingly rare but are typically malignant (glioblastoma multiforme [GBM]) and carry a very poor prognosis.

Prognosis

Duration of the insult and age of the patient are important variables.

Diagnosis

MRI of the brain and orbits with contrast to evaluate for a mass lesion is essential in any case of unexplained progressive visual loss. CT with contrast is helpful in that it may show calcifications in meningiomas. Optic nerve sheath meningiomas may have a tram track appearance in axial sections. MR or CT angiography may be used to demonstrate compressive aneurysms.

Treatment

1. For compressive lesions, the main therapeutic approach is to resect the lesion and decompress the optic nerve.
   a. When a meningioma extrinsically compressing the nerve is causing visual loss, surgical excision is often the first-line therapy. If the meningioma has aggressive features, or residual tumor shows growth, then adjuvant radiation therapy may also be beneficial.
   b. For meningioma of the optic nerve sheath, the decision to operate can be more challenging because surgery may often be complicated by vision loss from disruption of blood supply to the optic nerve. Radiation of optic nerve sheath meningiomas has some benefit, but the effect is often temporary. As long as visual loss from an optic nerve sheath meningioma is minimal, observation with serial examinations is often the most reasonable option. When the clinical presentation and radiologic findings are characteristic, tissue diagnosis is often unnecessary.
   c. Malignant adult optic nerve gliomas have a relatively poor prognosis and are treated as would GBMs in other locations, with a combination of resection, radiation, and chemotherapy.

Neoplastic Optic Neuropathies

Background

The optic nerve may rarely be affected by malignant infiltration through the leptomeningeal space or at the optic nerve head. The most common scenario is

of leukemic infiltration, which is an emergency, because permanent visual loss may result without prompt treatment. In addition, paraneoplastic optic neuropathies may very rarely occur in association with the anti-CRMP5 protein.

Diagnosis

Visual loss and papillitis in the setting of leukemia is highly suggestive of leukemic optic neuropathy. If leptomeningeal disease is suspected, an LP should be performed to assess CSF cytology.

Prognosis and Treatment

Urgent radiation to the optic nerve head or chemotherapy may lead to quick resolution of the optic neuropathy.

Radiation-Induced Optic Neuropathy

Background

1. Radiation necrosis of the optic nerves can occur in patients previously treated with radiation for tumor near the optic nerves.
2. The concomitant use of some chemotherapeutic agents appears to accelerate the process.

Pathophysiology

Radiation may either induce a vasculitis or have direct neurotoxic properties.

Prognosis

Although prognosis is generally poor, there are exceptions.

Diagnosis

The diagnosis is usually made once recurrence of the tumor originally treated is excluded. There may be edema of the optic nerve head as well as surrounding cotton wool spots caused by a concomitant radiation-induced retinopathy. MRI may show enhancement of the nerve.

Treatment

1. This condition, which may occur a year or more after radiation to the optic nerve, is virtually untreatable.
2. There are advocates for the following treatments.
   a. Hyperbaric oxygen for at least 20 sessions for 90 minutes at 2.4

atmospheric pressure.

b. IV Solu Medrol 1 g/d for 3 days followed by a 2-week oral taper may be used at the same time.

c. The addition of pentoxifylline 400 mg two or three times a day has also been recommended.

d. Bevacizumab has shown some benefit in anecdotal reports.

Leber Hereditary Optic Neuropathy

Background

This mitochondrial disease presents with acute to subacute severe, painless visual loss in in one eye, typically followed within weeks to months by a similar occurrence in the fellow eye. It usually occurs in young males but may occur in females and has been reported in older patients as well.

Pathophysiology

Most cases of this condition are caused by point mutations at mitochondrial loci 11778, 3460, or 14484. Because these genes are encoded by mitochondrial DNA, there is strictly maternal inheritance. Ninety percent of affected individuals are men; women may be affected, but they are more frequently asymptomatic carriers. Improvement or stabilization of vision is a rare occurrence but is more common in patients with the 14484 mutation.

Diagnosis

A family history compatible with mitochondrial inheritance may aid the diagnosis, but frequently patients have no family history of optic neuropathy due to LHON's low penetrance. The metabolic nature of the disease leads to maculopapillary bundle injury–producing cecocentral scotomas. Edema in the retinal nerve fiber layer surrounding the optic nerve and telangiectatic blood vessels on and near the disc in the early phases are characteristic.

Treatment

1. Idebenone has shown modest success in mitigating visual loss in the unaffected fellow eye after the initial presentation.
2. In general, patients with Leber hereditary optic neuropathy (LHON) mutations should be counseled to avoid additional toxins that stress mitochondrial energy metabolism, such as tobacco and alcohol.
3. Trials are underway to study the gene therapy delivered through intravitreal

injection, and preliminary results have been promising.

Dominant Optic Atrophy (Kjer Disease)

Background

Patients with this condition present with chronic progressive bilateral optic neuropathies in childhood.

Pathophysiology

The mutation is in the nuclear *OPA* gene, which encodes a protein involved in mitochondrial function.

Diagnosis

Visual loss can be mild to moderate but typically is not severe. Patients may be identified, for example, after failing a screening vision examination in grade school. Optic nerve atrophy, often with significant cupping, is suggestive. Imaging should be used to evaluate for a compressive lesion before genetic testing is pursued.

Prognosis

Vision generally stabilizes at no worse than 20/200 but may also be significantly better.

Treatment

There is no known treatment.

Nutritional and Toxic Optic Neuropathies

Background

Certain toxins and medications may produce damage to the optic nerve as may chronic nutritional deficiencies.

Pathophysiology

This depends on the agent and in most cases is unclear. Excessive use of tobacco and alcohol have been associated with bilateral optic neuropathies (tobacco–alcohol amblyopia), but it is likely that the damage actually results from associated nutritional deficiencies. Mitochondrial dysfunction appears to be a final common pathway for many of these disorders.

Prognosis

Prognosis depends on etiology. In the case of ethambutol toxicity, there may be improvement with cessation of therapy.

Diagnosis

The diagnosis should be considered whenever there is slowly progressive loss of optic nerve function in both eyes in the setting of a potentially toxic agent or poor nutritional status. Vitamin B_{12} deficiency may cause bilateral optic neuropathies as well as neuropathy, dementia, and posterior column degeneration. Visual field loss tends to manifest as cecocentral scotomas.

Treatment

1. The first therapy is to remove the offending agent. The second is to correct metabolic deficiencies (e.g., vitamin B_{12}) with supplementation.
2. In the early phases of methanol and ethylene glycol poisoning, administration of ethanol or fomepizole helps to block the metabolism of the toxin. Bicarbonate aids in the treatment of the acidosis and dialysis speeds elimination of the toxin.

Traumatic Optic Neuropathies

Background

This entity is considered when vision loss after head injury is not explained by direct trauma to structures of the globe.

Pathophysiology

In some cases, trauma results in direct compression of the nerve by blood or bony fragments. In the absence of such findings, the injury is felt to result from shear injury as the nerve is transiently forced against the decelerating bony orbit.

Prognosis

Some cases improve spontaneously, whereas others require surgical decompression. In other cases, the prognosis can be poor, without effective treatment.

Diagnosis

In unilateral cases, there should be a relative afferent pupillary light defect.

High-quality neuro-imaging is a necessity. CT is superior to MRI in that it is better at detecting fractures and bony fragments.

Treatment

1. If a compressive lesion (fragment of bone or hematoma) can be demonstrated, surgical decompression should be considered. In cases where an orbital hematoma is compressing the optic nerve, a lateral canthotomy may be helpful.
2. Systemic steroids may be tried for a few days to reduce swelling around the optic nerve, but their efficacy has never been well established.

DISORDERS OF THE SELLA AND CHIASM

Background

Compression of the optic chiasm typically causes a bitemporal hemianopia because of compromise of decussating fibers subserving the temporal field of each eye. The most common cause of chiasmal injury is compression by a tumor, most commonly by a pituitary adenoma. If the adenoma is prolactin-secreting, the patient may have loss of libido, amenorrhea, and galactorrhea from the hormonal imbalance. Acute bitemporal field defects may occur from sudden hemorrhage within a pituitary tumor (pituitary apoplexy) that may also cause acute ophthalmoplegia as the expanding tumor and hematoma extends laterally into the cavernous sinus. Craniopharyngiomas, which are more frequent in children and typically include cystic spaces and calcium deposits, may compress the chiasm from above. Other causes of chiasmal injury include Rathke cleft cysts, meningiomas, and trauma, whereas intrinsic disease may take the form of demyelination or a hypothalamic/optic pathway glioma.

Presentation

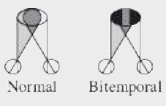
Early compression from below (i.e., pituitary adenomas) may lead to superior bitemporal defects, whereas compression from above (e.g., craniopharyngioma) may lead to inferior bitemporal defects. If the chiasm is fixed anteriorly, optic tract compression may lead to homonymous hemianopia, whereas a posteriorly fixed chiasm may result in optic nerve compression by

the tumor. If an optic nerve is affected posteriorly at its junction with the optic chiasm, then an ipsilateral central or complete scotoma may be accompanied by a superotemporal defect in the contralateral eye, together known as a junctional scotoma (a summary of various visual complications of sellar tumors may be found in Table 17-2).

Treatment

1. Surgical resection is the first-line treatment for most pituitary adenomas leading to visual loss. An endoscopic transnasal transsphenoidal approach is typically used. An open craniotomy may also be necessary, especially for meningiomas.
2. Prolactinomas may shrink in response to dopamine agonists such as cabergoline and bromocriptine.
3. Growth hormone–secreting tumors may respond to somatostatin analogues such as octreotide in conjunction with surgery.
4. Radiation therapy may be used to treat residual tumor.

Table 17-2 Visual Symptoms of Sellar Lesions

Defect	Location	Illustration
Bitemporal hemianopia	Optic chiasm	
Superior bitemporal defects	Chiasm from below	
Inferior bitemporal defects	Chiasm from above	
Central, cecocentral, arcuate, or altitudinal defects	Optic nerve (postfixed chiasm)	
Central in ipsilateral eye and superior temporal in contralateral eye	Junction of optic nerve and chiasm	
Hemifield slide: Bitemporal hemianopia reduces the area of overlapping visual field, making it harder to align the eyes in cases of latent strabismus.	Horizontal diplopia (nonparalytic)	
See-saw nystagmus: One eye extorts and depresses, whereas the other intorts and elevates.	Chiasm or junction of midbrain—	

Prognosis

1. After resection of pituitary adenomas, vision can improve substantially or even normalize, particularly if optic disc pallor is not already present. Persistent visual loss is more likely in the setting of optic disc pallor. Preserved retinal nerve fiber layer thickness on optical coherence tomography (OCT) also predicts good recovery of visual loss following decompression of the optic nerves or chiasm.
2. Complications of tumor resection include CSF leak, meningitis, cranial neuropathies, diabetes insipidus, loss of vision because of chiasmal or optic nerve injury, and rarely death.

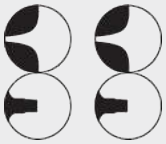
RETROCHIASMIC VISUAL FIELD LOSS

Background

Lesions situated behind the optic chiasm (affecting the optic tract, lateral geniculate nucleus, optic radiations, or occipital lobe) will cause a contralateral homonymous field defect. Field defects are more congruous (having the same configuration in each eye) with more posterior lesions, whereas an incomplete lesion of the optic tract can produce incongruous homonymous field loss. Ischemic lesions of the lateral geniculate nucleus may cause loss of either the contralateral central sector (when the lateral choroidal artery is involved) or the superior and inferior sectors (when the anterior choroidal artery is involved). Lesions involving the optic radiations in the parietal lobe or superior occipital cortex cause inferior field defects, whereas those involving the Meyer loop in the temporal lobe or the inferior occipital cortex will cause superior field defects (Table 17-3). Ischemic lesions to the occipital lobe may result in two unique phenomena:

Table 17-3 Retrochiasmatic Visual Loss

Location	Field Defect	Features	Illustration
Optic tract	Homonymous	Typically incongruous	

	hemianopia		
Lateral geniculate nucleus	Sectoral hemianopia. Pattern depends on which feeder artery is occluded	**Anterior choroidal artery:** Quadruple sectoranopia **Lateral choroidal artery:** Horizontal sectoranopia	
Optic radiation	Inferior quadrantanopia	—	
Meyer loop	Superior quadrantanopia	—	
Occipital cortex	Homonymous hemianopia	Typically congruous. May spare macular vision with PCA stroke. Temporal crescent spared if anterior occipital cortex is preserved.	

PCA, posterior cerebral artery.

1. Macular sparing homonymous hemianopia, which occurs because the occipital tip responsible for central vision has dual blood supply from the middle and posterior cerebral arteries.
2. Homonymous field deficit with sparing of the temporal crescent, which refers to preservation of the most temporal field in the eye contralateral to the lesion, results from sparing of the most anterior portion of the primary visual cortex.

Prognosis

Recovery of fields depends on the etiology. Recovery that occurs in the case of stroke mostly occurs within the first 6 months.

Treatment

1. Some patients with homonymous hemianopia may benefit from prism with the base to the blind field that moves a portion of the field that cannot be seen into a functioning part of the visual field. However, most patients do not adapt well to this therapy, limiting its use.
2. Patients with a left homonymous hemianopia have trouble finding the beginning of the next line when they are reading. A ruler or a piece of string placed at the left edge of the print is helpful to them.

3. Those with a right homonymous hemianopia may find themselves mistakenly moving to another line before completing one line of text. Using the index finger to focus attention on a single line is helpful.
4. Finally, there are advocates of visual restitution therapy, which involves repetitive visual stimuli along the transition zone between the scotoma and the intact visual field. Although some studies have shown a few degrees of field expansion compared with controls, the improvement may simply be a result of increased ease and frequency of saccades into the hemianopic field. When fixation has been controlled, no objective improvement was seen even when patients reported subjective improvement.

NONORGANIC VISUAL LOSS

Nonorganic visual loss may occur as a manifestation of subconscious anxiety (conversion disorder) or in patients consciously pretending to have visual loss (malingering).

Prognosis

With appropriate therapy, the prognosis for conversion disorder is generally good.

Diagnosis

Diagnosing nonorganic visual loss can be challenging and must be tailored to the individual presentation (Table 17-4).

1. Severe monocular visual loss
   - **a.** A normal examination of the eye structures *and* the absence of a relative afferent pupillary defect.
   - **b.** Techniques that test the acuity in the "affected" eye without the patient's knowledge. One example is to use red/green goggles and colored filter overlaid on an acuity chart.
   - **c.** "Clover-leaf" or spiral-shaped visual field loss documented by perimetry.
2. Severe visual field constriction
   - **a.** Demonstration of "tubular fields," in which the diameter of the perceived visual field does not expand with increased test distance and a

proportionally increased size of the test object.

3. Monocular hemifield deficit
   a. Demonstration that the field deficit does not resolve with binocular field testing, as it should

4. Binocular hemifield deficit
   a. Demonstration of normal finger pointing and saccades to the "blind" hemifield

5. Complete bilateral visual loss
   a. Demonstration of intact optokinetic nystagmus or ability to track a salient stimulus such as a $100 bill or a mirror reflecting the patient's own face

Treatment

In cases of conversion disorder, treatment must include appropriate attention to psychological stressors. Pharmacologic therapy of anxiety or depression may be helpful. It is critical to establish whether the patient is the victim of physical, sexual, or emotional abuse.

Table 17-4 Tests to Detect Nonorganic Visual Loss

Tests for Severe Visual Loss	
Shock technique	Show the patient a funny or emotionally evocative phrase in a font too small for them to read and watch for an appropriate reaction that reveals a better acuity.
Narcissus effect	Rotate a mirror in front of the patient and look for pursuit. Optokinetic nystagmus (OKNs): Rotate an optokinetic drum in front of the patient. Failure to suppress OKNs indicates acuity more than 20/200.
Tests for Malingering	
Proprioception	Ask the patient to bring his or her fingers together in front of him or her, a task easily done with only proprioception. The malingerer will often think that vision is required and "fail" the test.
John Hancock sign	The malingerer may not be able to sign his or her name even though vision is typically not required.
Forced choice	Test: The patient is asked to choose the correct response out of two on a number of tasks. Even with no vision, success rate should be <50%, but in malingerers, it is often much less.
Unilateral Visual Loss	
Prism test	Place a four diopter base-out prism in front of the affected eye while fixating

	on a Snellen letter. If eye movement is detected by the examiner or diplopia acknowledged by the patient, the acuity is near that of the Snellen letter.
Red-green glass test	A chart with letters, some red and some green, is visualized by the patient while wearing red-green glasses. If the right eye (behind the red lens) is blind, they should only be able to see green letters. Because they do not know which letters are red and which are green, there is no way to fake this test. A similar effect can be achieved by using polarized glasses with a polarized letter chart.
Tests for Peripheral Field Loss	
Tubular field loss	Place the patient in front of a black tangent screen and test his or her visual fields with a 2-mm target, 1 m away. Record the extent of preserved visual field with chalk. Now test again at 2 m using a 4-mm stimulus. Optics requires that field diameter should expand with longer distances, but in nonorganic cases, it often remains the same size.
"Strength" testing	While the patient is fixating on your nose with his or her constricted eye, explain that you are testing strength. Ask him or her to make fists in the far periphery. In the case of nonorganic visual loss, the results may differ substantially from confrontational field testing.

VISUAL HALLUCINATIONS AND ILLUSIONS

Background

Visual hallucinations refer to the perception of visual stimuli that do not exist. Illusions describe visual phenomena that are a distortion of a real perception. They occur in myriad settings, with causes including structural lesions, drug intoxications, and psychiatric conditions.

Pathophysiology

Migraines are probably the most common cause of cortical visual hallucinations, often causing geometric patterns referred to as fortification spectra. Palinopsia, which is an abnormal persistence of images or a trail behind a moving visual target, may occur in the setting of certain medications (such as nefazodone, clomiphene, baclofen, topiramate), illicit hallucinogenic drugs, as well as disturbance of the posterior visual pathways caused by seizure, stroke, or tumor. Occipital seizures produce recurrent, stereotyped visual hallucinations that typically have simple geometric shapes. Charles

Bonnet syndrome refers to complex visual illusions that occur as a release phenomenon in patients with visual loss. Although the images are often said to be nonthreatening, they can be disturbing to many patients, and it is helpful to provide reassurance that this does not represent psychological disease. Peduncular hallucinosis refers to vivid, complex recurrent hallucinations that may occur in patients with midbrain or thalamic lesions that damage ascending reticular systems.

Prognosis

This depends on the cause. In the case of drug-induced palinopsia, the symptoms may persist for months after removal of the responsible medication.

Diagnosis

A detailed history, accompanied by ancillary studies such as neuroimaging, electroencephalogram (EEG), and/or toxicology screens, is important to establish the correct cause of visual hallucinations.

Treatment

1. It can be difficult to suppress the hallucinations relating to Charles Bonnet syndrome.
2. Occipital seizures may respond to one or more anticonvulsant medications.
3. Migraine auras may not respond to abortive therapy but may be reduced in frequency with migraine prophylactic medications such as valproic acid, topiramate, amitriptyline, and propranolol.

ASYMMETRIC PUPILS (ANISOCORIA)

Background

The most common cause of pupillary asymmetry is physiologic anisocoria, which occurs in up to 15% to 30% of normal individuals. Pupil asymmetry may also occur commonly following intraocular surgery, including cataract surgery. Anisocoria accompanied by ocular motility or eyelid abnormalities may suggest either a third nerve palsy or Horner syndrome.

Pathophysiology

The pupil is innervated by both the sympathetic system (which dilates the pupil) and the parasympathetic system (which constricts via the third cranial nerve). Anisocoria may result from disruption of either system. The most essential entities to diagnose quickly are an aneurysmal third nerve palsy, which typically affects pupillary function early, and a Horner syndrome from a carotid dissection, which is a risk factor for a stroke.

Prognosis

Abnormally small pupils rarely cause much problem for the patient unless there is a cataract present. Large pupils may result in photosensitivity, glare from light, or mild blurring of vision when reading if accommodation is affected.

Diagnosis

Two simple general principles can be applied to determine if the larger or smaller pupil is abnormal. First, the abnormal pupil is the one that does not constrict or dilate normally. Second, the degree of anisocoria in dark and bright light may suggest the etiology. If anisocoria is greater in bright light, the problem is with the larger pupil not constricting adequately, either from iris sphincter injury, a tonic pupil, or an oculomotor nerve palsy. If the anisocoria is worse in the dark, the likely cause is a Horner syndrome, which is preventing the smaller pupil from dilating. Specific eye drops confirm a Horner syndrome and localize the lesion to the first, second, or third order neuron (Table 17-5). Eye drop testing may also be used to determine the cause of a dilated pupil (Table 17-6).

Table 17-5 Drops Used to Confirm and Localize a Horner Syndrome

Drug	Cocaine (10%)	Hydroxyamphetamine (1%)	Apraclonidine (0.5%)
Mechanism of Action	Blocks reuptake of NE from the third-order neuron's terminal at the iris dilator and dilates the normal	Enhances release of NE from the third-order neuron	Activation of the a_1 receptors on the iris dilator muscle occurs because of denervation

	pupil		hypersensitivity.
Effect on Anisocoria	Exacerbates anisocoria of HS of any order	Exacerbates anisocoria only in third-order HS	Reverses anisocoria and ptosis because of any HS
Reason	No NE is in the final synapse of the Horner eye (no matter which neuron in the chain is injured)	First- and second-order lesions leave the third-order neuron intact, so even the side with the HS will dilate.	Normal pupil will not dilate because α_1 activation is offset by preganglionic α_2 activity.

NE, norepinephrine; HS, Horner syndrome.

Table 17-6 Drops Used to Determine the Cause of a Dilated Pupil

Drug	Pilocarpine (0.1%, dilute)	Pilocarpine (1%, concentrated)
Mechanism of Action	Pilocarpine is a cholinergic medication that activates the parasympathetic system. Dilute pilocarpine will activate only pupillary constrictors that have denervation hypersensitivity.	One percent pilocarpine will constrict any dilated pupil unless the receptors have been pharmacologically blocked by an atropine-like parasympathetic blocker.
Effect	Will constrict the large pupils of Adie syndrome and some third nerve palsies. It has no effect on pharmacologically dilated pupils.	If the pupil constricts, the cause is not pharmacologic unless the pharmacologic dilation in process of wearing off, then pilocarpine will constrict the pupil.

Treatment

Before any of the following measures are taken, management of the underlying cause of the anisocoria is critical (e.g., treatment of aneurysm causing a third cranial neuropathy, anticoagulation for a carotid dissection causing a Horner syndrome).

1. Small pupils, such as from Horner syndrome, cause little problem to the patient and require no treatment.
2. Partial ptosis because of Horner syndrome can be fixed surgically if necessary.
3. Dilated pupils, as from an Adie pupil, third cranial nerve palsy, or as an

effect of drugs or trauma, cause more visual problems and may require treatment.

a. If the pupillary sphincter is responsive, a drug such as pilocarpine can be used to make the pupil smaller. Unfortunately, this is not without treatment risk. Pilocarpine is associated with a risk of retinal detachment, and the lowest effective dose should be used. Commercially, this is 0.25%, but more dilute solutions such as 0.125% can be obtained from a compounding pharmacy. It may have to be used two to three times a day to maintain miosis.

b. Another solution is the fitting of a contact lens that has a painted ring at the periphery, thus making a small aperture.

DISORDERS OF EYELID POSITION

Ptosis

Background

Ptosis may occur as a result of mechanical, congenital, neurologic, neuromuscular, or myopathic etiologies. Slight asymmetries of lid position are common; usually, the patient is the best source of information regarding their importance.

Anatomy

The primary muscle that raises the upper eyelid is the levator palpebrae, which is skeletal muscle innervated by the third cranial nerve. The levator palpebrae originates at the lesser wing of the sphenoid bone near the optic canal and has an aponeurosis that connects to the superior tarsal plate and skin of the eyelid. The superior tarsal muscle (Müller's muscle) is a smooth muscle that attaches the underside of the levator palpebrae to the superior tarsal plate and is innervated by oculosympathetic fibers.

Diagnosis

Most cases of acquired upper eyelid ptosis are caused by levator dehiscence, third nerve palsy, Horner syndrome, or myasthenia gravis. The following

features may distinguish between these causes:

1. *Levator dehiscence*, a weakening of the insertion of the levator palpebrae muscle to its aponeurosis, is a form of mechanical ptosis distinguished by a raised upper eyelid crease and preserved levator function (excursion of the upper lid more than 15 mm between downward gaze and upward gaze). Levator dehiscence may occur from aging, contact lens use, or after cataract surgery.
2. Complete or marked ptosis with reduced levator function suggests involvement of the superior division of the *third nerve*.
3. The upper eyelid ptosis of *Horner syndrome* is typically associated with ipsilateral miosis and sometimes anhydrosis. It may improve with topical application of the α agonists, including phenylephrine and apraclonidine. Elevation of the lower eyelid (inverse ptosis) may also occur with Horner syndrome because of impairment of sympathetic innervation to the poorly defined inferior tarsal muscle.
4. Ptosis related to *myasthenia gravi*s varies during the exam; may improve with ice pack test, rest test, or Tensilon test; and be accompanied by a Cogan lid twitch. Other features of myasthenia gravis, including ocular motility abnormalities, orbicularis oculi weakness, or proximal weakness, may be present.

Review of old photographs may help determine the chronicity of cases of eyelid asymmetry or ptosis.

Prognosis

Prognosis is a function of cause.

Treatment

1. Treatment of underlying causes of third nerve palsies, Horner syndrome, or myasthenia gravis may result in improvement of ptosis.
2. Persistent mild or severe upper eyelid ptosis related to neurologic (third nerve palsy or Horner syndrome), myopathic, or mechanical (levator dehiscence, congenital ptosis) causes may be helped by surgical procedures that lift the lid.
   a. Caution must be exercised because there is a risk that in myopathies, the ptosis may be the first expression of what later will involve other eye

muscles.

b. If the surgical procedure leaves the patient with a partial inability to close the lid and the patient loses the protective Bell reaction, exposure keratopathy may lead to a corneal ulcer. This is particularly common in cases of chronic progressive external ophthalmoplegia (CPEO).

3. In some cases, "lid crutches" fitted to the back of a pair of glasses by a skilled optician can be helpful.

Eyelid Retraction

Background

Eyelid retraction occurs when there is overstimulation of the levator palpebrae muscles or the sympathetic fibers to the superior tarsal muscles. It is evident as scleral show between the eyelid margin and the iris and may give the appearance of exophthalmos.

Pathophysiology

1. Thyroid eye disease is the most common cause of acquired upper eyelid retraction, resulting from overstimulation of the sympathetic fibers to the tarsal muscles and scarring of the levator palpebrae muscle or the eyelid itself. It may be accompanied by a lid lag, or deficiency of lid lowering during downgaze.
2. Eyelid retraction as a feature of dorsal midbrain syndrome (Parinaud syndrome) is called Collier sign. It occurs when posterior commissure fibers, which inhibit the central caudal nucleus (which innervates the levator palpebrae muscles), are damaged.
3. Eyelid retraction may be compensatory and caused by effort to overcome ptosis of the opposite eyelid or weakness of the ipsilateral superior rectus muscle.

Prognosis

This is a function of etiology.

Treatment

Although one might expect that successful treatment of Graves disease would

eliminate this problem, this is not always the case.

1. An ophthalmic plastic surgeon can weaken the small sympathetically driven superior tarsal muscle to reduce eyelid retraction.
2. In cases of thyroid lid retraction, an equally successful and simpler procedure is to create a small laterally placed adhesion between the upper and lower lids. This is done by abrading equal lengths of the lid margin of the upper and lower lid and then bringing them into anatomic apposition by means of a suture that passes through both lid margins in a mattress stitch fashion. It should be left in place 2 to 3 weeks and then removed.

DISORDERS OF EYE MOVEMENTS

Myopathies

Degenerative Myopathies

Background

Slowly progressive and often with a suggestive family history, this group of entities expresses itself in many parts of the body in addition to the eye. The patient may have limitation of extraocular motility and bilateral ptosis. The pupil is spared (Table 17-7).

Pathophysiology

Some myopathies affecting the extraocular muscles reflect a disorder of the mitochondria, giving rise to the "ragged red fibers" seen pathologically, whereas others result from somatic mutations affecting myocyte function. The strabismus in mitochondrial myopathies is often symmetric so that the patient experiences no diplopia.

Prognosis

These entities usually have a steady downhill course over a prolonged period.

Diagnosis

The diagnosis depends on characteristic clinical, biopsy, and electrophysiologic findings.

Treatment

1. Degenerative myopathies of the ocular muscles such as CPEO are largely not treatable in any way that would restore normal eye movement. A special caution must be exercised because these conditions often present first with lid ptosis before there are other expressions.

Table 17-7 Myopathies Affecting Extraocular Muscles

Myopathy	Progressive External Ophthalmoplegia	Kearns–Sayre Syndrome	Myotonic Dystrophy	Oculopharyng Muscular Dystrophy
Pathophysiology	Mitochondrial mutations, such as transfer RNA	Large mitochondrial mutations	CTG repeat in a muscle protein kinase gene	GCG repeat in polyadenyla binding prot gene
Associated symptoms	Ptosis. The EOM limitation is equal in both eyes, so typically there is no diplopia.	Like CPEO plus pigmentary degeneration of retina and heart block	Ptosis without strabismus, myotonia, diabetes, cardiac defects, balding, cataracts	Ptosis, dyspha presenting a age 40 year more comm French Canadians

CTG, cytosine-thymine-guanine; GCG, guanine-cytosine-guanine; EOM, extraocular muscles; CPEO, chronic progressive external ophthalmoplegia.

2. If a surgical procedure is done to lift the lid and later the patient loses Bell reaction as the superior rectus loses function or develops a weakness of orbicularis function, a corneal ulcer may develop. (Treatment for this is discussed in the section on Seventh (Facial Motor) Cranial Nerve Palsies.)
3. Because lid ptosis is so disfiguring and disturbing visually, lid crutches in this condition are the best solution. Once the extraocular muscle weakness has reached a steady state, prism glasses can be given to allow single binocular vision in most cases. Prisms are especially effective in this condition because there is little or no eye movement.

Myopathy of Graves Disease

Background

Autoimmune effect on the extraocular muscles in some patients with Grave

disease leads to muscle hypertrophy, diplopia, proptosis, and, if severe, compressive optic neuropathies.

Pathophysiology

1. The muscles most commonly affected are the inferior rectus and the medial rectus, in that order, resulting in diplopia.
2. The muscle becomes inelastic and stiff and restricts movement in the direction of its agonist.
3. Progressive proptosis occurs from extraocular muscle enlargement and hypertrophy of orbital fat.
4. Compressive optic neuropathy occurs from crowding of the optic nerve at the orbital apex.

Treatment

1. Persistent diplopia from thyroid eye disease is usually responsive to a combination of muscle recession operations and prism.
2. Surgery should be delayed until the active phase of the orbitopathy has passed.
3. IV steroid treatments may decrease the inflammation and reduce symptoms in some cases.
4. Radiation to the orbit is sometimes used in severe cases, but its efficacy remains in question and it may be complicated by postradiation side effects.
5. In the case of optic nerve injury, removal of a bony wall of the orbit can decompress the nerve and prevent further loss of vision.

Orbital Trauma

Background

Direct mechanical trauma to the orbit can result in a complex array of eye movement disorders, either by restricting extraocular muscles or injuring ocular motor nerves. The principles of management share many features.

Pathophysiology

1. It is in this group of entities that detailed CT imaging of the orbital walls and contents is indispensable because its ability to show bony abnormalities is superior to MRI.

2. One has to make decisions rapidly about the cause of ocular muscle dysfunction. As time passes, scarring becomes an issue that will complicate later repairs; thus, any problems such as entrapment of muscle in fractures and muscle disinsertions from the globe need to be dealt with surgically early on. At the same time, a remarkable amount of orbital deformity can be well tolerated.
3. Hemorrhage or inflammation of or around the affected muscle may develop later.

Prognosis

The prognosis depends entirely on the cause and degree of damage.

Diagnosis

This is usually straightforward given the history.

Treatment

1. When a final status has been reached, combinations of muscle surgery with appropriate prism fine-tuning can have as their goal at least some degree of single vision in the straight-ahead and downgaze positions.
   a. These are the most important positions for adults to have single vision and should be the first goal of all therapies.
   b. If this cannot be achieved, a patch, usually on the eye with the worse motility, may be the only solution.
2. Iatrogenic trauma to eye muscles is also common after cataract, retina, orbital, and sinus surgery. A large proportion of these seem to be restrictive myopathies, and appropriate recessions of the affected muscles are usually in order. Peribulbar anesthesia may cause trauma to the muscle cone and appears to be of highest incidence in the left eye reflecting a greater difficulty in precise injection by right-handed surgeons.

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Background

Diplopia and ptosis can be the presenting symptoms of ocular myasthenia gravis. The pattern of ocular misalignment can mimic any disorder affecting alignment of the eyes including pupil-sparing third nerve palsy, fourth nerve palsy, sixth nerve palsies, or INO. Double vision and ptosis fluctuate and are often worse at the end of the day or with fatigue.

Diagnosis

1. Myasthenia gravis is suspected when the exam is highly variable, with fluctuating ptosis, changing degrees of ocular misalignment, or fatigability of vertical gaze holding and lid position during sustained upward gaze for 1 minute.
2. Cogan's lid twitch, an extra "hop" of the eyelid when looking from downward gaze to primary gaze, suggests myasthenia gravis.
3. Rest or Ice-Pack test may temporarily improve the ptosis or eye movements.
4. Orbicularis oculi weakness is usually present.
5. Acetylcholine receptor antibody testing is only positive in 50% of patients with ocular myasthenia.
6. In patients with negative antibody testing, single fiber EMG may be useful to make the diagnosis, as it is more sensitive test to identify a neuromuscular junction disorder.

Prognosis

When ocular myasthenia gravis occurs in isolation (without systemic myasthenia), there is approximately a 50% chance that the patient will develop systemic symptoms within 2 years.

Treatment

1. Isolated ocular myasthenia may be observed without systemic treatment, using occlusion of one eye with either an eye patch or by frosting one lens of a pair of glasses.
2. In patients with continuous double vision or marked ptosis, systemic therapy with a cholinesterase inhibitor (e.g., pyridostigmine) or prednisone could be

considered. Cholinesterase inhibitors are less effective at treating double vision than symptoms of generalized myasthenia but are helpful in some patients. Prednisone used intermittently and at low doses may be effective to manage diplopia. Some observational studies have concluded that systemic steroid therapy may lower the conversion rate to systemic myasthenia gravis, but there have been no conclusive trials to date.

3. Fluctuation in the pattern and degree of ocular misalignment makes prisms or surgical therapeutic solutions ineffective.

Botulism

Background

Flaccid paralysis may be caused by the botulinum toxin, which is released by the bacterium *Clostridium botulinum* and may contaminate certain foods or bodily wounds. The toxin is usually preformed in food but is elaborated by bacteria in wound infection.

Pathophysiology

The botulinum toxins inhibit acetylcholine release at the presynaptic neuromuscular junction. Flaccid paralysis ensues.

Diagnosis

Botulism should be suspected in any patient with paralysis beginning in the ocular muscles and "descending" to the limbs and respiratory muscles, without sensory symptoms. The main features are nausea, vomiting, dysphagia, diplopia, dilated or fixed pupils, and an extremely dry mouth refractory to drinking fluids. Autonomic and respiratory weakness may develop. The toxin may be isolated in serum, stool, or recently consumed foods. Single-fiber electromyography can confirm localization to the neuromuscular junction.

Prognosis

Recovery occurs over 1 to 3 months. Survival is 90% to 95% with intensive care, but delayed treatment and older age predict a less favorable outcome.

Treatment

1. Rigorous supportive and respiratory care is the mainstay of treatment to keep the patient alive through the illness.
2. Trivalent A-B-E antitoxin can slow disease progression, although it will not speed reversal of active symptoms. Serum sickness occurs in a subset of patients.

DISORDERS OF THE OCULAR MOTOR NERVES

Third Cranial Nerve Palsies

Background

Third nerve palsies result in any combination of impaired adduction, elevation, or depression of the eye as well as dilation of the pupil and upper eyelid ptosis. The most common causes are microvascular/vasculopathic ("diabetic third nerve palsy"), tumor-related, and compression by aneurysm. Less commonly, third nerve palsy can be related to ischemia from GCA. Because of the possibility of aneurysm compression, an evaluation to determine the cause is more important with this nerve than with cranial nerves IV or VI.

Pathophysiology

1. The third cranial nerve arises in the dorsal midbrain. The nerve fascicle passes through the red nucleus and cerebral peduncle to exit into the interpeduncular cistern. It passes in close proximity to the posterior communicating artery before entering the cavernous sinus. It then passes along the lateral wall of the cavernous sinus before dividing into superior (innervating the levator muscle and superior rectus muscle) and inferior (innervating the medial rectus, inferior rectus, and iris sphincter muscle) divisions in the anterior cavernous sinus.
2. Parasympathetic fibers that constrict the pupil are located superficially in the nerve and tend to be involved early from compressive etiologies.
3. Third nerve palsies can be classified partial or complete; the term complete means that there is complete deficits of all movements attributable to the third nerve as well as complete ptosis of the eyelid. In a complete palsy,

sparing of the pupil is reassuring that an aneurysm is not the cause, although rare exceptions occur. A partial third nerve palsy that spares the pupil could progress to involve the pupil, so no reassurance should be taken from the lack of pupil involvement if the third nerve palsy is not complete.

4. Nuclear third nerve palsies cause bilateral ptosis (the central caudal nucleus innervates bilaterally) and may affect elevation of the contralateral eye (the superior rectus fibers decussate).

Prognosis

1. If tumor or aneurysm is the cause, the prognosis for recovery is poor, especially if the paralysis has been present for a long time and if aberrant regeneration has begun.
2. Pupil-sparing palsies in which the cause is believed to be vasculopathic have a better prognosis, although several months may pass before resolution.

Diagnosis

1. A third nerve palsy is considered with any combination of larger pupil, upper eyelid ptosis, impaired elevation, impaired depression, or impaired adduction. An acute partial third nerve palsy with or without pupil involvement is an emergency requiring imaging with MR angiogram or CT angiogram to rule out a posterior communicating artery aneurysm. Imaging with an MRI brain with and without contrast may also localize the injury to other sites including the brainstem, skull base, cavernous sinus, or superior orbital fissure/orbital apex.
2. ESR and CRP should be checked in patients older than 55 years to evaluate the possibility of GCA.
3. Ocular myasthenia could also be considered in the differential in cases that are painless and sparing the pupil.
4. In the setting of a normal MRI with and without contrast and MRA, a microvascular third nerve palsy is likely.

Treatment

1. Treating the underlying cause may result in improvement of the third nerve palsy.
2. Most microvascular third cranial nerve palsies will resolve spontaneously

within the first 2 to 3 months.

3. A well-established, complete third nerve palsy is challenging for correction by prism or surgery, and the patient's expectations should be modified accordingly.
4. Patching or a frosted lens may be used to treat double vision.
5. Surgeons often wait 6 months before considering surgery. The surgical repair of paralytic ocular muscle palsies for the most part depends on the presence of some tone in the weak muscle and another functioning muscle whose tone can be grafted to the tone of the dysfunctional muscle. In the case of third cranial nerve palsies, the only muscle available for transplantation is the superior oblique, which may have its insertion moved close to that of the superior rectus.
   a. In a complete third nerve palsy, adjustable sutures are advised. The ptosis that some patients consider cosmetically unacceptable can usually be helped by appropriate surgery, but the double vision now exposed remains a challenge. Reports of successful outcomes are at the case report level and not routinely expected.
   b. If the third nerve palsy is partial, there may be options for the combination of surgery and prism usage with a goal of at least single vision in straight-ahead and in straight-ahead down positions.
   c. Later on, if aberrant regeneration emerges, the situation becomes even more complex.

Fourth Cranial Nerve Palsies

Background

Fourth nerve (trochlear) palsies produce vertical and torsional binocular diplopia, although many patients only recognize the vertical component.

Pathophysiology

The fourth nerve nuclei are located in the dorsal lower midbrain adjacent to the medial longitudinal fasciculus (MLF) and periaqueductal gray. The fourth nerve fascicles decussate posteriorly passing through the anterior medullary vellum before exiting the brainstem. At this site, the fourth nerve, the smallest of the ocular motor nerves, is susceptible to concussive forces from the

tentorium with traumatic brain injury. The fourth nerves pass anteriorly along the tentorium into the cavernous sinus, positioned inferior to the third nerve. The fourth nerve passes through the superior orbital fissure to innervate the superior oblique muscle which acts primarily to depress the eye in the adducted position and intort the eye. Most acquired cases are caused by head trauma or are idiopathic (presumed microvascular). Congenital fourth nerve palsies are common and often unrecognized by the patient until double vision develops in adulthood.

Prognosis

There is often considerable or complete spontaneous recovery of idiopathic microvascular palsies in 2 to 3 months. The prognosis in traumatic cases is not as good; in these cases, the palsies may be bilateral because of trauma at the site of the anterior medullary vellum.

Diagnosis

1. The patient may report vertical double vision which is worse looking away from the side of the fourth nerve palsy and may also be worse when looking down (reading). In congenital cases, they may report a history of intermittent double vision months or years prior.
2. Impaired depression of the affected eye in the adducted position may be apparent, but ocular alignment testing with either alternate-cover technique or Maddox rod is often necessary. Park's three-step test can be used to diagnose an isolated fourth nerve palsy. A "positive test" is a hyperdeviation of the affected eye which is greater in contralateral gaze, downward gaze, and with head tilt toward the affected side.
3. When asked to look at a horizontal line, the patient with double vision from a fourth nerve palsy sees a horizontal line as two lines that come closer together at one end pointing like an arrow to the affected eye.
4. Careful inspection of the fundus may reveal excyclodeviation of the eye.
5. A patient with a bilateral fourth nerve palsy often prefers a chin-down position to a head tilt. This is because there is typically an exotropia that is improved in upgaze.
6. Injury to the trochlear nucleus or fascicles within the midbrain is rare and results in a contralateral fourth nerve palsy, which may be accompanied by an internuclear ophthalmoplegia (INO).

Treatment

1. Because of the length of the fourth nerve, recovery may take several months if the injury occurs in the proximal portion of the nerve.
2. The patient may have already discovered that tilting the head to the side opposite the weak muscle solves many of the double-vision problems.
   a. For many partial fourth nerve palsies, the major problem for the patient is vertical double vision in downgaze. A separate pair of reading glasses with a vertical prism may be all that is needed.
3. If the vertical deviation is beyond what can be solved by prism (usually when the total prism power would have to be in the teens), strabismus surgery with a superior oblique resection may be necessary.
4. Another approach is surgical weakening of the ipsilateral antagonist, the inferior oblique. This operation simultaneously addresses the torsional problem and the hyperdeviation. In long-standing fourth nerve palsies, this is not adequate to correct diplopia. Depending on the measurements in the various fields of gaze, surgery on the contralateral muscles that control vertical movements, the superior rectus, and inferior rectus and even the ipsilateral vertical muscles may be necessary.

Sixth Cranial Nerve Palsies

Background

Sixth nerve palsies result in binocular horizontal diplopia which is greater in gaze toward the affected side. Because of the straightforward nature of this problem, it provides an excellent example of the difference in therapy of a muscle weakness versus the therapy of a muscle paralysis.

Pathophysiology

The sixth nerve nuclei are located in the medial dorsal pons at the level of the middle cerebellar peduncle and facial colliculus. Lateral saccades are initiated by neurons in the paramedian pontine reticular formation (PPRF) that project to neurons in the sixth nerve nucleus. The sixth nerve fascicle courses anteriorly through the pontine tegmentum and basis pontis, passing through the medial lemniscus and pyramidal tracts before exiting the brainstem. The peripheral sixth nerve ascends along the clivus in the prepontine cistern,

piercing the dura at Dorello canal on the petrous apex. At this site, the sixth nerve enters the cavernous sinus, where it is located adjacent (inferolateral) to the ICA. The sixth nerve exits the cavernous sinus and enters the orbit at the superior orbital fissure. The long course of the nerve from the brainstem, along the skull base, through the cavernous sinus, and into the orbit make it susceptible to numerous types of injury:

1. Compression along the skull base (clivus or petrous apex), within the cavernous sinus (ICA aneurysm or meningioma), or superior orbital fissure.
2. Increased ICP exerting pressure on the sixth nerves which are fixed at Dorello canal.
3. Microvascular/ischemic.
4. Intramedullary lesions (e.g. stoke, demyelination, tumor) affecting the sixth nerve fascicle.

Injury to the sixth nerve nucleus results in an ipsilateral horizontal gaze palsy because of involvement of the sixth nerve nucleus neurons and the interneurons of the MLF projecting to the contralateral third nerve nucleus and controlling conjugate horizontal eye movements.

Prognosis

Prognosis depends on the cause, but in cases of ischemic mononeuropathy, maximum recovery can be expected in 2 to 3 months.

Diagnosis

1. Exam shows a limitation of abduction of the affected eye. In cases of minor paralysis, alternate-cover testing may be necessary to show an esodeviation (inward turning of the eye) that is greater in gaze toward the affected side.
2. If the lateral rectus muscle is completely paralyzed, the eye will abduct only as far as the midline. This is accomplished by the relaxation of the medial rectus plus the normal elastic forces within the orbit. Over time, the eye will not even reach the midline as a contracture of the medial rectus develops.
3. Restriction (mechanical limitation) of abduction by the medial rectus muscle as occurs with thyroid eye disease or infiltrative disease of the orbit (tumor) should be excluded with forced duction testing. During forced duction testing, the eye is anesthetized with eye drops and forceps or a cue tip is used to force the eye in the direction of limited movement. If the eye does

not move with forced duction, the cause is likely to be restrictive.

Treatment

1. If there is no evidence of active lateral rectus function, there is no procedure one can do on that muscle to make it function better. The only solution is to bring in muscle tone from other muscles, usually the superior and inferior rectus muscle of the same side, using a muscle-sharing procedure.
   a. The medial rectus muscle can be weakened by means of a recession and chemodenervation with Botox (5 units), but this alone will not be enough to straighten the eye. Some active tone must be supplied by a functioning muscle to counteract the tone in the medial rectus.
   b. The analysis can be complicated by medial rectus contraction even though there is some lateral rectus tone.
   c. To discover this situation, perform a test in which the eye is grasped by some device and active contraction against this hold by the lateral rectus with the eye in the adducted position is demonstrated.
2. If there is tone in the lateral rectus as evidenced by abduction beyond the midline or by active pulling on the forceps when the eye is adducted and the patient is asked to abduct, tightening by means of shortening the muscle but leaving its insertion on the globe unchanged will move the position of the eye laterally into alignment with the fellow eye.
   a. Experienced eye muscle surgeons have a rough idea of how much tightening to do along with weakening of the medial rectus by means of recessing the insertion on the globe in order to achieve alignment.
   b. The weakening of the medial rectus can be done in such a way that the muscle insertion location can be adjusted after the effect of the anesthetic is over (the adjustable suture technique).
3. Surgery is not usually considered until all hope of spontaneous recovery has passed, usually 6 months.
   a. As a sixth nerve palsy recovers, there is usually a period during which the patient has single vision in part of the horizontal field of gaze and diplopia in the rest. During this period, partial taping of the lens to block vision in the eye with the weak muscle may be useful.
   b. Most clinicians who deal with these problems encourage patients to exercise the paretic eye muscle. This is done by alternately patching one

eye on 1 day and the other eye on the next.

c. Again, as with the third and fourth, in milder cases, a prism in the glasses may suffice.

Seventh (Facial Motor) Cranial Nerve Palsies

Background

This condition is commonly seen in any center with an active neurologic service.

Pathophysiology

The seventh nerve is vulnerable to inflammation- (e.g., Lyme disease, sarcoidosis, Guillain–Barré syndrome), trauma-, and tumor-induced damage. Idiopathic seventh nerve palsies (i.e., Bell palsy) is felt to be caused by herpes simplex virus type 1 (HSV-1). If the lesion is proximal, weakness of the muscles of facial expression may be accompanied by hyperacusis (nerve to the stapedius) and changes in taste (chorda tympani). Lower motor neuron facial palsies include the frontalis muscle, but it is spared in upper motor neuron lesions because of bilateral cortical supranuclear control.

Prognosis

There are two overriding principles that govern the prognosis in this condition.

1. If the paralysis of motor function is not associated with any anesthesia of the cornea, it becomes much less likely that there will be any scarring and loss of vision.
2. The second principle is that surgical closure of the lids should be done sooner rather than later. A common mistake is to wait until advanced ulceration or even scarring has developed before performing a tarsorrhaphy. Attempts to rectify the problem late in the course often result in permanent damage to the eye.

Diagnosis

Seeing how well the patient can close the eye most easily makes diagnosis.

Treatment

1. In mild cases—in which there is some preservation of lid closure a good Bell reaction, and the ultimate prognosis for recovery is good—treatment with intense daytime lubrication (usually the most viscous drops one can obtain) or an ointment at night may be sufficient. Manual closure of the eye by the patient's finger frequently during the day duplicates the blink.
2. In general, patching of the eye is disappointing.
   a. The ability of an eye to open under even the firmest of patches is remarkable. Under such a circumstance, one not only has an open lid but also has the added possibility of the patch rubbing against the corneal surface.
   b. If the patient or a friend is skilled and motivated, the use of tape, frequently attended to and changed after thorough cleaning of the skin of the lids, can keep the lid closed and is especially useful overnight.
3. A surgical lid closure should be done early in most cases that are likely to last for more than a few weeks.
   a. Often, it is enough to bring the lateral lid margins together, allowing just enough of an aperture medially to allow inspection of the eye and especially the cornea. A common technique is to abrade the lid margins and bring them in apposition to one another with a heavy suture on a bolster. The suture can be removed in a couple of weeks. An advantage of this is that the tarsorrhaphy can be gradually taken down as the condition improves. A disadvantage is that the lid margin and lashes are often permanently scarred. Also this technique is less useful if the medial portions of the lids must also be closed. There is more pull at this level, and the skin bridge that forms between the lids can stretch out to create an unsightly band across the interpalpebral fissure.
   b. A stronger bond using less of the lid margin can be created by splitting the lid on the gray line (the most superficial portion of the orbicularis oculi) for just 1 or 2 mm of depth. The two raw surfaces from the upper and lower lids can be brought together with an absorbable mattress suture. This bond is very strong, uses only a small amount of lid margin to be effective, and can be used medially as well as laterally.
4. Another approach is the insertion of gold weights into the upper lid, the use of springs, and reinnervation of the facial musculature by nerve grafting. These techniques are best handled by an experienced plastic surgeon.

5. If the corneal exposure has evolved to the point of frank ulceration, a soft contact lens in addition to lid closure may be necessary as a temporary aid to healing. Even so, a scar is likely.
6. Timely medical treatment of the underlying process (e.g., prednisone when appropriate for idiopathic Bell palsy) can speed recovery and reduce risk to the cornea. In the case of Bell palsy, treatment within 48 hours appears to reduce the risk of permanent weakness.

Multiple Cranial Nerves

Background

In general, the occurrence of deficits in III, IV, V_1, V_2, sympathetic fibers, and VI reflect cavernous sinus disease. Orbital apex syndrome may include all of the aforementioned except V_2, with the addition of reduced visual acuity from damage to the optic nerve (Table 17-8).

Pathophysiology

Depending on the location, in most cases, something of considerable size or capable of spread is necessary to cause such an entity. Meningioma, metastatic tumor, granulomatous disease, and certain infections are the usual causes.

Table 17-8 Syndromes of Multiple Cranial Neuropathies

II	III	IV	V_1	V_2	V_3	VI	VII	Horner	Syndrome
√	√	√	√			√		√	Orbital apex
	√	√	√	√		√		√	Cavernous sinus
	√	√	√	√	√	√		√	Cavernous sinus/Meckel cave
			√	√	√	√			Gradenigo syndrome (Petrous apex)
						√	√		Pontine

Prognosis

1. The best resort is that resolution of the underlying disease will alleviate the problem.
2. The next best hope is that there will be enough balance between opposing

groups (III vs. VI) that the eye will be in an almost straight-ahead position barring complete ptosis of the upper lid, which makes the whole issue moot. In general, these situations are complex and different from case to case; thus, therapy may be unique for each case.

3. This is an entity that is often detected too late for effective therapy.

Mucormycosis

Pathophysiology

Mucormycosis is a fungus with broad nonseptate hyphae that branch at right angles. It causes vascular invasion and damage but can also infiltrate ocular and orbital structures directly. It is typically seen in diabetic patients or patients who are immunosuppressed.

Diagnosis

Patients typically have headache and facial pain and may have proptosis or orbital cellulitis. Visual disturbances may result from strabismus by way of orbital apex or cavernous sinus disease. Visual loss can occur through invasive optic neuropathies or retinal/choroidal infarcts.

Prognosis

This condition progresses rapidly and has a poor prognosis, especially once it is apparent that the infection has spread beyond the sinuses.

Treatment

1. Consultation with ear, nose, and throat (ENT) and infectious disease specialists will be necessary. Often, a biopsy, *not a culture*, of the nasal tissue will be necessary to confirm the diagnosis.
2. Amphotericin B with doses beginning at 0.25 mg/kg and advancing up to 1.0 mg/kg will be necessary combined with debridement, perhaps including exenteration will be necessary.

SUPRANUCLEAR DISORDERS OF EYE MOVEMENT

Internuclear Ophthalmoplegia

Background

Although there are exceptions, most of which are case reports, the two major causes of this condition are demyelination and stroke; myasthenia gravis can produce a pseudo-INO, mimicking this condition.

Pathophysiology

1. INO is caused by damage to the MLF, which contains interneuron fibers from the abducens nucleus that are activated during ipsilateral gaze. The fibers decussate and activate the contralateral medial rectus subnucleus to adduct the fellow eye and maintain conjugate horizontal gaze.
2. In contrast to a medial rectus weakness, these patients' eyes can often fuse the two images in the primary positions allowing them to look straight ahead without double vision and to read in downgaze successfully because convergence is usually spared.

Prognosis

Prognosis depends on etiology, but INO from both demyelination and stroke recover to some extent.

Diagnosis

1. Impaired adduction on the side of the INO is typically present and may be accompanied by abducting nystagmus of the contralateral eye.

   When the range of adduction is full, weakness of the medial rectus may only be evident as slowing of the adducting saccade.
2. Convergence may be spared, although lesions in close proximity to the third nerve nuclei may also cause impaired convergence.
3. Bilateral INO results in a "wall-eye" appearance with an exotropia.
4. Upbeat nystagmus may accompany bilateral INO caused by impairment of the otolith pathways involved in vertical gaze holding that pass through the MLF.

Treatment

1. The strabismus therapies that might be applicable to a weakness of an individual muscle do not always work in this condition.
   a. Prism added to glasses is often enough to bring the images into alignment in the important two directions of gaze mentioned earlier (straight ahead and straight down).
   b. It is not usually possible to achieve normalization of eye movement that will allow single vision in all fields.
   c. Reportedly, surgery designed to affect alignment in one field without disturbing alignment in others (often involving a posterior fixation suture) has been successful, but these are anecdotal reports. The most we have been able to accomplish is to reduce the amount of head turn needed for single vision.
2. If the INO does not recover, it is often best just to reassure the patient with the knowledge that they can usually attain single vision, although in a limited field of gaze with either prism or a head turn.

Skew Deviations

Background

Skew deviation is a vertical strabismus in all fields of gaze that results from asymmetric vestibular tone mediating vertical eye position.

Pathophysiology

Skew deviations represent damage to the vestibular (otolith) outputs that normally govern relative vertical eye position in response to body or head tilt. These pathways course from each utricle to the vertical ocular motor centers and decussate in the pons. Skew can therefore occur from injury along almost anywhere in the brainstem tegmentum. Cerebellar disease may also cause skew as cerebellar outputs modulate the vestibular pathway. Part of their course follows the MLF so that skew deviations often occur in conjunction with INOs. Skew deviation may be seen alone or as part of a pathologic ocular tilt reaction, in which case it is accompanied by ocular torsion and head tilt toward the lower eye. Although skew can theoretically result from unilateral eighth nerve injury, this association is rare enough that the presence of a skew can help predict a central lesion in cases of vertigo.

Prognosis

Prognosis depends on cause and is therefore uncertain.

Diagnosis

1. Skew deviations may be more apparent at the extremes of lateral gaze and are therefore easily confused with fourth nerve palsies and inferior oblique palsies.
2. In most cases, skew deviations do not match the pattern of fourth nerve palsies and the head turn may often be in the direction of the higher eye.
3. The magnitude of skew deviations may decrease when the patient is placed in a supine position because gravitational effects on the utricle are removed.

Treatment

1. A small amount of residual hypertropia that interferes with vision in the primary position can be dealt with by prism. Rarely is the deviation of such an angle that muscle surgery is needed.
2. In such cases, however, a resection (tightening) of the inferior rectus muscle of the hyperdeviating eye can be helpful.

Gaze Paralysis

Pathophysiology

1. Horizontal gaze paralysis can result from damage to the contralateral frontal eye fields or to the ipsilateral pons, affecting either the PPRF or the abducens nucleus, which together initiate gaze. Injury to the sixth nerve nucleus is often accompanied by facial weakness that is ipsilateral to the side of the gaze palsy because of involvement of the seventh nerve fascicle which courses around the sixth nerve nucleus in the facial colliculus (the facial colliculus syndrome).
2. Vertical gaze paralysis tends to occur from midbrain lesions that injure either the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which initiates vertical saccades, or the nucleus of Cajal, which helps control vertical and torsional gaze holding.
3. Lesions affecting the cortex or cortical–brainstem connections (supranuclear

gaze paresis) typically cause paralysis of voluntary gaze but spare vestibular ocular reflexes governed by intrinsic brainstem circuits. Such supranuclear gaze paresis may be observed in progressive supranuclear palsy and has also been observed following cardiac arrest.

4. Patients with gaze paralysis do not have double vision. Because they are able to reach the midline by relaxation of the gaze direction that is functional, they may need no therapy at all. Learning to turn the head may be enough, particularly for horizontal gaze palsies. Patients with vertical gaze palsies are more disabled because it interferes with reading and looking upward.

Prognosis

Prognosis depends on the potential for elimination of the cause and viability of the remaining nervous tissue.

Diagnosis

Localization may be clarified by comparing voluntary gaze with vestibular-ocular reflexes (VORs) to differentiate between contralateral frontal or ipsilateral PPRF lesions (intact VORs) from abducens nuclear lesions (VORs affected). Associated neurologic signs and MRI help confirm the site of injury and elucidate the cause. If consciousness is impaired, one may consider the possibility that tonic gaze to one side is secondary to a contralateral frontal lobe seizure, in which case EEG may be useful.

Treatment

1. For those unable to look down, placing base-down prisms of appropriate strength into both lenses of the reading glasses is helpful. In general, it is less important for adults to look up, but in the same way, base-up prisms in distance glasses can be helpful for those patients. For those unable to look to the right, prisms in both lenses with base to the left will be helpful and vice versa for those unable to look left.
2. What can be done with prism can also be attempted surgically. Appropriate resections or recessions of yoke muscles will move the two eyes so that the needed direction of gaze is more easily attainable. Unfortunately, surgery is less precise and less predictable than prisms. If the surgery is not perfectly balanced between the two eyes, double vision may be generated.

Combined Supranuclear Disorders

The practitioner should be aware of other rarer supranuclear disorders and their implications for localization and diagnosis.

One-and-a-Half Syndrome

This refers to an ipsilateral gaze palsy (caused by ipsilateral abducens/PPRF injury) combined with an INO during contralateral gaze (caused by disruption of the MLF fibers originating in the contralateral pons, next to the ipsilateral abducens nucleus). This syndrome is most common in brainstem stroke but also occurs in MS.

Wall-Eyed Bilateral Internuclear Ophthalmoplegia

Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) presents with INO in either direction, accompanied by an exotropia. It localizes to the midbrain near the distal (rostral) course of the bilateral MLF and may also affect fibers responsible for convergence.

NYSTAGMUS AND RELATED CONDITIONS

Background

With a tremendous number of possible causes and clinical situations, nystagmus is usually part of a complex neurologic disorder of the brainstem or related to medication or substance toxicity.

Pathophysiology

Nystagmus is defined as a rhythmic motion of the eyes where the first phase is a slow drift away from fixation. If the second phase is also slow, then it is called pendular nystagmus, but if the second phase is fast (a corrective saccade), the phrase “jerk nystagmus” is used. In general, acquired nystagmus disturbs vision in direct proportion to the amplitude of the movement, producing a perceived instability of vision (oscillopsia), which can reduce vision substantially. Most commonly, the central vestibular system is disturbed, but injury to the peripheral vestibular system, afferent visual pathway, gaze-holding pathways, and cortex can also produce nystagmus.

Infantile nystagmus (congenital nystagmus) is a horizontal, mostly pendular, nystagmus that is characterized by an accelerating slow phase and may result from early-onset afferent visual loss (congenital sensory nystagmus) or miswiring (congenital motor nystagmus). Congenital nystagmus remains horizontal in upward gaze, and there is often a "null point," which refers to a position of gaze in which the nystagmus is minimized. Patients with congenital nystagmus do not complain of oscillopsia because of the presence of foveation periods.

Prognosis

The prognosis is variable but generally poor for spontaneous recovery.

Diagnosis

The clinician should carefully observe the nystagmus to determine whether it is jerk or pendular. The direction (horizontal, vertical, torsional, or a combination thereof) should be determined, as should the amplitude and degree to which the nystagmus is conjugated (moving in the same direction in each eye) or dissociated, meaning that the amplitude is greater in one eye. To assist the differentiation between various forms of nystagmus, the phases may be studied with the electrooculogram (EOG) or magnetic search coil. Examination of the fundus with direct ophthalmoscopy may help detect subtle cases (various types of nystagmus, their features, and putative localization are discussed in Table 17-9).

Treatment

1. If the nystagmus is limited to one eye, it can be ignored or the patient can wear a patch. The same is true if the nystagmus is only troublesome in a field of gaze other than the primary ones, straight ahead, or straight down.
2. Periodic alternating nystagmus is a horizontal jerk nystagmus that displays a progressive decrease in frequency, followed by a pause and then nystagmus in the opposite direction. Typically, it results from damage to the nodulus and uvula of the cerebellum. It responds well to the γ-aminobutyric acid (GABA) agonist baclofen.
3. Nystagmus associated with familial episodic ataxia is responsive to acetazolamide.

4. Acquired pendular nystagmus is a frequent consequence of MS when demyelination affects the neural integrator, a network of neurons that helps keep the eye held in eccentric position when necessary (medial vestibular nucleus, flocculus). It may be responsive to gabapentin or the glutamate antagonist, memantine.
5. Oculomasticatory myorhythmia is a rare convergence–divergence nystagmus that is accompanied by chewing motions. It is pathognomonic for central nervous system (CNS) Whipple disease (infection of the nervous system with the bacterium, *Tropheryma whipplei*) and therefore requires treatment with IV ceftriaxone followed by chronic sulfamethoxazole and trimethoprim (Bactrim) therapy.

Table 17-9 Types, Features, and Likely Localization of Nystagmus

Nystagmus	Type	Direction	Special Features	Putative Localization
Early-Onset Nystagmus				
Infantile nystagmus	P	H	Null point Slow phase accelerates	Afferent pathways
Latent nystagmus	J	H	Fast phase directed away from the nonfixating eye	Nucleus of optic tract
Spasmus nutans	P	H	Unilateral shimmering nystagmus (~15 Hz), torticollis, and head nodding	Mimicked by optic pathway glioma (chiasm)
Nystagmus Associated with Lesions to the Visual System				
Monocular visual loss	P	V	Dissociated or monocular	Optic nerve
See-saw nystagmus	P, J	V, T	See-saw movements	Chiasm, midbrain–thalamus
Vestibular Nystagmus				
Peripheral vestibular nystagmus	J	H, TV, TH	Follow Alexander's law[a] Fixation inhibits	Labyrinth or eighth nerve

Central vestibular nystagmus	—	—	Pure directional Fixation does not inhibit	
Upbeat	J	V	—	MVN or midbrain
Downbeat	J	V	Accentuated laterally	Cervicomedullary junction
Torsional	J	T	—	Lateral medulla, rarely midbrain
Horizontal	J	H	—	Medial vestibular nucleus
Periodic alternating (cerebellum)	J	H	Changes direction after break	Uvula/nodulus nystagmus
Acquired Pendular Nystagmus				
With disorders of myelin	P	V, H, T	Disconjugate	Neural integrator
Oculomasticatory myorhythmia	P	CON/DIV	With chewing motions Only with Whipple disease	Nucleus reticularis tegmenti pontis
Oculopalatal tremor	P	V	With palatal tremor	Triangle of Mollaret
Nystagmus of Cortical Origin				
Ictal nystagmus	J, P	H	+/- Pupillary oscillations	Parieto-occipital lobe
Disruption of pursuit centers	J	H	Slow phase away from lesion	Parietal lobe

[a]Alexander's law states that the intensity of the nystagmus increases when gaze is in the direction of the fast phase.

P, pendular; H, horizontal; J, jerk; V, vertical; T, torsional; TV, torsional-vertical; TH, torsional-horizontal; MVN, medial vestibular nucleus; CON/DIV, convergence–divergence.

5. Congenital nystagmus treatments include prismatic therapy or surgical maneuvers to move the null point closer to primary gaze.

a. Prismatic therapy that forces the patient to position the eyes in the null point in order to look straight ahead is therefore a helpful and simple therapy.

b. Alternatively, a surgical procedure can be used to move the null point closer to primary gaze. These are variations on the so-called "Kestenbaum procedure." They can be applied to one or, more commonly, both eyes. The challenge again is to be so skilled or fortunate that things end up equal in the two eyes so that nystagmus is not replaced by diplopia.

7. Treatment with botulinum toxin (Botox) would be a good solution, and success has been reported, but the results are as often disappointing. The effect is temporary, but more troublesome is the tendency for Botox to spread to muscles one does not wish to weaken, with resultant complicated diplopia and even more troublesome, upper lid ptosis (see Table 17-10 for a summary of treatments for nystagmus).
8. One entity that can be responsive to therapy is neuromyotonia, which is a momentary contraction of an individual muscle.
   a. A common example is orbicularis myokymia in which individual fascicles of the orbicularis muscle contract for a moment. Patients with orbicularis myokymia should have their parotid glands palpated because tumors in this region can give this symptom. More commonly, however, it is a stress and fatigue symptom.
   b. Superior oblique myokymia is another common expression of neuromyotonia and has similar causes.
   c. Finally, one of the other extraocular muscles can be involved, particularly after its nerve has been irradiated.
   d. One consistent feature of myokymia and neuromyotonia is that the twitching is brought out by sustained use of the muscle such as in the case of the orbicularis squeezing the lids together. The second feature is that the muscle usually can be demonstrated to be a little deficient in its function.
   e. All three conditions are commonly responsive to gabapentin or carbamazepine.
   f. Combined surgical weakening of the superior oblique and inferior oblique muscles of an eye with superior oblique myokymia can be helpful in cases not responsive to drugs.

Table 17-10 Surgical and Medical Treatments of Nystagmus

Nystagmus	Treatment	Proposed Mechanism
Infantile nystagmus	Horizontal rectus muscle tenotomy	Null point approximation toward primary gaze
	Contact lenses	Decreased nystagmus through afferent feedback
	Surgery to create divergence	Patient must converge, which dampens IN

	Kestenbaum procedure: resection of horizontal recti	Null point approximation toward primary gaze
	Anderson procedure: recession of horizontal recti	Null point approximation toward primary gaze
	Prisms	Bring the null point into primary gaze
Periodic alternating nystagmus	Baclofen Large horizontal recti recession	GABA agonist Change in null position
Downbeat nystagmus	3,4-Diaminopyridine	Restores inhibition of upward drift by cerebellum through K^+ blockade
Acquired pendular nystagmus	Gabapentin Memantine	NMDA receptor inhibition Glutamate antagonism
	Servomechanical device	Prisms move to adjust the image in step with the nystagmus
Acquired nystagmus	Botulinum A injection	Weakening of muscles responsible for nystagmus
Latent nystagmus	Botulinum A injection	Avoidance of gaze that brings out LN
Oculopalatal tremor	Vertical rectus muscle disinsertion	Weakening of vertical movements

IN, infantile nystagmus; GABA, γ-aminobutyric acid; NMDA, *N*-methyl D-aspartase; LN, latent nystagmus.

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18 Toxic and Metabolic Disorders

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HEPATIC (PORTOSYSTEMIC) ENCEPHALOPATHY

Background

1. Hepatic encephalopathy describes the neurologic manifestations of liver failure.
2. The clinical categories of hepatic encephalopathy are:
   - **a.** Acute hepatic encephalopathy
   - **b.** Chronic recurrent hepatic encephalopathy
   - **c.** Chronic progressive hepatic encephalopathy
     - **1)** Wilson disease
     - **2)** Acquired non-wilsonian hepatocerebral degeneration

Pathophysiology

1. The sine qua non for the development of hepatic encephalopathy is shunting of blood from the portal circulation to the systemic circulation with inadequate detoxification by a normally functioning liver.
2. This may occur because of endogenous liver disease (e.g., hepatitis, cirrhosis), portosystemic shunts (intrahepatic or extrahepatic), or both.
3. Clinical and experimental evidence suggest multiple potential mechanisms underlying the neurologic effects of portosystemic shunting of blood of which the two best characterized are:
   - **a.** Imbalanced excitatory and inhibitory signaling through the γ-aminobutyric acid (GABA)-A receptor complex. Causes of dysfunctional regulation

include endogenous benzodiazepine-like substances incompletely metabolized by the liver, excess generation of neurosteroids, and other allosteric modulators of GABA signaling. Apart from changes in pharmacokinetics, there is benzodiazepine hypersensitivity in hepatic encephalopathy. The modest benefit of the benzodiazepine antagonist, flumazenil, may relate to this mechanism.

b. Neurotoxins not cleared by the liver of which ammonia is best characterized. Ammonia that is inadequately detoxified by the hepatic urea cycle reaches the brain where it is normally metabolized by the glutamate–glutamine system in astrocytes. When this system becomes saturated, ammonia reaches neurons where it is directly toxic, thereby producing the encephalopathy. The typical astrocytic changes seen in all forms of hepatic encephalopathy (Alzheimer type II gliosis) may be because of the upregulation of the glutamate–glutamine detoxification system in these cells. The upregulation results in diffuse cellular swelling and consequent increased intracranial pressure (ICP). Improvement of hepatic encephalopathy with lowering of the serum ammonia concentration is taken as evidence for the pathogenic role of ammonia.

Prognosis

1. Hepatic encephalopathy may be acute, recurrent, subacute, or chronic.
2. The prognosis depends on the underlying cause.

Diagnosis

1. The major clinical manifestations of hepatic encephalopathy are:
   a. Alteration of the level of consciousness including confusion with or without agitation (delirium), drowsiness, stupor, and coma.
   b. Movement disorders, the most frequent of which are asterixis, myoclonus, and tremor.
   c. Symptoms and signs of corticospinal tract disease are common (i.e., leg weakness, spasticity, increased tendon reflexes, and Babinski signs) and occasionally are the sole manifestation of hepatic encephalopathy ("hepatic paraplegia").
   d. Extrapyramidal symptoms and signs (i.e., rigidity, bradykinesia, and

dysarthria) are common, particularly in the chronic hepatocerebral degenerations.

2. Hepatic encephalopathy should be considered in a patient with unexplained encephalopathy who might have liver disease, portosystemic shunting, or both. The diagnosis is more likely when:
   a. The blood ammonia is elevated. Arterial ammonia may be slightly better correlated with the clinical state than venous ammonia, but both are unreliable. Hepatic encephalopathy is a clinical diagnosis.
   b. There is high-intensity signal in the basal ganglia (particularly the putamen and globus pallidus) on T1-weighted magnetic resonance imaging (MRI). This signal may represent deposition of paramagnetic substances (e.g., manganese and copper), although the reason for this deposition is unknown.
   c. High-amplitude triphasic sharp waves are seen on the electroencephalogram (EEG). Although not specific for hepatic encephalopathy, the finding suggests a metabolic cause.

Treatment

1. For acute episode of encephalopathy, thorough search for provoking events particularly focusing on infections (e.g., spontaneous bacterial peritonitis) and gastrointestinal (GI) bleeding.
2. Reduce sedating drugs to a minimum.
3. Correct fluid and electrolyte disturbances.
4. Reduce protein load by
   a. Prescribing a low-protein diet but providing enough calories to prevent proteolysis. Each liter of 10% dextrose in water provides 400 kcal. If nasogastric feeding is possible, 10% dextrose in water and lipids may be given to provide about 25 kcal/kg/d. The diet should be supplemented with vitamins (folate 1 mg/d, vitamin K 10 mg/d, and multivitamins).
   b. Administering cathartics to help eliminate whatever protein remains in the bowel. Magnesium citrate 20 mL or sorbitol 50 g in 200 mL water may be administered via nasogastric tube or by mouth (p.o.).
   c. Administering lactulose (a synthetic disaccharide that cannot be digested in the upper GI tract) will allow large-bowel bacteria to metabolize the sugar, thus producing hydrogen ions that convert ammonia (NH_3) to

ammonium (NH_4). Lactulose is not neurotoxic and is eliminated in the stool. Lactulose 30 to 50 mL (0.65 g/mL) may be administered p.o., by nasogastric tube, or by retention enema three times a day (t.i.d.).

5. For persistent encephalopathy, add rifaximin 550 mg twice daily or 400 mg t.i.d. to reduce ammonia production by gut flora.
6. Flumazenil (Romazicon) (0.2 mg/min intravenous [IV]) may have a temporary beneficial effect on encephalopathy lasting few hours.
7. Hepatic transplantation may be lifesaving for patients with hepatic failure and reverses most of the neurologic manifestations of hepatic encephalopathy. In general, the longer the encephalopathy has been present, the lower the chance that it will be improved with liver transplantation.

RENAL ENCEPHALOPATHY

Background

1. Describes encephalopathy in association with renal insufficiency or initiation of dialysis.
2. Clinical categories are:
   a. Uremic encephalopathy
   b. Dialysis disequilibrium syndrome

Pathophysiology

1. In uremia, toxins (e.g., guanidine compounds, myo-inositol, polyamines, and others) accumulate impairing cerebral function.
2. Secondary hyperparathyroidism and resultant hypercalcemia.
3. Electrolyte imbalance from renal regulatory disturbance.
4. Severe hypertension and associated encephalopathy including clinicoradiologic syndrome of posterior reversible encephalopathy syndrome (PRES).
5. Dialysis disequilibrium syndrome caused by:
   a. Cerebral edema secondary to rapid lowering of blood osmolality following initiation of dialysis.
   b. Rapid correction of hyponatremia with resulting demyelination of pontine

and extrapontine areas (generally called central pontine myelinolysis or CPM).

Prognosis

1. Untreated, uremia progresses to generalized seizures, coma, and ultimately death. With dialysis, there is usually a time lag of a few days between start of dialysis and improvement of cognition.
2. Dialysis disequilibrium syndrome is generally self-limited. Rarely, it can progress to coma and death.

Diagnosis

1. Clinical manifestations of uremia
   - **a.** Initial mild difficulty with concentration progressing to apparent confusion often with neuropsychiatric changes such as irritability or depression. Severe uremia leads to decreased level of consciousness and eventual coma. Acute kidney injury causes more pronounced cognitive changes compared to chronic kidney injury.
   - **b.** Movement disorders such as asterixis and spontaneous myoclonic jerks. These movements disappear with unconsciousness.
   - **c.** Generalized convulsions.
   - **d.** Uremia is infrequent with glomerular filtration fraction above 10% of normal. A reliable correlation between serum creatinine concentration or blood urea nitrogen (BUN) level and encephalopathy does not exist. At present, there is no clear biomarker of uremic encephalopathy.
   - **e.** EEG usually shows nonspecific changes such as slowing. During convulsions, ictal changes seen in EEG.
   - **f.** Imaging including MRI does not generally show specific changes. PRES from malignant hypertension associated with characteristic subcortical T2 hyperintense lesions on MRI.
2. Clinical features of dialysis disequilibrium syndrome
   - **a.** Spectrum of symptoms ranging from mild fatigue, headache, and nausea to convulsions, coma, and death. Patients at risk include those with very elevated blood urea concentration in chronic kidney disease subjected to rapid correction in initial dialysis session.

b. EEG typically shows nonspecific signs of encephalopathy.
c. MRI may show demyelination in pontine and extrapontine regions in CPM.

Treatment

1. Gentle correction of electrolyte abnormalities particularly hyponatremia and hypercalcemia.
2. In cases of PRES, gentle lowering of blood pressure and treatment of seizure clusters.
3. If encephalopathy persists after treatment of aforementioned factors, uremic encephalopathy is an indication for starting dialysis.
4. In patients starting hemodialysis with chronically high blood urea, dialysis time is generally decreased initially in combination with reduced blood flow rate. Decrease in serum osmolality can be minimized by using a high-osmolality dialysate such as high-glucose dialysate, although done uncommonly in practice.
5. For concern of increased ICP following dialysis, IV mannitol can be used to increase serum osmolality and decrease cerebral edema.

HYPEROSMOLALITY AND HYPERTONICITY

Background

1. Hyperosmolality is defined as serum osmolality greater than 325 mOsm/L.
2. Osmolality may be measured directly or estimated using the formula:

$$2(Na^+ + K^+) + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}$$

3. The difference between measured and calculated osmolality is the osmolal gap (normally <10).
4. Effective osmolality is called tonicity. Substances that cross cell membranes freely (e.g., urea) may raise osmolality but have little or no effect on tonicity.

Pathophysiology

1. As can readily be appreciated from the determinants of osmolality, in most clinical settings, hyperosmolality is caused by hypernatremia, hyperglycemia, azotemia, or the iatrogenic addition of extrinsic osmoles (e.g., alcohols, mannitol, glycerol).
2. *Hypernatremia* is defined as serum sodium (Na) concentration greater than 145 mEq/L. In all tissues other than the nervous system, hypernatremia leads to attraction of intracellular water, leading to cell shrinkage. The nervous system is unique in that it is capable of generating solute (e.g., idiogenic osmoles) such as glutamine and taurine to minimize cell shrinkage. When hypernatremia is prolonged or unusually severe (serum Na over 160 mEq/L), these mechanisms fail, leading to encephalopathy. When hypernatremia occurs, thirst increases and antidiuretic hormone (ADH) is released, leading to renal retention of pure water and thereby lowering serum Na toward normal. Hypernatremia is thus caused by a defect in thirst, inadequate release or effect of ADH, loss of hypotonic fluid, retention of Na, or inadequate access to water (especially in elderly and infants).
3. *Hyperglycemia* is nearly always caused by diabetes mellitus, caused either by inadequate insulin production or by end-organ insulin resistance. In neurologic patients, this is often precipitated by the therapeutic use of glucocorticoids and some antiepileptic drugs such as phenytoin.
4. *Azotemia* is caused by renal failure or inadequate renal perfusion (prerenal azotemia).
5. The ingestion of alcohols (e.g., ethanol, methanol) contributes to the osmolal gap, thereby increasing osmolality and tonicity.
6. *Hyperosmolar* agents such as mannitol or glycerol are often used in neurologic patients and may result in hyperosmolality.
7. Pertinent to almost all metabolic encephalopathies is the rate of change of the metabolite, slower elevations or depressions being better tolerated than acute ones.

Prognosis

1. Hyperosmolality usually produces a generalized encephalopathy without localizing or lateralizing features, but an underlying focal lesion (e.g., stroke, multiple sclerosis, neoplasm) may become symptomatic under the metabolic stress of a hyperosmolar state.

2. The prognosis of the hyperosmolality itself is good, but the long-term outlook depends on the cause.
3. For unknown reasons, hyperosmolality alone, particularly when caused by hyperglycemia, may lead to continuous partial seizures, even when careful studies fail to uncover any underlying lesion. These seizures generally respond promptly to lowering of the serum glucose.

Diagnosis

1. The diagnosis is made by calculating the serum osmolality using the formula $2(Na^+ + K^+)$ + glucose/18 + BUN/2.8 and by directly measuring osmolality using freezing point depression.
2. The difference between the measured and calculated osmolality is termed the "osmolal gap," which should be less than 10 mOsm/L in normal circumstances.
3. An increased osmolal gap reflects the presence of solute, such as alcohols, ethylene glycol, or therapeutic substances, such as mannitol, sorbitol, or glycerol.

Treatment

1. Calculate the water losses using the following approach:
   a. Calculate the normal total body water (NTBW) as follows:
   Body weight (in kilogram) × 0.6 = NTBW
   b. Calculate the total body Na (Tris-buffered saline [TBS]) as follows:
   NTBW × 140 mEq/L = TBS
   c. Calculate the patient's body water (PBW) as follows:
   TBS/patient's serum Na = PBW
   d. Calculate the patient's water deficit (PWD) as follows:
   NTBW − PBW = PWD
2. Replace the water losses so that the serum Na falls no faster than 2 mEq/L/h (too rapid correction may result in brain edema) using:
   a. Normal saline in hypovolemic patients (i.e., those with azotemia and/or hypotension) to restore plasma volume followed by repletion of free water deficit.
   b. Water in hypervolemic patients.

c. Renal dialysis if there is acute or chronic renal failure.

3. Insulin is administered (with frequent blood sugar testing) if there is hyperglycemia.
   a. Intramuscular (IM) and subcutaneous insulin may be unpredictably absorbed, particularly in hypovolemic patients, because of poor tissue perfusion.
   b. Rapid-acting insulin 0.1 U/kg by IV push followed by 0.05 U/kg/h by continuous IV infusion is usually sufficient to reduce the blood sugar adequately and safely.

HYPONATREMIA

Background

Hyponatremia is defined as a serum Na of less than 135 mEq/L.

Pathophysiology

1. Hyponatremia may be isotonic (e.g., infusion of salt-poor solutions, hyperlipidemia, or hyperproteinemia), hypertonic (e.g., hyperglycemia, mannitol), or hypotonic (impairment of free water excretion or an enormous free water load, as in psychogenic water drinking).
2. Tonicity (effective osmolality) is measured in the clinical laboratory. The difference between the calculated and measured osmolarity (the osmolal gap) should not exceed 10 mOsm/L (see section on treatment of hypernatremia earlier).

Prognosis

1. The prognosis of hyponatremia depends on the rate and magnitude of the fall in serum Na and its cause.
2. In acute hyponatremia (a few hours or less), seizures and severe cerebral edema may be rapidly life threatening at serum Na levels as high as 125 mEq/L, whereas patients may tolerate very low serum Na levels (even below 110 mEq/L) if the process develops slowly. Rapid correction of

acute hyponatremia may be lifesaving, whereas rapid correction of chronic hyponatremia may be dangerous. Nervous system cells compensate for chronic hyponatremia by excreting solute to avoid water retention. If upon this substrate, serum Na rapidly rises, brain cells can rapidly shrink, causing osmotic demyelination (formerly known as central and extra pontine myelinolysis).

3. The cause of hypotonic hyponatremia is best determined by dividing all possibilities into three categories on the basis of the clinical estimate of the state of the extracellular fluid space. Blood pressure and heart rate with orthostatic measurements, the degree of engorgement of the neck veins, and the presence or absence of the third heart sound (S3) allow all patients with hypotonic hyponatremia to be categorized into three types:
   a. Hypovolemic (reduced effective blood volume): hypotension, tachycardia with orthostatic worsening
   b. Hypervolemic (edematous states)
   c. Isovolemic (retention of free water)

Diagnosis

1. The diagnosis is made by measurements of the serum Na and serum osmolality, followed by an assessment of extracellular volume.
2. The major diagnoses in each category are:
   a. Hypertonic hyponatremia
      1) Alcohols
      2) Sugars
   b. Isotonic hyponatremia (artifactual or pseudohyponatremia)
      1) Lipids
      2) Proteins
   c. Hypotonic hyponatremia
      1) Hypovolemic
         a) GI Na losses
         b) Hemorrhage
         c) Renal salt wasting (including cerebral salt wasting syndrome)
         d) Diuretic excess
         e) Adrenal insufficiency
      2) Hypervolemic

a) Congestive heart failure
b) Hepatic failure with ascites
c) Nephrotic syndrome

3) Isovolemic hyponatremia
a) Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
b) Psychogenic water drinking
c) Acute and chronic renal failure
d) Resetting of the osmostat (the sick cell syndrome)

Treatment

1. Hypertonic hyponatremia
a. Treat the underlying disorder (e.g., hyperglycemia, exposure to mannitol).
b. Replace only estimated salt losses.

2. Isotonic hyponatremia
a. No fluid treatment for pseudohyponatremia disorders (e.g., hyperlipidemia, hyperproteinemia)
b. Reduce Na-poor solutions if possible (dextrose, mannitol).

3. Hypotonic hyponatremia
a. Hypovolemic hypotonic hyponatremia
1) Replace volume with isotonic saline.
2) Treat underlying renal, adrenal, gastroenterologic conditions.
3) Recognize and treat causes of cerebral salt wasting (e.g., intracerebral or subarachnoid hemorrhage).

b. Hypervolemic hypotonic hyponatremia
1) Free water restriction
2) Treat underlying edematous disorders (congestive heart failure, liver failure, nephrotic syndrome).

c. Isovolemic hypotonic hyponatremia
1) Chronic, slowly developing
a) Water restriction
b) Antagonize ADH with lithium, demeclocycline, or conivaptan if water restriction fails.

2) Acute (less than 48 hours), rapidly developing

a) Three percent saline (containing 513 mEq/L of Na) 300 to 500 mL IV over 1 hour will correct at about 1 mEq/L/h for 4 hours and then slow the correction rate to less than 10 mEq/L per 24 hours.
b) Free water restriction or normal (0.9%) saline

HYPOKALEMIA

Background

Hypokalemia is defined as a serum potassium level below 3.5 mEq/L.

Pathophysiology

1. Serum potassium may be low because of abnormal intracellular or extracellular potassium balance or because of excessive potassium losses (renal or extrarenal).
2. Hypokalemia because of excessive cellular potassium uptake may be caused by:
   a. Insulin
   b. Catecholamines
   c. β_2-Adrenergic agonists
   d. Hypokalemic periodic paralysis
   e. Alkalosis
   f. Hypothermia
3. Extrarenal potassium loss (urine K^+ less than 20 mEq/d) may be caused by:
   a. Diarrhea (low serum bicarbonate)
   b. Cathartics; sweating (normal serum bicarbonate)
   c. Vomiting (high serum bicarbonate)
4. Renal potassium loss (urine K^+ more than 20 mEq/d) may be caused by:
   a. Hyperreninemia
   b. Hyperaldosteronism
   c. Renal tubular acidosis
   d. Diuretic use
   e. Hypomagnesemia

f. Excessive glycyrrhizic acid (licorice) intake

Prognosis

Severe hypokalemia (serum potassium less than 1.5 mEq/L) may be life threatening because of cardiac arrhythmia and severe muscle weakness.

Diagnosis

1. The diagnosis of hypokalemia is made by serum potassium measurement.
2. Urinary potassium measurement may help determine whether the potassium loss is renal or extrarenal, but it should be borne in mind that such measurements are only valid in the face of a normal dietary and urinary Na because Na restriction may result in some masking of renal potassium wastage.
3. The measured serum Na bicarbonate, plasma renin, plasma aldosterone, urinary chloride levels, and blood pressure may also help in the differential diagnosis of the cause of hypokalemia.
4. The electrocardiogram (ECG) usually shows a characteristic pattern consisting of U waves and a lengthened repolarization time (Q–U interval), a circumstance that predisposes to dangerous arrhythmias.

Treatment

1. Correct potassium balance problems, if possible (e.g., reduce β_2-adrenergic agonists).
2. Dietary Na restriction (less than 80 mEq/d) will reduce renal potassium losses.
3. Give oral potassium chloride (KCl) for mild hypokalemia (30 to 35 mEq/d).
4. For moderate (1.5 to 3.0 mEq/L) or severe (less than 1.5 mEq/L) hypokalemia, especially with cardiac arrhythmias and/or severe muscle weakness, IV KCl may be administered at the rate of 15 mEq over 15 minutes with continuous cardiac monitoring, aiming for a 1-mEq/L increase in the serum potassium. Thereafter, the rate should be slowed to less than 5 mEq/h of a solution of KCl no more concentrated than 60 mEq/L.
5. Hypokalemia is often associated with hypomagnesemia. Repleting magnesium may help with repletion of apparently treatment resistant

hypokalemia.

HYPERKALEMIA

Background

Hyperkalemia is defined as a serum potassium concentration of greater than 5 mEq/L.

Pathophysiology

1. Hyperkalemia may be seen in circumstances that may or may not cause an excess of whole-body potassium.
2. The common causes of hyperkalemia without an excess of potassium are:
   - **a.** Muscle injury (e.g., trauma, persistent seizures, muscle infarction)
   - **b.** β_2-Adrenergic antagonists (e.g., propranolol)
   - **c.** Insulin resistance
   - **d.** Metabolic acidosis
   - **e.** Digitalis poisoning
   - **f.** Depolarizing muscle relaxants (e.g., succinylcholine)
   - **g.** Hyperkalemic periodic paralysis (muscle Na channel mutation)
3. Common causes of hyperkalemia caused by whole-body potassium excess include:
   - **a.** Addison disease
   - **b.** Aldosterone deficiency or antagonism (e.g., hyporeninemia; angiotensin-converting enzyme [ACE] inhibitor therapy; nonsteroidal anti-inflammatory drugs [NSAIDs]; heparin)
   - **c.** Aldosterone resistance (e.g., renal failure, renal tubular disorders, potassium-sparing diuretics)

Prognosis

1. The prognosis of hyperkalemia depends on its effects on the ECG and muscle membranes.
2. The first sign of hyperkalemia is usually peaking of the T wave of the ECG,

which usually occurs with a potassium level of about 6.0 mEq/L. As the potassium rises, the QRS complex widens, followed by reduction in its amplitude and then disappearance of the T wave.

3. Muscle weakness usually develops when the potassium is greater than 8 mEq/L.

Diagnosis

1. Hyperkalemia is suspected when the characteristic ECG pattern is seen, particularly when combined with weakness and sometimes, with paresthesias.
2. The diagnosis is confirmed with measurement of the serum potassium.

Treatment

1. If hyperkalemia is considered life threatening because it is producing ECG changes and/or severe muscle weakness, one should treat by protecting the heart against life-threatening arrhythmias, promoting redistribution of potassium into cells, and enhancing potassium removal.
2. Cardiac protection: calcium gluconate 10% solution, 20 mL by rapid IV infusion
3. Redistribution into cells
   - **a.** Glucose 50 g/h IV
   - **b.** Insulin 5 units IV push every 15 minutes
   - **c.** Albuterol 10 to 20 mg by inhaler
4. Enhance removal of potassium
   - **a.** Na polystyrene sulfonate (Kayexalate) 15 to 60 g with sorbitol p.o. or 50 to 100 g with retention enema
   - **b.** Hemodialysis
   - **c.** Loop diuretics
     - **1)** Furosemide 40 to 240 mg IV over 30 minutes
     - **2)** Ethacrynic acid 50 to 100 mg IV over 30 minutes
     - **3)** Bumetanide 1 to 8 mg IV over 30 minutes

HYPERCALCEMIA

Background

1. Neurologic syndromes appear with serum concentrations of calcium above 12 mg/dL if serum albumin is normal. With low serum albumin, ionized calcium is higher and neurologic manifestations appear at lower electrolyte levels.
2. Anorexia, constipation, nausea, fatigue, and headache are early features. At higher levels of calcium, confusion, coma, rigidity, and myoclonus occur. Convulsions are rare.

Pathophysiology

In younger individuals, the most common cause is hyperparathyroidism and in older persons, it is bone tumors including widespread metastases and multiple myeloma. Excess intake of vitamin D, sarcoidosis, thiazide diuretic use, Paget disease, Addison disease, and prolonged immobilization are less frequent causes of hypercalcemia.

Prognosis

All features are reversible unless there has been respiratory arrest.

Diagnosis

1. Determination of serum concentrations of calcium and albumin is required.
2. Parathyroid hormone levels and evaluation for the earlier underlying diseases (bone imaging, chest x-ray, serum protein electrophoresis immunoelectrophoresis) are required if there is no apparent explanation for the syndrome.
3. The QT interval is often shortened.

Treatment

1. Hydration with normal saline at high rates of infusion is the primary treatment. Four liters of IV fluids per 24 hours is appropriate if there is no congestive heart failure.
2. After adequate hydration, saline diuresis with furosemide can control mild hypercalcemia.

3. For severe symptoms with Ca^{++} level over 12 mg/dL, calcitonin is given, 4 to 8 U/kg subcutaneously every 6 to 12 hours. This is rapidly effective.
4. Pamidronate is more slow acting (3 to 5 days) but with prolonged effect. Doses range from 30 to 60 mg for calcium levels of 12 to 14 mg/dL to 90 mg for calcium levels over 16 mg/dL. The drug is infused slowly, over about 3 hours, in 300 mL normal saline.

VITAMIN DEFICIENCY, DEPENDENCY, AND TOXICITY

Vitamin A

Background

1. Vitamin A deficiency is an important cause of blindness in large parts of the world but is rare in economically developed countries.
2. Vitamin A intoxication is seen in people who engage in megavitamin therapy or who have ingested large amounts of animal tissue that concentrates vitamin A (e.g., bear liver).

Pathophysiology

In many developing countries, general malnutrition is the major cause of vitamin A deficiency, whereas in developed countries, it is usually related to malabsorption or an unconventional diet.

Prognosis

1. If treated early, the neurologic manifestations are usually completely reversible.
2. Once blindness has occurred, little can be done to reverse the visual loss.

Diagnosis

1. Night blindness and dry eyes are probably the earliest symptoms of vitamin A deficiency.
2. Dry pruritic skin is also an early symptom of this deficiency.

3. Hypervitaminosis A may cause the syndrome of pseudotumor cerebri.

Treatment

1. Vitamin A 1,000 units daily for 6 months should be given and a normal diet should be restored.
2. Vitamin A up to 100,000 units daily for 6 months with restoration of a normal diet may be needed for moderate or advanced symptoms.
3. Long-term use of vitamin A is not advisable because it may produce hypercoagulable state with consequent increased ICP (pseudotumor cerebri) possibly caused by cerebral venous thrombosis. Treatment for this consists of discontinuation of vitamin A.

Vitamin B_1 (Thiamine) Deficiency

Background

1. Vitamin B_1 (thiamine) deficiency occurs in parts of the world where polished rice is a major dietary staple or in people who are malnourished for any reason.
2. In developed countries, it is strongly linked to alcoholism and is increasingly found in malnourished, chronically ill patients or following gastric bypass surgery.

Pathophysiology

Thiamine is the coenzyme in thiamine pyrophosphate catalysis of decarboxylation of pyruvic acid and α-ketoglutaric acid.

Prognosis

Treatment of Wernicke encephalopathy (the central nervous system [CNS] disease caused by thiamine deficiency) is usually quite successful, but the longer treatment is delayed, the greater the probability of irreversible brain disease (see later section).

Diagnosis

1. Thiamine deficiency should be assumed to be present in all malnourished people including, but not limited to, those with alcoholism.

2. The full triad of Wernicke encephalopathy (i.e., mental change, ataxia, and oculomotor findings) is present in only a minority of those people later found to have Wernicke encephalopathy by pathologic study. The most frequent symptom is cognitive change, which varies from mild mental slowness to psychosis to disorientation to coma. The other typical findings of ophthalmoplegia and ataxia are present in a third or fewer. There can also be atypical findings such as autonomic dysfunction, seizures, and hearing loss.
3. Measurement of 24-hour urine thiamine excretion is available, and red blood cell transketolase may be measured.
4. As confirmation of the diagnosis, lesions characteristic of Wernicke encephalopathy (i.e., small mammillary bodies and/or hypothalamic peri-third ventricular necrosis) may be seen on MRI.

Treatment

1. Thiamine 100 mg by rapid IV infusion followed by
2. Thiamine 25 mg daily for several months and restoration of a normal diet

Vitamin B_2 (Riboflavin) Deficiency

Background

Riboflavin deficiency is caused by general malnutrition or malabsorption.

Pathophysiology

Riboflavin is a coenzyme in the flavoprotein enzyme system.

Prognosis

Treatment is usually successful unless the disease is far advanced.

Diagnosis

1. The clinical syndrome of cheilosis, angular stomatitis, visual loss, night blindness, glossitis, and burning feet in a susceptible person suggests the diagnosis.
2. Twenty-four-hour urinary riboflavin excretion measurements are available (less than 50 μg per 24 hours indicates the deficiency) but are rarely used

except in problematic diagnostic dilemmas.

Treatment

1. Riboflavin 5 mg p.o. t.i.d.
2. Vitamin A replacement may help in relieving riboflavin-induced ocular symptoms (see section on Treatment of Vitamin A).
3. Restoration of a normal diet

Niacin (Nicotinic Acid, Nicotinamide, B_3) Deficiency

Background

Niacin deficiency (pellagra) is usually associated with general malnutrition and often with alcoholism.

Pathophysiology

Niacin is the coenzyme for nicotinamide dinucleotide codehydrogenase for the metabolism of alcohol, lactate, and L-hydroxybutyrate.

Prognosis

Untreated pellagra is lethal, but if recognized during life, it will usually respond favorably to therapy.

Diagnosis

1. The characteristic triad of dermatitis (sun sensitivity with scaling eruption followed by hyperpigmentation), diarrhea, and mental symptoms (usually a disorder of attention and/or mood followed by confusion, drowsiness, stupor, and coma) suggests the diagnosis in the setting of malnutrition.
2. The diagnosis can be confirmed with a 24-hour urinary niacin excretion of less than 3 mg per 24 hours.

Treatment

1. Niacin or nicotinamide 50 mg p.o. 10 times daily for 3 weeks
2. In patients unable to take oral feedings, nicotinamide may be given IV 100

mg/d for 5 to 7 days.

3. Resumption of a normal diet is important for long-term recovery.
4. If pyridoxine deficiency is also deemed to be present (e.g., isoniazid therapy), vitamin B_6 (pyridoxine) must also be replaced because it is required for the normal conversion of tryptophan to niacin.

Vitamin B_6 (Pyridoxine) Deficiency, Dependency, and Toxicity

Background

1. Pyridoxine deficiency is rarely seen in developed countries except in people who are taking isoniazid, an antituberculosis drug that is an antagonist of pyridoxine.
2. Cycloserine, hydralazine, and penicillamine also may lead to pyridoxine deficiency.
3. Pyridoxine toxicity is seen in people who take more than the recommended daily allowance of 2 mg because of perceived health benefits of megavitamin therapy.

Pathophysiology

Pyridoxine is a cofactor in the conversion of tryptophan to 5-hydroxytryptophan and the conversion of homocysteine to cystathionine.

Prognosis

Treatment usually results in complete resolution of the complaints.

Diagnosis

1. Pyridoxine deficiency causes a generalized sensory and motor neuropathy.
2. Pyridoxine dependency is a rare autosomal recessive condition that leads to neonatal seizures.
3. Pyridoxine overuse also causes a peripheral neuropathy:
   a. Long-term low-dose (about 50 mg/d) exposure to pyridoxine leads to a small-fiber neuropathy.
   b. Shorter exposure to very high doses (over 100 mg/d) may produce a

primary sensory neuronopathy that is less likely to improve with cessation of exposure to the vitamin.

Treatment

1. For pyridoxine deficiency caused by:
   a. Malnutrition: 50 mg/d p.o. for several weeks followed by 2 mg/d and resumption of a normal diet
   b. Pyridoxine antagonists: 50 mg/d *only* while taking the antagonist
2. For pyridoxine dependency: 10 mg by rapid IV infusion to terminate neonatal seizures and then 75 mg/d for life
3. Pyridoxine toxicity: Discontinue pyridoxine supplementation.

Vitamin B_{12} (Cobalamin) Deficiency

Background

1. Vitamin B_{12} deficiency may result from inadequate dietary intake, but this is infrequent because the daily requirement is small (2 μg/d) and the body stores are high (4 mg or about a 7-year supply).
2. Vegans who assiduously avoid animal protein may become cobalamin-deficient, but this process requires many years.
3. Normal salivary amylase is required to separate cobalamin from food. In rare circumstances (e.g., Sjögren syndrome), salivary amylase deficiency may cause cobalamin deficiency.
4. More commonly, cobalamin deficiency is caused by failure to mobilize vitamin B_{12} from the GI tract because of insufficient intrinsic factor, most often caused by autoimmune gastritis (pernicious anemia).
5. Aging alone may lead to enough gastric parietal cell atrophy to cause intrinsic factor deficiency and consequent vitamin B_{12} deficiency.
6. In rare circumstances, the ingested cobalamin may be consumed before absorption by a parasite (the fish tapeworm *Diphyllobothrium latum*) or may be inaccessible to cells because of a genetically determined deficiency in one of the cobalamin-carrying proteins (transcobalamin I and II).
7. HIV infection may lead to abnormal cobalamin function by an unknown mechanism, possibly involving abnormal transmethylation. This may explain

why the pathology of HIV-induced spongiform myelopathy is so similar to that of the myelopathy caused by cobalamin deficiency.

Pathophysiology

1. Cobalamin is bound to salivary R protein. In the duodenum, pancreatic enzymes digest the R protein allowing cobalamin to be bound to intrinsic factor that is synthesized in gastric parietal cells. The cobalamin-intrinsic factor dimer is absorbed by specific receptors in the microvilli of the distal ileum. The newly absorbed cobalamin enters the portal circulation bound to transcobalamin II. Transcobalamin I is bound to previously absorbed cobalamin.
2. Inside cells, cobalamin is converted to its two active forms, methylcobalamin and adenosylcobalamin.
   a. Methylcobalamin is the coenzyme for the enzyme methionine synthetase (also known as methyltransferase), which catalyzes the conversion of homocysteine to methionine. Cobalamin is then remethylated to methylcobalamin by a methyl group donated by methyltetrahydrofolate (serum folate). By this process, the demethylated folate may participate in the formation of thymidylate, which is required for DNA synthesis. These interlocking reactions account for the fact that many of the clinical manifestations of vitamin B_{12} and folate deficiencies are similar.
   b. Cobalamin also participates in an important metabolic pathway that is independent of folate. In mitochondria, adenosylcobalamin acts as a coenzyme for methylmalonyl-coenzyme A (CoA) mutase, which catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA. Thus, homocysteine and methylmalonic acid act as biologic markers for the intracellular effectiveness of cobalamin's two coenzymes.

Prognosis

1. The clinical features of the cobalamin deficiency syndrome are predominantly demyelination of the lateral and posterior columns of the spinal cord (subacute combined degeneration), the white matter of the brain, and of the optic nerves. A peripheral neuropathy may also be present.
2. Patients usually present with upper extremity paresthesias followed by stiffness of the legs, slowness of thinking, and reduced visual acuity. For

unknown reasons, the optic neuropathy or mental change may dominate the clinical picture in some patients.

3. Most of the manifestations of the disease are reversible with appropriate therapy, but advanced disease may not completely respond.
4. Exposure to nitrous oxide may precipitate an acute presentation of cobalamin deficiency (anesthesia paresthetica) because it is an inhibitor of methyltransferase, one of the enzymes for which cobalamin is a coenzyme.

Diagnosis

1. Hypersegmented (i.e., greater than five lobes) polymorphonuclear leukocytes are often seen on the peripheral blood smear.
2. Bone marrow may show megaloblasts (i.e., red blood cell precursors with a relatively immature nucleus compared to the cytoplasm).
3. Vitamin B_{12} levels are usually low.
   - **a.** When less than 100 pg/mL, cobalamin deficiency is likely.
   - **b.** When between 100 and 180 pg/mL, cobalamin deficiency is possible.
   - **c.** When over 180 pg/mL, cobalamin deficiency is unlikely.
4. Serum methylmalonic acid is the most specific test for intracellular cobalamin failure. Levels above 0.5 μmol/L suggest intracellular cobalamin failure.
5. The Schilling test may be useful to determine the cause of vitamin B_{12} deficiency, although usually not done clinically.
   - **a.** Phase I is aimed at determining whether the patient can absorb crystalline vitamin B_{12}.
   - **b.** Phase II identifies those who are vitamin B_{12}–deficient because of intrinsic factor deficiency.
   - **c.** The phase III Schilling test, in which radiolabeled vitamin B_{12} is attached to albumin, is used to identify those patients who are unable to extract vitamin B_{12} from food because of an inadequately acidic environment.
6. Anti–intrinsic factor antibodies are specific but insensitive for autoimmune gastritis.
7. Anti–parietal cell antibodies are sensitive but not specific for autoimmune gastritis.

Treatment

1. Cyanocobalamin 1,000 µg IM daily for 1 week, followed by weekly injections for 1 month, followed by monthly injections for life
2. Cyanocobalamin 1 mg/d p.o. may be effective, particularly in elderly patients with gastric atrophy. Methylmalonic acid levels should be monitored to ensure that the treatment is having the expected metabolic effect.
3. Discontinue exposure to nitrous oxide.

Vitamin B_9 (Folate) Deficiency

Background

1. Folate is synthesized by plants and microorganisms. Its major dietary source is green, leafy vegetables.
2. The daily requirement is 50 µg except in pregnant and lactating women, for whom it is increased approximately 10-fold.
3. Folate is ingested as a polyglutamate, which is metabolized to pteroylmonoglutamate and absorbed in the jejunum. In the bowel mucosal cells, it is reduced to tetrahydrofolate and methylated to methyltetrahydrofolate (serum folate).
4. Only about a 12-week supply of folate is stored in the body, so folate deficiency may become rapidly evident with malnutrition.

Pathophysiology

1. Folate interacts intimately with vitamin B_{12} (cobalamin). Serum folate (methyltetrahydrofolate) is the methyl donor that reconstitutes cobalamin into methylcobalamin in the conversion of homocysteine to methionine. Thus, a reduction in homocysteine levels is a reflection of the effectiveness of both folate and vitamin B_{12} in the methyltransferase (methionine synthetase) reaction.
2. Once demethylated, tetrahydrofolate undergoes polyglutamation and is converted to 5,10-methylene tetrahydrofolate, which catalyzed by thymidylate synthase, generates deoxythymidine monophosphate for the synthesis of the thymidine needed for DNA synthesis.
3. Vitamin B_{12} deficiency causes release of folate from cells and interferes with its utilization, leading to an elevated serum folate level (the folate

trap).

4. When vitamin B_{12} is repleted, the folate level may fall precipitously, leading to a folate-deficiency state unmasked by the cobalamin therapy.

Prognosis

1. Pure folate deficiency is rare because it is usually associated with generalized malnutrition, but it may be seen when folate inhibitors have been administered (e.g., methotrexate and sulfonamides are inhibitors of dihydrofolate reductase and phenytoin interferes with folate absorption).
2. Folate deficiency during gestation is associated with neural tube defects.
3. In adults, pure folate deficiency probably causes a sensorimotor length-dependent polyneuropathy. In most cases, folate repletion leads to reversal of the neurologic deficits and adequate provision of folate during pregnancy reduces the risk of neural tube defects.

Diagnosis

1. The blood and bone marrow changes of folate deficiency are indistinguishable from those caused by vitamin B_{12} deficiency.
2. A low serum folate level is specific but not particularly sensitive.
3. If the serum folate level is normal, but folate deficiency is suspected on clinical grounds, a red blood cell folate level should be obtained because it reflects the average intracellular folate level over the life span of the red blood cell and therefore is not unduly affected by recent dietary intake.

Treatment

1. Folic acid 1 mg/d p.o.
2. Resumption of a normal diet
3. For patients on folate antagonists, folinic acid (leucovorin, citrovorum factor) 15 mg p.o. is given every 6 hours for 10 doses starting 24 hours after the dose of methotrexate. If folate deficiency develops from phenytoin, another antiepileptic drug should be chosen because folate replacement may reduce the antiepileptic efficacy of phenytoin.
4. In pregnant women, daily folic acid 400 μg supplementation is recommended. For women with a history of neural tube defects, the daily recommended dose is 4 mg. In those women who take the larger dose, it

should be administered as a dedicated folic acid capsule and not by taking additional multivitamin capsules because that practice may lead to toxicity from other vitamins, particularly vitamin A (see section on vitamin A intoxication earlier).

Vitamin C (Ascorbic Acid) Deficiency

Background

Vitamin C deficiency (scurvy) is rare in developed countries, occurring almost exclusively in generally malnourished people who are poor, elderly, alcoholic, or adherents to unusual diets.

Pathology

1. Ascorbic acid is found in citrus fruits, green vegetables, and tomatoes and is absorbed from the small intestine via a transport system.
2. It has multiple functions, including acting as an antioxidant, a promoter of iron absorption, and a cofactor in the conversion of dopamine to norepinephrine and the synthesis of carnitine.
3. Consuming less than 10 mg of ascorbic acid daily will result in deficiency in a few months.

Prognosis

1. Vitamin C deficiency is characterized by symptoms and signs of abnormal connective tissue such as perifollicular hemorrhages and bleeding from the gums. Neurologic symptoms include weakness, fatigue, depression, and confusion.
2. Treatment usually results in complete remission of the clinical syndrome.
3. "Megadoses" of vitamin C (i.e., greater than 2 g/d) may result in GI bleeding and oxalate kidney stones, but no hypervitaminosis C syndrome of the nervous system is known.

Diagnosis

A vitamin C plasma concentration of less than 11 μmmol/L is considered abnormal, but most patients with scurvy and neurologic impairment have an undetectable plasma vitamin C level.

Treatment

Vitamin C 100 mg four times a day (q.i.d.) for 1 week, followed by 100 mg t.i.d. for 1 month and resumption of a normal diet.

Vitamin D Deficiency

Background

1. Vitamin D (1,25-dihydroxycholecalciferal; vitamin D_3) is the least typical of the vitamins in that it can be synthesized in the skin in amounts adequate for metabolic needs provided there is adequate sun exposure.
2. Vitamin D deficiency or resistance is the cause of rickets in the growing skeleton and osteomalacia in adults.

Pathophysiology

1. Ultraviolet radiation converts provitamin D_3 (dihydrocholesterol) to vitamin D_3 in the skin.
2. In the liver, vitamin D_3 is converted to hydroxylated D_3 and then a final hydroxylation step is performed typically in the kidneys to yield the biologically active vitamin D (1,25 dihydroxyvitamin D_3).

Prognosis

1. Vitamin D metabolism is intimately linked with numerous disorders of calcium and phosphate metabolism. The precise prognosis varies depending on the cause of the disorder.
2. In vitamin D deficiency related to intestinal malabsorption in adults, the symptoms may be expected to dramatically improve with vitamin D repletion.

Diagnosis

1. Vitamin D deficiency causes a syndrome of pain and proximal muscle weakness. It is suspected when a painful myopathic syndrome is encountered in a patient who is at risk for osteomalacia (e.g., a patient with inadequate exposure to sunlight; antiepileptic drug treatment; hepatic and/or renal failure; inadequate dietary vitamin D).

2. There is emerging evidence that low vitamin D levels may cause persistent fatigue.
3. Vitamin D levels can be measured in the serum to confirm the diagnosis.

Treatment

1. For dietary deficiency or inadequate exposure to sunlight: vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) 800 to 4,000 IU (0.02 to 0.1 mg) daily for 8 weeks, followed by 400 IU/d until the deficiency (e.g., inadequate exposure to light or inadequate diet) is resolved.
2. For tetany: 10% calcium gluconate, 10 to 20 mg IV.
3. For patients on antiepileptic drugs: Add 1,000 IU/d and monitor serum calcium and 1,25-hydroxyvitamin D_3 levels.

Vitamin E (Tocopherol) Deficiency

Background

1. Vitamin E is a family of fat-soluble tocopherols, which is never deficient for dietary reasons.
2. All vitamin E deficiency is caused by severe malabsorption or genetic disorders that affect the transport or receptors for vitamin E.

Pathophysiology

1. Of the eight naturally occurring tocopherols, RRR-α-tocopherol is the most biologically active.
2. It is taken up by the liver as chylomicrons, incorporated into very-low-density lipoprotein, and stored in brain, fat, and muscle.
3. Abetalipoproteinemia causes severe vitamin E deficiency by reducing both absorption and transport capacity.

Prognosis

1. Vitamin E deficiency and resistance are manifested in the nervous system as a spinocerebellar degeneration, variable peripheral neuropathy, sometimes with features of myopathy, progressive external ophthalmoplegia, and pigmentary retinopathy.
2. Response to treatment depends on the precise cause, but early symptoms

may respond well to vitamin E treatment.

Diagnosis

Serum α-tocopherol level of less than 5 μg/mL or less than 0.8 mg of tocopherol per gram of total lipid is considered abnormal.

Treatment

1. For patients with pure vitamin E deficiency: α-tocopherol 800 to 1,200 mg/d. Patients with cholestatic liver disease require higher doses.
2. For patients with abetalipoproteinemia: α-tocopherol 5,000 to 7,000 mg/d

Vitamin K Deficiency

Background

Vitamin K is a family of fat-soluble quinones that are involved in the coagulation cascade.

Pathophysiology

1. Vitamin K_1 (phylloquinone) is found in vegetables, particularly leafy vegetables (e.g., spinach), and vitamin K_2 (menaquinone) is synthesized by gut flora.
2. The fat-absorption mechanisms mediated by the pancreas allow for absorption of vitamin K, after which it may be stored in the liver and transported bound to lipoproteins.
3. Vitamin K is a cofactor necessary for the binding of calcium to a number of proteins involved with coagulation, including prothrombin.
4. Vitamin K deficiency may lead to bleeding, including the predisposition for intracerebral, intraventricular, subarachnoid, subdural, and epidural hemorrhages.

Prognosis

Treatment with vitamin K will rapidly reverse the coagulation abnormalities, but the prognosis depends on the location and extent of any hemorrhages that occurred prior to treatment.

Diagnosis

1. An elevated international normalized ratio (INR) in a susceptible person (i.e., a patient with known fat malabsorption, use of antibiotics that sterilize the bowel, use of warfarin, or in infancy) suggests vitamin K deficiency.
2. Vitamin K levels may be measured in problematic cases.

Treatment

Vitamin K 10 mg IV followed by 1 to 2 mg/d p.o. or 1 to 2 mg/wk parenterally until the underlying cause is resolved.

Iron Deficiency

Background

Iron is necessary in several essential biochemical steps including in respiration, DNA production, and cell proliferation.

Pathophysiology

1. Majority of iron is recycled physiologically via macrophages. Small daily need of about 1 to 2 mg.
2. Causes of iron deficiency include blood loss (e.g., menstrual periods, GI bleeding, hookworm infection), increased demand such as during pregnancy, or decreased absorption such as with gastrectomy or inflammatory bowel disease.
3. During progressive iron deficiency, iron pool is initially depleted prior to development of anemia, and patients may have vague neurologic symptoms prior to anemia.
4. The pathophysiologic basis of neurocognitive symptoms of iron deficiency is unclear.

Prognosis

Neurocognitive symptoms often respond first to iron repletion even before anemia.

Diagnosis

1. Associated with restless leg syndrome, a disorder marked by uncomfortable sensation in legs at rest typically in the evening relieved by movement.
2. With depletion of iron stores, pica or appetite for substances that are not food may be present. Appetite for ice (pagophagia) is considered more specific for iron deficiency.
3. Ferritin is the most sensitive and specific indicator of total iron stores in the body with cutoff value of 30 μg/L. Ferritin is also an acute phase reactant and elevated in states of inflammation. Iron deficiency anemia generally also produces transferrin saturation less than 16%.
4. Progressive iron deficiency leads to microcytic anemia.

Treatment

1. Life-threatening anemia is treated with blood cell transfusion.
2. Iron deficiency with intact GI absorption is generally treated with oral iron supplementation. Many formulations are available. A standard starting regimen is ferrous sulfate 325 mg tablet t.i.d. However, the dose is adjusted according to degree of iron deficits on subsequent checks.
   a. Side effects of oral iron supplementation include metallic taste, abdominal pain, or GI disturbance.
3. IV iron supplementation is used for patients who cannot absorb oral iron or cannot tolerate the side effects of oral iron. Dose of iron supplementation can be calculated from degree of iron deficits. Many practitioners also give one time dose of 1,000 mg of elemental iron (exact dose depending on formulation) for most patients.
   a. Allergic reactions are low for most formulations with the exception of high molecular weight iron dextran, which is generally avoided.

Copper Deficiency

Background

Copper is essential in several enzymatic reactions including in the respiratory chain, neurotransmitter synthesis, and antioxidant reactions.

Pathophysiology

1. Most common cause of deficiency is following GI surgery or from

malabsorption syndromes such as inflammatory bowel disease.
2. Zinc overdose either from supplementation or denture cream reduces GI copper absorption resulting in deficiency. Rarely, other medications with copper chelation properties may cause a similar syndrome.

Prognosis

Copper supplementation generally reverses hematologic abnormalities. Neurologic symptoms stabilize but improvement is more variable. Optic neuropathy in particular may not improve but rather stabilize.

Diagnosis

1. Copper deficiency presents as myeloneuropathy characterized most often by gait disorder with spasticity and sensory symptoms. Clinically, there are combined long-tract pyramidal signs and dorsum column dysfunction in addition to neuropathic symptoms of paresthesias and distal impaired pain/temperature sensation. In nerve conduction studies, there is an axonal sensorimotor polyneuropathy.
2. Optic neuropathy can also occur concurrently.
3. Anemia and leukopenia may be present.
4. Serum copper and ceruloplasmin levels are low in copper deficiency states.

Treatment

1. Repleted generally with dose of 2 mg of elemental copper daily. IV dosing may be given if GI absorption is insufficient. Some practitioners give higher doses early (e.g., 6 to 8 mg daily) and then lower doses after a few weeks.
2. There may be concurrent deficiencies (such as vitamin B_{12} and E) especially when cause is GI malabsorption. These should be repleted as well.

HEAVY-METAL POISONING

Lead

Background

1. Lead toxicity is a potential cause of intellectual impairment in children.

2. Despite dramatic lowering of children's blood lead levels in recent years as a result of stringent public health policy in developed countries, lead toxicity still occurs and is a cause of neuropsychological problems.
3. In children, toxicity is usually the result of pica, and it is most common between the ages of 1 and 3 years. Residential remodeling also causes exposure because inorganic lead is present in older paints (both interior, which still line the walls of many older buildings, and some modern exterior paints).
4. Lead encephalopathy is more common in summer than in winter.

Pathophysiology

1. The organic lead compound tetraethyl lead is a gasoline additive that is present in high concentrations in the atmosphere around tanks used to store gasoline and in dirt collected from urban areas near heavily traveled intersections and expressways.
2. Lead paint remains a source in some parts of the world.

Prognosis

1. Lead encephalopathy
   a. Epidemiology
      1) Encephalopathy occurs in children who ingest large amounts of lead salts.
      2) Toxicity occurs only rarely in adults and mainly in those exposed to tetraethyl lead, which is lipid-soluble and reaches high levels in the CNS.
   b. Signs and symptoms
      1) The usual symptoms of lead encephalopathy are personality change, lethargy, and irritability progressing to somnolence and ataxia and, finally, seizures, coma, and death.
      2) In children, acute episodes of lead encephalopathy may recur, superimposed on a state of chronic lead intoxication.
      3) ICP may be elevated in childhood and adult lead encephalopathy.
   c. Prognosis: The mortality of acute lead encephalopathy is less than 5% in the best of hands, but 40% of victims are left with permanent and significant residual neurologic deficits that may include dementia, ataxia, spasticity, and seizures.

2. Lead colic is the most common manifestation of lead poisoning in adults.
   a. The patient becomes anorectic and constipated and often has nausea and vomiting. There is abdominal pain but no tenderness. Characteristically, the patient presses on the abdomen to relieve the discomfort.
   b. Lead colic generally accompanies lead encephalopathy in children.
3. Neuromuscular manifestations of lead poisoning (lead neuropathy)
   a. Slowing of motor nerve conduction velocity is an early sign of lead poisoning in children, but symptomatic neuropathy is rare.
   b. In adults, however, symptomatic neuropathy is common in lead poisoning.
   c. Typically, lead neuropathy is motor, but paresthesias and sensory changes may occur.
   d. Extensors are weakened before flexors, and the most used muscle groups (usually the extensors of the wrist) are involved earliest.
4. There is still controversy regarding chronic low-level lead exposure in children as a cause of attention deficit disorder with hyperactivity.

Diagnosis

1. Physical examination: The main physical finding of lead poisoning, not always present, is lead lines at the gum margins. These occur in a minority of patients and mainly when there is poor dental hygiene.
2. Blood smear: In chronic lead exposure, there is a microcytic anemia that may be superimposed on an iron deficiency anemia. Basophilic stippling is seen in a minority of cases, and the bone marrow may show ringed sideroblasts.
3. Urine: Lead toxicity causes proximal renal tubular dysfunction associated with glycosuria, phosphaturia, and aminoaciduria.
4. Radiographs: Lead lines may be seen in the long bones. In children who have recently ingested lead-containing paint, radiopaque flecks may be seen in the abdomen.
5. Laboratory evidence of increased body lead burden
   a. The serum lead level is the most useful screening test, although it does not reflect the total body lead burden accurately.
      1) Lead levels that are measured from capillary blood (obtained from a finger stick) are subject to contamination by lead on the skin. Consequently, a cleanly obtained venous specimen is preferred.

2) The 24-hour urinary lead excretion test has the same limitations as the serum lead level test. Lead levels of greater than 10 µg/dL (0.483 µmol/L) are of concern, but there is some evidence that any level of lead could be associated with long-term neurobehavioral problems.

b. An ethylenediaminetetraacetic acid (EDTA) test measures total body lead burden more accurately than does a single serum or urinary level test.

1) This test is dangerous in children with high lead burdens because EDTA may mobilize lead from the tissues and precipitate encephalopathy. Therefore, it should not be performed in a child who has a serum lead level higher than 70 µg/dL or who has symptoms of early encephalopathy.

2) The test is performed by administering calcium EDTA in one or three doses of 25 mg/kg IV at 8-hour intervals. A 24-hour urine specimen is collected, and the total lead excreted in 24 hours is measured.

3) A positive test has greater than 500 mg of lead excreted per 24 hours or greater than 1 mg of lead excreted per 24 hours per milligram of EDTA administered.

c. Several tests measure the toxic effects of lead on porphyrin metabolism. These tests are generally the most sensitive measures of lead toxicity.

1) δ-Aminolevulinic acid (δ-ALA) dehydratase activity in erythrocytes is the most sensitive test of lead poisoning, but it is not readily available.

2) Urinary or serum δ-ALA levels higher than 20 mg/dL are indicative of lead toxicity.

3) Urinary coproporphyrin excretion greater than 150 mg per 24 hours is indicative of lead toxicity.

4) Erythrocyte protoporphyrin (EP) levels higher than 190 mg/dL of whole blood are diagnostic of lead poisoning in the absence of either iron deficiency or erythropoietic protoporphyria, both of which may also elevate EP levels.

Treatment

I. Encephalopathy

a. For lead encephalopathy caused by the ingestion of inorganic lead, chelation therapy with EDTA and dimercaprol or British anti-Lewisite (BAL) is instituted.

1) The immediate medical needs of the patient, which may include

seizure control, lowering of elevated ICP, and protection of the airway, take precedence.

2) A urine flow of 350 to 500 mL/m^2/d is established. Overhydration, especially with free water, endangers the patient with increased ICP and should be avoided.
3) Dimercaprol is given at a dose of 500 mg/m^2/d by deep IM injection in divided doses every 4 hours for children younger than 10 years of age. The adult dose is 3 mg/kg/d in divided doses every 4 hours.
4) Four hours after the initial dimercaprol injection, simultaneous injections of dimercaprol and EDTA are given in separate sites. The dose for EDTA is 1,500 mg/m^2/d IM in divided doses every 4 hours for children younger than 10 years, and 12.5 mg/kg/d for adults. In adults, EDTA may be administered as a continuous IV infusion of a solution of EDTA in 5% dextrose in water at a concentration no greater than 0.5%. The maximum adult dose is 7.5 g/d.
5) The usual course of therapy is 5 days.
6) Because of the danger of vomiting with dimercaprol, food is withheld for the first 3 days and then is given only if the patient is fully alert and without GI upset. Iron therapy is not administered simultaneously with dimercaprol. Electrolytes, including calcium and phosphate levels, are measured daily. SIADH frequently accompanies lead encephalopathy.
7) Increased ICP is managed with osmotic agents. There is inadequate evidence to support the use of corticosteroids. (There is some evidence of an adverse interaction of EDTA and steroids, so some experts avoid their concurrent use.)

b. Side effects of chelation therapy

1) Dimercaprol may produce lacrimation, blepharospasm, paresthesias, nausea, vomiting, tachycardia, and hypertension. Its use is contraindicated in the presence of glucose-6-phosphate dehydrogenase deficiency.
2) EDTA may produce renal injury, cardiac conduction abnormalities, and electrolyte disorders. Renal function, calcium, and electrolytes are followed daily, and urine output is carefully monitored and maintained.
3) The IM injection of EDTA is painful. It is commonly mixed with procaine at a final concentration of 5%.

2. Lead colic and lead neuropathy in adults
   a. These conditions require immediate attention but are not emergencies. The cornerstone of therapy is removal of the patient from the offending environment and elimination of sources of future lead exposure.
   b. In patients who are very symptomatic and in those with serum lead levels of 100 µg/dL or greater (or EP levels higher than 190 µg/dL, whole blood), a course of chelation therapy with dimercaprol plus EDTA is given and followed with a course of oral penicillamine or succimer (dimercaptosuccinic acid).
   c. In mildly symptomatic patients without markedly elevated serum lead or EP levels, a course of oral penicillamine or succimer is probably adequate.
   d. Lead colic responds acutely to calcium gluconate, 1 g IV, repeated as necessary.

3. Long-term therapy
   a. A 5-day course of dimercaprol plus EDTA usually removes about 50% of the soft-tissue stores of lead and reduces the serum lead level by a corresponding amount.
      1) After chelation therapy is stopped, lead may be mobilized from bone, again raising the soft-tissue and serum lead concentrations. Consequently, the serum lead should be checked every few days after completion of a course of chelation therapy and another course given if the serum lead rises about 80 µg/dL.
      2) Some patients may require three or four courses of chelation therapy.
   b. Succimer may be used for the oral therapy of lead intoxication.
      1) The drug is administered at a dose of 30 mg/kg/d or 1,050 mg/m^2 in three divided doses for 5 days. The dose is then reduced to 20 mg/kg/d or 700 mg/m^2 in two divided doses for 14 more days.
      2) It is important to treat concurrent iron deficiency.
      3) Adverse effects of treatment include GI upset, allergic rashes, and elevated liver enzymes.
      4) The drug has an unpleasant odor, which reduces patient compliance. The capsules may be opened and the drug sprinkled into juice or a food vehicle.
   c. Penicillamine is not generally used any longer in lead poisoning. It was widely used prior to the introduction of succimer to promote the further

excretion of lead following a course of dimercaprol plus EDTA. Its use now is reserved for patients who require oral chelation therapy but who cannot tolerate succimer.

1) It is administered orally at a dosage of 600 mg/m^2/d in a single dose. It should be administered on an empty stomach, at least 2 hours apart from meals. The therapy must be continued for 3 to 6 months.

2) Toxic reactions to penicillamine include nephrotic syndrome, optic neuritis, a neuromuscular junction syndrome akin to myasthenia gravis, and blood dyscrasias.

4. Tetraethyl lead can be absorbed through the respiratory tract and, unlike inorganic lead salts, can produce encephalopathy in adults.

a. The usual treatment is chelation therapy with dimercaprol plus EDTA, although there is no strong evidence of its effectiveness.

b. Serum lead levels and EP concentrations are not helpful in monitoring treatment of acute poisoning with tetraethyl lead.

c. Both diagnosis and therapy must be based on clinical findings.

5. Asymptomatic lead exposure in children

a. Children at high risk for lead poisoning should have serum lead levels screened every 6 months.

b. Management is based on the serum lead level.

1) Serum lead levels less than 10 µg/dL require only continued routine screening.

2) Serum lead levels of 10 to 20 µg/dL may require more frequent screening and discussion with the family about eliminating potential sources of environmental lead.

3) Serum lead levels of 20 to 45 µg/dL demand an evaluation of the patient's medical status, with particular attention to nutrition and possible anemia or iron deficiency and vigorous efforts to remove the patient from environmental lead exposure. A course of oral chelation therapy with succimer should be considered.

4) Serum lead levels of 45 to 69 µg/dL require medical and probably neuropsychological evaluations, removal from the source of exposure, and immediate chelation therapy with succimer or EDTA.

5) Serum lead levels of 70 µg/dL or greater require immediate inpatient chelation therapy with EDTA plus dimercaprol.

Mercury

Background

Mercury toxicity may occur as a result of exposure to elemental mercury vapor, inorganic mercury, or organic mercury, such as methylmercury.

Pathophysiology

1. Mercury salts and mercury vapor are potential environmental toxins in the chemical, paint, and paper industries, especially in chlorine production.
   - **a.** Mercury vapor and dust are absorbed through the skin and lungs, and ingested mercury salts are absorbed from the gut.
   - **b.** Elemental liquid mercury is poorly absorbed from the GI tract unless it is finely divided.
2. Organic mercury compounds pose the greatest threat to the nervous system.
   - **a.** Phenolic and methoxy methylmercury are degraded to inorganic mercury in the body and are metabolized as inorganic mercury salts.
   - **b.** Alkyl mercury, primarily methylmercury and ethylmercury, is produced as a waste product in the plastics and agricultural fungicide industries. It is well absorbed through skin and is highly lipid-soluble, reaching high concentrations in the CNS.

Prognosis

1. Acute mercury poisoning from a brief exposure to a large amount of mercury produces stomatitis and a metallic taste; a sensation of constriction of the throat; ulcers on the tongue and palate; GI upset with nausea, vomiting, and bloody diarrhea; abdominal pain; acute renal failure; and circulatory collapse. The neurologic manifestations include lethargy, excitement, hyperreflexia, and tremor.
2. Chronic inorganic mercury poisoning produces stomatitis and a metallic taste, loss of appetite, a blue line along the gingival margin, hypertrophied gums, tremor, chorea, ataxia, nephrotic syndrome, and erythrism (a syndrome of personality change, shyness, and irritability). Pink disease, or acrodynia, occurs in children. It is characterized by irritability, insomnia, stomatitis, loss of teeth, hypertension, and erythema.
3. Organic mercury intoxication produces fatigue, apathy, memory loss,

emotional instability, severe ataxia, dysarthria, tremor, dysphagia, paresthesia, and, characteristically, constriction of the visual fields. This may progress to seizures, coma, and death. Organic mercury also crosses the placenta and can produce retardation and paralysis in the offspring of asymptomatic mothers. Renal lesions with proximal tubular dysfunction also occur.

Diagnosis

1. Mercury poisoning must be diagnosed by the history of exposure and the clinical picture.
2. Whole-blood levels of mercury are normally less than 10 μg/L. A level greater than 50 μg/L is considered toxic.

Treatment

1. The aims of therapy are to remove unabsorbed mercury from the GI tract, chelate mercury that has already been absorbed, and prevent acute renal failure.
2. Emesis or gastric lavage is used to empty the stomach, which is then rinsed with a proteinaceous solution (egg white, albumin, or skim milk) or charcoal. Because of the locally corrosive nature of mercury salts, the trachea is intubated if the patient is not fully alert.
3. Na formaldehyde sulfoxylate may decrease mercury absorption by chemically reducing mercuric salts to the less-soluble form of metallic mercury. Two-hundred and fifty milliliters of a 5% solution may be instilled into the duodenum.
4. Dimercaprol can be given at a dosage of 4 to 5 mg/kg IM every 4 hours, with no dose exceeding 300 mg. After the first 24 hours, the frequency of doses is reduced to every 6 hours for 2 to 3 days and then 8 hours for the remainder of a 10-day course. *N*-acetyl-D,L-penicillamine may be the best chelating agent for mercury compounds, but it is not generally available.
5. Administer IV fluids to maintain urine flow, and mannitol 1 g/kg IV is given if the patient is oliguric. Dialysis may be necessary if the kidneys have failed and the patient is severely intoxicated. Electrolyte management might be difficult because of the diuresis induced by mercury salts, with Na and potassium losses as well as volume depletion.

3. Inorganic mercury poisoning is most often chronic. There is enterohepatic circulation of alkyl mercury, so excretion may be promoted by binding the mercury compound in the small intestine with an unabsorbable resin. Cholestyramine, 16 to 24 g/d in divided doses, may be given together with enough of an osmotic cathartic (e.g., sorbitol) to prevent constipation. The dosage of cholestyramine in children has not been established.

Arsenic

Background

1. Organic arsenicals were once used as a treatment for syphilis and as diuretics, but they are no longer in clinical use.
2. Most toxicity is now caused by intentional ingestion for the purpose of murder or suicide.
3. Occasionally, iatrogenic poisoning occurs from arsenic-containing antiparasitic agents used in the treatment of trypanosomiasis (e.g., tryparsamide, carbarsone, and arsenite) and from compounded antipsoriasis creams.

Pathophysiology

1. The primary source of arsenic poisoning today is pesticide ingestion, either accidentally in children and agricultural workers or intentionally for suicide or homicide.
2. Arsenic-containing rat poison is no longer in widespread use but is still stored in some homes and farms.

Prognosis

1. Acute poisoning
   - **a.** Acutely, arsenic produces capillary endothelial damage with leakage, especially in the splanchnic circulation. Nausea, vomiting, abdominal pains, and muscle cramps also occur.
   - **b.** With somewhat larger doses, intravascular hemolysis can occur, which may lead to acute renal failure. Abnormalities are present on the ECG, and stomatitis appears.
   - **c.** With lethal doses, a sequence of shock, coma, and death occurs in 20 to 48

hours.

2. Chronic poisoning
   a. GI symptoms are less prominent than with acute poisoning, but weight loss, anorexia, nausea, and diarrhea or constipation may occur.
   b. Neurologic toxicity may be manifested by a sensorimotor neuropathy, excessive salivation and sweating, and encephalopathy.
   c. The encephalopathy, in its early stages, consists of fatigue, drowsiness, headache, and confusion, but it may progress to seizures, coma, and death.
   d. There may be increased cerebrospinal fluid (CSF) protein and a mild pleocytosis along with fever that may be mistaken for an infection.
   e. Dermatologic signs can be diagnostic, with characteristic arsenical keratoses and transverse lines in the nails (Mees lines).
   f. Hepatic and renal damage may occur.

Diagnosis

1. Acute arsenic intoxication is recognized by a history of ingestion by the clinical presentation and serum levels. In acute intoxication, the urinary arsenic excretion may be extremely high.
2. Chronic arsenic poisoning
   a. Chronic arsenic poisoning is suggested by the clinical picture, especially the dermatologic manifestations.
   b. The upper limits of normal urinary arsenic excretion are not sharply defined, but levels higher than 0.1 mg/L are suggestive of abnormally high exposure. Concentration of arsenic in the nails or hair greater than 0.1 mg/kg is indicative, but not diagnostic, of arsenic poisoning.
   c. Individuals who are chronically exposed to arsenic may harbor large amounts in their tissues and excrete large amounts without developing symptoms of toxicity.
   d. With chronic arsenic ingestion, there is increased urinary coproporphyrinogen III but normal urinary α-ALA excretion.

Treatment

1. Removal from exposure and elimination of unabsorbed arsenic from the GI tract by the use of emesis or gastric lavage and osmotic cathartics are the initial steps.

2. Dimercaprol is an effective chelating agent for arsenic.
   a. The usual course consists of 4 to 5 mg/kg IM every 4 hours for 24 hours, followed by the same dose every 6 hours for 2 to 3 days, which is followed by tapering doses to complete a 10-day course.
   b. Neuropathy may require months to resolve.
3. Fluid and electrolyte disturbances must be rapidly repaired, and intravascular volume must be protected with electrolyte and albumin solutions. Pressors may be required in cases of acute poisoning.
4. The abdominal pain of acute arsenic poisoning may be severe and require large doses of narcotics.

Thallium

Background

Thallium was once used as a treatment for several human diseases including syphilis, gout, and tuberculosis, but it is no longer in any pharmaceuticals.

Pathophysiology

1. Thallium is the primary ingredient in some depilatories and rat poisons. Poisoning usually occurs as a result of accidental ingestion of these materials.
2. The thallous ion is similar in size to potassium, allowing it to interfere with potassium-dependent reactions.

Prognosis

1. Alopecia is the hallmark of thallium intoxication.
2. Neurologic manifestations are prominent: ataxia, chorea, restlessness, and hallucinations, progressing to coma and death.
3. Blindness, facial paralysis, and peripheral neuropathy may occur. Nausea, vomiting, constipation, and liver and renal damage may also occur.

Diagnosis

1. Normal urine thallium concentration is less than 0.3 μg/L.
2. Alopecia may occur with thallium urine levels above 20 μg/L, and major

neurologic effects occur with levels above 50 μg/L.

Treatment

1. Removal from exposure and elimination of unabsorbed thallium from the GI tract with emesis or gastric lavage and catharsis are the primary modes of therapy.
2. Prussian blue (potassium ferric hexacyanoferrate) may be introduced by tube into the duodenum and may decrease thallium absorption. The dose is 250 mg/kg, given over 24 hours in two to four divided doses.

CARBON MONOXIDE POISONING

Background

Carbon monoxide is the most common cause of death by poisoning, either by accidental exposure (e.g., smoke) or intentional exposure for the purpose of murder or suicide.

Pathophysiology

1. The acute manifestations of carbon monoxide inhalation are those of hypoxia without cyanosis.
   - **a.** The "cherry-red" appearance cited in textbooks is uncommon.
   - **b.** The earliest neurologic dysfunction is lethargy, which may progress to coma. Headache is common.
   - **c.** Retinal hemorrhages occur.
   - **d.** As hypoxia becomes more severe, brainstem functions fail.
   - **e.** Cardiac ischemia and acute myocardial infarction may occur.
2. The patient may recover completely from the acute episode if rescued in time or may be left with residual neurologic dysfunction.
   - **a.** Characteristically, the basal ganglia are the most vulnerable structures (particularly the globus pallidus).
   - **b.** The patient might also recover completely from the acute intoxication only to succumb to a massive subacute demyelination of the cerebral white matter that begins 1 to 3 weeks after exposure.

Prognosis

The outcome depends on the length of the exposure.

Diagnosis

1. The history is usually sufficient to make the diagnosis. The cherry-red appearance might also give a clue. Generally, if the patient has inhaled smoke or flame, rather than air contaminated by carbon monoxide, the damage to the respiratory epithelium by heat or oxides of nitrogen is of more immediate concern than carbon monoxide poisoning.
2. Many blood gas laboratories can measure carbon monoxide saturation of blood. (Note that venous blood is adequate for carbon monoxide determinations.)
   - **a.** In the absence of lung disease or a right-to-left shunt, SaO_2, while the patient is breathing 100% oxygen, will, by subtraction, give an estimate of the carbon monoxide saturation.
   - **b.** The PaO_2 is of no use in estimating carbon monoxide saturation because it will not be affected by the combination of hemoglobin with carbon monoxide.

Treatment

1. The primary therapy for carbon monoxide intoxication is to remove the patient from exposure as rapidly as possible and to administer 100% oxygen.
   - **a.** A patient with symptoms of hypoxia or carbon monoxide saturation greater than about 40% should be observed in the hospital for at least 48 hours and maintained on supplemental oxygen until the carbon monoxide concentration falls below 20%.
   - **b.** For severely poisoned patients, hyperbaric oxygen chamber or exchange transfusion may be of benefit.
2. Any maneuvers that reduce the tissue demand for oxygen should be undertaken.
   - **a.** Patients are kept at rest and tranquilized if they are hyperactive from encephalopathy or other causes.
   - **b.** Hyperthermia is treated vigorously.

3. Fire victims frequently inhale both carbon monoxide and cyanide (a product of combustion of many plastics and synthetic materials). Although methemoglobin-forming agents such as amyl nitrite and Na nitrite are routinely used to treat cyanide poisoning, they reduce the oxygen-carrying capacity of the blood and should probably be avoided when carbon monoxide levels are high.
4. Residual movement disorders are common after severe carbon monoxide poisoning.
   a. Choreoathetosis, myoclonus, and a parkinsonian syndrome can occur. These disorders are treated symptomatically in the same manner as movement disorders of other causes (see Chapter 14).
   b. For parkinsonism associated with carbon monoxide intoxication, direct-acting dopamine agonists (bromocriptine, pramipexole, pergolide) may be more effective than L-dopa.
5. There is no known treatment for or specific means of preventing the delayed massive demyelination that sometimes follows carbon monoxide poisoning.

ACETYLCHOLINESTERASE INHIBITOR POISONING

Background

Acetylcholinesterase (AChE) (the enzyme that catalyzes the hydrolysis of acetylcholine at cholinergic synapses) is blocked either competitively or irreversibly by many naturally occurring substances and agents used for chemical warfare and insecticides.

Pathophysiology

1. The usual source of AChE inhibitors is organophosphorus insecticides. Acute poisoning may occur through ingestion, inhalation, or absorption through the skin.
2. Chronic poisoning produces chronic peripheral neuropathy. Its only treatment is discontinuation of exposure to the toxin.

Clinical Features

1. Acute AChE inhibitor poisoning causes a combination of local effects, systemic muscarinic and nicotinic effects, and CNS toxicity.
2. Local effects
   a. Inhalation exposure produces symptoms referable to the eyes, mucous membranes of the nose and pharynx, and the bronchial smooth muscle. Pupillary constriction, conjunctival congestion, watery nasal discharge, wheezing, and increased respiratory secretions are all prominent.
   b. Ingestion of AChE inhibitors produces anorexia, nausea, vomiting, abdominal cramps, and diarrhea.
   c. Skin exposure produces localized swelling and muscle fasciculations.
3. Muscarinic effects include salivation, sweating, lacrimation, bradycardia, and hypotension. Severe poisoning produces involuntary urination and defecation.
4. Nicotinic effects referable to the neuromuscular junction include muscle fatigue, weakness, and fasciculations that progress to paralysis. The immediate life-threatening effect of AChE inhibitor intoxication is respiratory paralysis, which is especially dangerous when combined with bronchospasm and copious bronchial secretions.
5. CNS toxicity is manifested by confusion, ataxia, dysarthria, and diminished deep tendon reflexes, which may progress to seizures and coma.

Diagnosis

1. The clinical presentation and a history of exposure are the key elements to diagnosis.
2. Some clinical laboratories assay AChE activity in plasma and erythrocytes. Although the normal range for AChE activity is broad, patients with significant systemic AChE inhibitor toxicity all have extremely low levels.

Treatment

1. Exposure is terminated by removing the patient from contaminated air, washing the skin copiously with water, or gastric lavage as indicated.
2. The airway must be protected, especially if gastric lavage is required, and respiratory assistance must be provided if necessary. Frequent suctioning of

respiratory secretions is required.

3. Circulatory collapse is treated with maintenance of fluid volume and pressors as necessary.
4. Seizures are treated by the usual methods (see Chapter 2).
5. Muscarinic effects can be blocked with atropine given in large doses.
   a. Therapy should begin with 2 mg IV atropine and be repeated every 3 to 5 minutes until muscarinic symptoms disappear and bradycardia is reversed.
   b. If the patient is alert, doses of atropine may then be given p.o. as required. IV doses will need to be repeated every few hours in comatose patients.
6. Reversal of peripheral AChE may be achieved with pralidoxime for the proportion of the enzyme that has not "irreversibly" bound the inhibitor.
   a. The initial dose for adults is 1 g, infused IV over 2 or more minutes.
   b. If improvement is not noted within 20 minutes, the dose is repeated.
   c. The earlier pralidoxime is administered in the course of intoxication, the greater is its effect. It may need to be repeated every 8 to 12 hours.
   d. Pralidoxime does not reach CNS AChE, and compounds that do so are not generally available.

ETHANOL (ALCOHOL)

Background

1. An alcohol is an organic compound in which a hydroxyl group is bound to the carbon of an alkyl group. Many alcohols are potentially damaging to the nervous system, but the three most common in clinical practice are ethyl alcohol, methyl alcohol, and ethylene glycol.
2. Ethyl alcohol accounts for the most neurologic toxicity of any drug or toxin.
3. Because alcoholism is often associated with malnutrition, the neurologic complications of alcoholism are a mixture of those caused by the direct effects of alcohol (and/or its metabolites) and those of malnutrition.

Pathophysiology

1. Pharmacokinetics of ethyl alcohol
   a. Ethanol is completely absorbed from the GI tract within 2 hours but less

rapidly if there is food in the stomach at the time of ingestion.

b. Ethanol is metabolized by the liver, and it is more rapidly metabolized in those who drink regularly and heavily than in occasional drinkers.

c. The rate of ethanol metabolism is approximately 7 to 10 g/h, which represents about 1 oz of 90-proof spirits or 10 oz of beer per hour.

d. The lethal blood level of alcohol is about 5,000 mg/L. In a 70-kg man, this represents about 1 pt of 90-proof spirits distributed throughout the total body weight.

e. The toxicity from a dose of ethanol depends on the maximum blood ethanol level, the rapidity with which that level is obtained, the patient's prior experience with alcohol, and the presence of other drugs.

Prognosis

1. Acute alcohol intoxication is completely reversible unless there has been respiratory arrest.
2. Chronic alcohol toxicity may be associated with irreversible loss of neurologic function either because of the direct effects of alcohol and/or the effects of malnutrition.

Diagnosis

1. The history suggests alcohol as the possible cause of a neurologic problem.
2. Acute alcohol toxicity may be confirmed with a blood level of more than 100 mg/dL, but tolerance may develop such that individuals who imbibe regularly can be asymptomatic with levels as high as 800 mg/dL.

Treatment

1. Alcohol intoxication

a. For mild intoxication, the most important aspect of management is ensuring that patients do not endanger themselves or others by attempting to drive. Analeptics, such as caffeine, amphetamines, and theophylline, do not help "sober up" the patient or improve driving performance.

b. Moderate intoxication with alcohol poses little danger to patients if they are merely observed until ready to make their own way home. If there has been ingestion within the preceding 2 hours, emesis, gastric lavage, and

catharsis may be used to prevent further absorption. As with mild intoxication, analeptics are of no use.

c. The chief danger in severe ethanol intoxication is respiratory depression. As long as adequate supportive care is provided before significant hypoxia occurs, the outlook is excellent. Within 24 hours, the alcohol will be metabolized.

1) The blood alcohol level may be measured directly or estimated by measuring the serum osmolality. Each 100 mg/L of blood ethanol raises the serum osmolarity by approximately 2 mOsm/L.

2) Tracheal intubation and respiratory support are provided at the earliest sign of respiratory depression. Respiratory support should be continued until the patient is fully awake.

3) Gastric lavage is performed if there is a possibility of alcohol or other drug ingestion within the preceding 2 hours. If the patient is not fully awake, a cuffed endotracheal tube is inserted before gastric lavage is undertaken.

4) Frequently, life-threatening ethanol ingestion is accompanied by ingestion of other CNS depressants. This possibility should be considered if the patient's mental status is depressed out of proportion to the blood ethanol level or if unexpected neurologic signs are present.

5) Fluids are given to maintain adequate blood pressure and urine output, but there is no need to induce a forced diuresis.

6) If the patient is suspected of being a chronic alcoholic or having severe liver disease, blood is drawn for determination of glucose and electrolytes. Thiamine 50 mg IV and dextrose 50 g IV are administered in the event of complicating Wernicke encephalopathy or hypoglycemia.

7) Chronic alcoholics are frequently potassium-depleted and may require replacement with KCl. Acid–base balance needs to be maintained, and alcoholic ketoacidosis is treated appropriately with IV glucose and fluids.

8) If the blood ethanol level is extremely high (more than 7,000 mg/L) peritoneal dialysis or hemodialysis may be justified to reduce the ethanol level rapidly.

9) Although fructose administration hastens ethanol metabolism, its risk does not justify the benefit obtained.

2. Alcohol withdrawal

a. Mild withdrawal syndrome

1) Clinical manifestations of mild ethanol withdrawal are anxiety, weakness, tremulousness, sweating, and tachycardia.

2) In the absence of other intercurrent illness, such as coronary artery disease or infection, patients may be observed by responsible family or others at home.

3) Patients are given thiamine, 50 mg IM, and a prescription for multivitamins if they are malnourished. They are instructed to maintain adequate hydration and food intake during the period of withdrawal.

4) A benzodiazepine tranquilizer minimizes the symptoms of withdrawal.

a) In general, one may begin with chlordiazepoxide, 25 to 50 mg p.o. every 4 hours, for the first 48 to 72 hours and then taper the dosage over 5 to 7 days.

b) Diazepam is equally effective. The initial dosage is 5 to 10 mg p.o. every 4 to 6 hours.

b. Moderate and severe withdrawal syndromes

1) Patients who are febrile, irrational, hallucinating, or agitated must be hospitalized until these manifestations have resolved.

2) Deficits in hydration and potassium are replaced with appropriate solutions. Hypotension usually responds to rigorous volume replacement.

3) Ethanol withdrawal may be precipitated by an intercurrent illness, often an infection. Such illnesses must be detected and treated appropriately.

4) Chronic alcoholics are subject to bleeding disorders from liver disease or thrombocytopenia. Consequently, acetaminophen, 600 mg or 1.2 g p.o. or per rectum, is preferred over aspirin for the treatment of hyperthermia.

5) The patient is usually magnesium-depleted. There is no good evidence that replacing magnesium has any effect on the course of the withdrawal syndrome, but many physicians elect to administer magnesium if the patient is admitted early in the course of withdrawal. Magnesium sulfate may be given in 50% solution, 1 to 2 mL IM, or the same amount may be mixed with IV electrolyte

solutions.

6) Severe liver disease may result in hypoglycemia, and starvation may result in ketoacidosis. Consequently, glucose is administered early, either as a bolus of 25 to 50 g (if the patient is comatose) or as a dextrose-plus-electrolyte solution.

7) Thiamine, a minimum of 50 mg IV or 50 mg IM and up to several hundred milligrams subsequently, is administered to chronic alcoholics prior to glucose because of the risk of Wernicke encephalopathy.

c. Tranquilization

1) Benzodiazepines are the preferred drugs for sedation in alcohol withdrawal. Some centers are also developing protocols using phenobarbital for management of alcohol withdrawal.

2) Diazepam, chlordiazepoxide, and lorazepam are essentially identical in their therapeutic effects when used in equipotent doses.

a) Diazepam and chlordiazepoxide have a prolonged duration of action (12 to 36 hours), whereas lorazepam is shorter acting. All are well absorbed p.o., are erratically absorbed when administered IM, and have a rapid and predictable effect when given IV.

b) The primary danger from these drugs is excessive CNS depression after repeated doses because of the cumulative effect of successive doses given within 24 hours of each other. Respiratory arrest may occur occasionally with rapid IV injection of either drug, but the risk is minimized with small doses.

c) Diazepam can be administered IV in 2.5-mg or 5-mg doses every 5 minutes until the patient is calm and then 5 to 10 mg p.o. or by slow IV injection every 2 to 6 hours as necessary.

d) Chlordiazepoxide can be used in an identical manner, chlordiazepoxide 12.5 mg being equivalent to diazepam 2.5 mg.

e) Lorazepam can be used in an identical manner, with lorazepam 2 mg being equivalent to diazepam 5 mg.

3) Frequent observation is required to prevent cumulative toxicity and avoidance of excessive doses (diazepam approximately 5 mg, lorazepam 2 mg, or chlordiazepoxide approximately 25 mg) in any one IV injection. It is essential that each patient be treated individually with tranquilizers and reevaluated repeatedly rather than

using a fixed-dosage schedule.

d. Withdrawal seizures

1) Ethanol withdrawal seizures typically occur between 12 and 30 hours after cessation of regular ethanol ingestion, are generalized major motor convulsions, and are usually brief and one or two in number. They can occur earlier or later than this time and be prolonged, and status epilepticus may occur.

2) The interictal EEG is normal, and, except for periods of drug withdrawal, the patient is not predisposed to unprovoked seizures.

3) The diagnosis of ethanol withdrawal seizure can be made if the seizure fits the typical clinical pattern and there is no other cause. Seizures from other causes such as old cortical traumatic injuries or subdural hematoma are precipitated by ethanol withdrawal and should be treated appropriately (see Chapter 2).

4) Phenytoin

a) Phenytoin may partially protect against ethanol withdrawal seizures, but its use is not obligatory in this setting. Experts differ over the indications for phenytoin prophylaxis. Some administer phenytoin to all patients during the first 24 hours of withdrawal from heavy ethanol use. Others limit its use to those with a history of withdrawal seizures or with an underlying seizure disorder.

b) Patients not taking an antiepileptic medication are given a 1-g loading dose, either IV as a single dose infused over 20 to 30 minutes or p.o. divided into two or three doses, 1 to 2 hours apart. Patients are maintained on 300 mg/d p.o. or IV for 3 days and the dose is tapered over about 1 week.

c) Ethanol withdrawal seizures are not an indication for long-term anticonvulsant therapy.

5) After a withdrawal seizure has occurred, it is reasonable to observe the patient without therapy as long as other causes for the seizure (particularly head trauma, subdural hematoma, metabolic derangement, and CNS infection) have been excluded. Most withdrawal seizures will not recur or, if they do, will be brief.

6) Other antiepileptic drugs may be used prophylactically, including levetiracetam, carbamazepine, oxcarbazepine, and topiramate, although evidence of their safety and effectiveness in this setting is lacking. Valproate should generally be avoided because of its

potential for hepatic toxicity. Barbiturates should be avoided because they may potentiate the respiratory depressant effects of benzodiazepines used to treat withdrawal symptoms.

OTHER ALCOHOLS

1. Methyl alcohol (methanol; wood alcohol) is also found in windshield wiper fluid, gas line antifreeze, paint strippers, and industrial solvents. It is substituted for ethanol by chronic alcoholics.
   - **a.** Methanol causes an optic neuropathy with large symmetric scotomas that may be sudden in onset and are only partially reversible.
   - **b.** Intoxication is accompanied by systemic acidosis, drowsiness, dysarthria, and ataxia. In severe cases, seizures, tachypnea, and hypotension occur.
   - **c.** The systemic acidosis shows an anion gap, but it may not be evident for several hours.
   - **d.** Acidosis should be corrected and folic acid administered to enhance methanol elimination. Extreme cases require hemodialysis.
   - **e.** Ethanol impairs conversion of methanol to toxic metabolites, mainly formic acid, but has been superseded by fomepizole, which is discussed in the following section. Both can prevent tissue damage if administered early.
2. Ethylene glycol is found in antifreeze and is used in suicide attempts and attempted inebriation.
   - **a.** The early signs are those of alcohol intoxication.
   - **b.** An anion gap acidosis develops quickly and is typical of this overdose.
   - **c.** Renal failure caused by oxaluria follows, and there may be systemic hypotension and brain swelling. Many cases are fatal.
   - **d.** Fomepizole is a relatively specific antidote for methyl alcohol and ethylene alcohol intoxication that works by inhibiting alcohol dehydrogenase. The loading dose in patients not undergoing hemodialysis is 15 mg/kg followed by 10 mg/kg every 12 hours. In patients undergoing dialysis, the same doses are administered at intervals of 6 hours after the first dose, then every 4 hours. Infusions are given over 30 minutes.

WERNICKE ENCEPHALOPATHY

Background

Wernicke encephalopathy is a thiamine-deficiency disease that occurs in chronic alcoholics or patients with chronic malnutrition. Rare cases occur in patients who have had long stays in intensive care units (ICUs) and those with recurrent vomiting and anorexia from pregnancy (hyperemesis gravidarum), cancer chemotherapy, or pancreatitis.

Pathophysiology

1. Cardinal manifestations are confusion and memory loss, nystagmus, extraocular movement deficits (most often unilateral or bilateral sixth nerve palsies), and ataxia, occurring in any combination. These may be acute or subacute in onset.
2. Drowsiness, stupor, and even coma may occur.

Prognosis

1. With prompt treatment, the ocular abnormalities usually clear within days and nystagmus within hours, but about one-fourth of patients will be left with Korsakoff psychosis, in which the ability to form new memories is impaired.
2. Any patient with an appropriate predisposition who has any sign of ataxia, confusion, or extraocular movement abnormality should be treated for Wernicke encephalopathy.

Diagnosis

1. The diagnosis is often obvious clinically, but it can be confirmed with erythrocyte transketolase levels or thiamine levels.
2. The blood sample must be drawn before the administration of thiamine in order to be diagnostic.

Treatment

1. The treatment is with parenteral thiamine. The dosage required has not been

established, and some new guidelines suggest far higher doses than the customary 50 to 100 mg IV or IM immediately and then 50 mg/d p.o. or IM for 3 days thereafter; initial doses of 200 to 500 mg may be required to replenish stores in malnourished alcoholics. Except for rare immediate hypersensitivity reactions to IV administration, the vitamin causes no toxicity.

2. Prophylaxis
   - **a.** The administration of glucose before thiamine in a severely thiamine-deficient patient may precipitate Wernicke encephalopathy. It is therefore recommended that thiamine, at least 50 mg IV, be given before glucose in any patient in whom thiamine deficiency is a possibility, including those with coma of unknown cause.
   - **b.** Patients at risk for Wernicke encephalopathy should be treated with multivitamins, including vitamin B complex, along with thiamine.

OPIATES

Opiate Overdose

Background

1. Opiates are the pharmacologically active alkaloids that may be extracted from the poppy.
2. Commonly used opiates include opium (paregoric), morphine, heroin, hydromorphone, oxymorphone, oxycodone, levorphanol, hydrocodone, and codeine.

Pathophysiology

1. Depressed mental status, respiratory depression, and pinpoint pupils are the typical symptoms of acute opiate poisoning.
2. The body temperature may be subnormal, the blood pressure may be low, and the limbs and jaw are generally flaccid.
3. With very high doses, convulsions and pulmonary edema may occur.

Prognosis

1. If treated promptly, the neurologic effects of opiate intoxication are reversible.
2. Long-term complications are the result of hypoxemia, which is secondary to respiratory depression.

Diagnosis

1. The history suggests the use of opiates.
2. Depressed consciousness with very small, light-fixed pupils support the diagnosis and opiate levels confirm it.

Treatment

1. Patients who are cyanotic, have a respiratory rate below 10 per minute, or cannot protect their airways are intubated with an orotracheal or nasotracheal tube and given respiratory assistance with positive pressure ventilation.
2. Naloxone (Narcan), an opiate antagonist, is given in 0.4-mg increments by rapid IV injection until the patient is breathing normally or until a total of 10 mg has been given, at which point the diagnosis must be called into question.
   a. The duration of action of naloxone is only 1 to 4 hours, depending on the dose, which is shorter than the duration of commonly available opiates. Therefore, after the action of an opiate is reversed with naloxone, patients require close observation in the event that they relapse into coma. Repeated doses of naloxone may be required, especially in methadone intoxication because of the long duration of action of methadone (24 to 36 hours).
   b. Paradoxically, opiate addicts are more sensitive to narcotic antagonists than are patients who are not tolerant of opiates. Therefore, narcotic antagonists are administered in small IV doses (naloxone, 0.4 mg) every 2 to 3 minutes until the desired effect is achieved or until a total of 10 mg has been given.
      1) When given to opiate addicts, narcotic antagonists may precipitate severe acute withdrawal within minutes of IV injection if given in sufficient doses.
      2) Once the antagonist is administered, the withdrawal syndrome will be extremely resistant to reversal by the administration of opiates until the effect of the antagonists has waned.

c. One should not attempt to reverse all of the narcotic effects immediately with naloxone. Rather, the aim is to return the patient's spontaneous respiration and restore level of consciousness to the point where he or she can protect his or her own airway and make spontaneous postural adjustments in bed.

d. Narcotic antagonists, including naloxone, have an emetic effect. Therefore, in comatose patients, the trachea is protected by a cuffed endotracheal tube.

Opiate Withdrawal

Background

Opiate withdrawal symptoms become apparent 3 to 4 hours after exposure and peak 48 to 72 hours after the last exposure to drugs and may last as long as 7 to 10 days.

Pathophysiology

The withdrawal syndrome is mediated by endogenous opiate receptors, which are upregulated during the period of opiate use.

Prognosis

The withdrawal syndrome is unpleasant but not life threatening.

Diagnosis

Irritability, anxiety, lacrimation, and yawning often joined by signs of overactivity of the sympathetic nervous system (tachycardia, tremor, dilated pupils, sweating) suggest the diagnosis in a patient with history of opiate use.

Treatment

1. Although many of the symptoms of opiate withdrawal are dramatic, the potentially dangerous manifestation is dehydration caused by nausea, vomiting, sweating, and diarrhea, combined with failure to take in oral fluids. Consequently, the essential aspect of management of severe narcotic withdrawal is the administration of appropriate electrolyte solutions to maintain intravascular volume and electrolyte balance.

2. At any point in the course of the syndrome, as long as a narcotic antagonist has been administered, the symptoms may be rapidly relieved by narcotic administration. For example, morphine sulfate may be administered by IV injection in small incremental doses of 2 to 5 mg every 3 to 5 minutes until the desired effect is achieved.
3. Clonidine, an α-adrenergic agonist and antihypertensive agent, administered as a single dose of 5 μg/kg will alleviate the symptoms of opiate withdrawal. The patient may then be treated with a 2-week course of clonidine, beginning with a dosage of 0.1 mg every 4 to 6 hours, as necessary to prevent withdrawal symptoms; the dose is adjusted to a maximum of 1.2 mg/d or until oversedation or hypotension supervenes.
4. Methadone 20 mg p.o. once or twice daily blunts the withdrawal syndrome. The methadone may be tapered as the symptoms recede.
5. Many other approaches are used, including rapid detoxification under anesthesia (largely abandoned because of adverse outcomes), buprenorphine with combined naloxone, and small doses on narcotics for prevention of relapse. Most such regimens should be administered by those experienced in their use.

BARBITURATES

Background

Barbiturates do not occur naturally, so exposure is always caused by the use of sedative and antiepileptic drugs. Their use has been greatly reduced in comparison to past decades because more effective sedatives have replaced them.

Pathophysiology

Barbiturates bind to part of the GABA receptor, which controls a chloride channel, which in turn leads to hyperpolarization of neuronal cell membranes, leading to inhibition in the CNS.

Prognosis

Barbiturates do no direct damage to the nervous system, so every patient who receives medical attention before the development of CNS damage from hypoxia or shock has the potential to recover completely with adequate supportive therapy.

Diagnosis

1. A classification of the level of barbiturate intoxication has been devised.
   - **a.** Class 0: Patients who are asleep but can be aroused to purposeful activity
   - **b.** Class I: Patients who are unconscious but withdraw from noxious stimuli and whose muscle stretch reflexes are intact (the corneal reflex may be depressed)
   - **c.** Class II: Patients who are unconscious and do not respond to painful stimuli but who retain muscle stretch reflexes and have no respiratory or circulatory depression
   - **d.** Class III: Patients who are unconscious with loss of some or all reflexes but with spontaneous respiration and normal blood pressure
   - **e.** Class IV: Patients with respiratory depression, cyanosis, or shock
2. A history of the events surrounding the ingestion should be obtained. In particular, the concurrent ingestion of alcohol, other sedatives, or tranquilizers along with barbiturates is common, accounting for neurologic depression that is out of proportion to the dose or serum level of barbiturate taken.
3. Serum barbiturate levels are helpful, but they must be interpreted in the context of the clinical situation.
   - **a.** A high barbiturate level confirms the diagnosis of barbiturate intoxication and correlates with the duration of coma. However, the usual methods of measuring barbiturates do not distinguish between the different varieties of barbiturates, so the level must be interpreted with knowledge of the compound ingested.
   - **b.** The drug level may not correlate with the clinical status of the patient in several situations.
     - **1)** In mixed ingestions, the patient's nervous system may be more depressed than would be predicted from the barbiturate level.
     - **2)** Patients who take barbiturates habitually, either therapeutically or as drugs of abuse, can tolerate much higher levels of barbiturates than

those who have tolerance for the drug.

3) CNS stimulants (analeptic agents) may temporarily elevate a patient's mental status.

Treatment

1. Supportive therapy
   a. The lowest mortality is achieved with only supportive measures.
   b. Respiratory
      1) Patients in class IV require immediate endotracheal intubation and respiratory assistance.
      2) Patients in classes 0 to III require an endotracheal tube if gastric lavage is to be undertaken, if the cough reflex is absent, or if there is any doubt as to the adequacy of respirations.
   c. Cardiovascular: Hypotension occurs in barbiturate poisoning from decreased intravascular volume, from hypoxia with acidosis, and, at extremely high doses, from the direct myocardial depressant effects of barbiturates. The venous pooling of blood that follows may impair cardiac output further.
      1) The chief therapy of hypotension consists of correction of hypoxia, if it exists, and replacement of vascular volume. A central venous pressure (CVP) line is placed, and volume-expanding solutions are infused at about 20 mL/min until the CVP reaches 2 to 6 cm H_2O.
      2) Pressors may be required in patients with severe intoxication in which the blood pressure does not respond to volume replacement. In general, the pressor chosen is infused at a rate that is sufficient to maintain systolic blood pressure at about 90 mm Hg, but the urine output is the ultimate guide. In cases of ingestion of long-acting and intermediate-acting barbiturates, which are excreted primarily in the urine, dopamine is the pressor of choice.
   d. Other supportive measures
      1) Frequent turning, attention to skin care, and other supportive measures are necessary for comatose patients.
      2) Frequent suctioning of intubated patients, pulmonary physical therapy, and prompt antibiotic treatment of respiratory infections are also required.

2. Removal of unabsorbed drug from the GI tract is helpful only if the patient is

seen within 3 hours of ingestion. The only exceptions are the rare patients who ingest large amounts of barbiturates and develop a resultant ileus. Because of their intestinal hypomotility, these patients retain unabsorbed drug in the gut for many hours.

a. Emesis should be induced only in patients with mild ingestion who are awake and able to protect their own airways from aspiration.

b. Gastric lavage may be undertaken in patients who are seen within 3 hours of ingestion, but it should be performed only with a cuffed endotracheal tube in place.

c. After the stomach is evacuated, if bowel sounds are present, an osmotic cathartic may be administered.

1) Sorbitol, 50 g mixed with about 200 mL of water, or magnesium citrate, 200 mL of the standard commercial solution, may be used.

2) Activated charcoal will bind barbiturates and may be given along with the cathartic; the usual dose is 30 g.

3. Removal of absorbed barbiturate from the body

a. Both forced diuresis and, in the case of the phenobarbital, alkalinization of the urine hasten excretion of barbiturates. However, these methods pose risks of volume and Na overload and have failed to improve outcome. Therefore, they are not generally recommended.

b. Hemodialysis is more effective for removing intermediate- and long-acting barbiturates than short-acting compounds. The indications for its use are:

1) Renal or hepatic insufficiency severe enough to prevent the elimination of the drug.

2) Shock or prolonged coma that does not respond to conservative management.

3) Ingestion of a lethal dose of drug (3 g of a short-acting or 5 g of a long-acting barbiturate).

4) A serum drug level predictive of prolonged coma (approximately 3.5 mg/dL for short-acting barbiturates or 8 mg/dL for phenobarbital).

4. Complications of barbiturate intoxication result primarily from prolonged coma, but pneumonia and bladder infections are encountered frequently. Acute renal failure caused by acute tubular necrosis or nontraumatic rhabdomyolysis can also occur.

5. Psychiatric evaluation and care are provided to all patients who ingest

overdoses of drugs intentionally.

Barbiturate Withdrawal

1. Acute barbiturate withdrawal presents similarly to alcohol withdrawal, with tremor, delirium, and seizures being prominent. In contrast to ethanol withdrawal, the seizures associated with withdrawal from short-acting barbiturates are often severe.
2. IV barbiturate is the treatment of choice.
   a. Pentobarbital may be given in 25-mg increments every 5 to 10 minutes until symptoms abate.
   b. Diazepam is generally effective, but the combination of barbiturate and diazepam frequently produces respiratory depression.
3. After the acute symptoms are under control, the patient may be withdrawn from barbiturates gradually. As with ethanol withdrawal, careful attention is directed to fluid and electrolyte balance, antipyresis, and prevention of infectious complications.

Poisoning with Benzodiazepine and Other Nonbarbiturate Central Nervous System Depressants

1. The basic therapy for acute intoxication with all CNS depressants is similar to that for barbiturate intoxication. The respiratory and cardiovascular systems are stabilized, unabsorbed drug is removed by lavage and catharsis, and the elimination of the drug from the body is hastened by whatever techniques are feasible for each drug.
2. Benzodiazepines
   a. Diazepam and chlordiazepoxide taken alone p.o. generally do not produce life-threatening intoxication in medically sound patients. Respiratory depression is of significance only in patients with intrinsic lung disease or in cases of mixed ingestion.
   b. Treatment of benzodiazepine intoxication consists of eliminating the unabsorbed drug from the GI tract and supporting the patients until they awaken.

STIMULANTS (AMPHETAMINES, COCAINE,

PHENCYCLIDINE)

Background

Stimulant drugs are usually ingested for recreational purposes or for weight loss (appetite suppression).

Pathophysiology

1. Stimulant drugs work by increasing the effective concentrations of catecholamines at synapses in the CNS.
2. This may occur by releasing of preformed catecholamine in synaptic vesicles (amphetamine, phencyclidine) and/or by blocking reuptake of released catecholamine in the synapse (cocaine).

Prognosis

1. Acute stimulant toxicity produces psychosis, hyperpyrexia, hypertension, dilated pupils, vomiting, and diarrhea.
2. Life-threatening effects of severe intoxication include cardiac arrhythmias, intracerebral hemorrhage, seizures, coma, and respiratory arrest.

Treatment

1. Sedation with neuroleptics controls psychotic manifestations. Haloperidol 1 to 2 mg IV or chlorpromazine 50 mg IM may be given initially and every 30 minutes until the patient is calm. Oral therapy with atypical neuroleptic drugs may then be used. Risperdal 2 to 4 mg p.o. daily (q.d.) or olanzapine 5 to 10 mg q.d. is a reasonable choice.
2. Hyperpyrexia can be controlled with a cooling blanket and vigorous wetting with towels soaked in tepid water.
3. Arrhythmias are treated with appropriate drugs.
4. Seizures are short-term problems if no irreversible CNS damage occurs from hypoxia or cardiac arrest. They should be treated with the usual measures (see Chapter 2).
5. Unabsorbed drug is removed with emesis, lavage, catharsis, or all three, as appropriate. Lavage may be of benefit even several hours after ingestion.

5. Acidification of the urine hastens the excretion of amphetamines and should be used in the event of severe intoxication. Ammonium chloride may be administered p.o. or IV at a total dosage of 8 to 12 g/d, and the urine pH is checked frequently. Ammonium chloride is contraindicated in shock, systemic acidosis of any cause, hepatic failure, or portosystemic shunting.
7. Severe hypertension is best treated with an α-blocking agent, such as phentolamine (Regitine). Moderate hypertension responds to chlorpromazine.

ANTICHOLINERGIC AND POLYCYCLIC ANTIDEPRESSANT TOXICITY

Background

Many anticholinergic drugs were derived from nature (e.g., belladonna), but nearly all clinical toxicity is the result of exposure to drugs that are primarily anticholinergic (e.g., scopolamine) and have anticholinergic side effects (e.g., polycyclic antidepressants).

Pathophysiology

Anticholinergic drugs work by competitively or noncompetitively binding the muscarinic and/or nicotinic acetylcholine receptors.

Prognosis

1. The acute toxic effects of anticholinergic drugs are hyperpyrexia, dilated pupils, hypertension, tachycardia, and dryness of the skin and mucous membranes.
2. The life-threatening manifestations are coma, seizures, cardiac arrhythmias, and cardiac conduction defects.

Diagnosis

The diagnosis is made with a history of anticholinergic drug use and the characteristic clinical syndrome.

Treatment

1. The initial emergency treatment is the same as for any overdose: stabilization of respiratory and cardiac status and elimination of unabsorbed drug from the GI tract.
2. Cardiac conduction defects and arrhythmias are prominent in tricyclic intoxication. The patient should be on a cardiac monitor, a temporary transvenous pacemaker should be readily available, and the patient should be placed in an intensive or coronary care unit. Lidocaine is effective for ventricular arrhythmias. Propranolol should be used with extreme care if a conduction defect is present.
3. Hyperpyrexia can be controlled with a cooling blanket or by vigorous rubdowns with towels soaked in tepid water. Chlorpromazine may increase the effectiveness of hypothermic methods.
4. Severe hypertension responds to the administration of an α-blocker such as phentolamine.
5. Physostigmine is reported to antagonize the CNS toxicity of tricyclics and other anticholinergics.
   - **a.** Physostigmine injection may serve as a diagnostic test to confirm anticholinergic ingestion.
     - **1)** Physostigmine 1 mg is injected subcutaneously, IM, or slowly IV, which will produce peripheral cholinergic signs within 30 minutes if no anticholinergics have been ingested.
     - **2)** These signs include bradycardia, salivation, lacrimation, and papillary constriction.
     - **3)** In a patient who has ingested anticholinergics, the injection will produce no significant effect.
   - **b.** For the treatment of anticholinergic overdose, 1-mg doses of physostigmine are injected IM or slowly IV at 20-minute intervals until 4 mg has been administered or cholinergic signs appear.
   - **c.** Indications
     - **1)** Physostigmine is most effective against the toxic delirium of anticholinergic overdose. It will occasionally awaken a comatose patient.
     - **2)** However, physostigmine is itself toxic, so its use should be reserved for patients with life-threatening complications of tricyclic overdose, respiratory depression, intractable seizures, or severe hypertension.

d. Side effects

1) If excessive physostigmine is administered, cholinergic side effects may themselves exert harmful effects.

2) Excessive respiratory secretions, salivation, and bronchospasm can interfere with pulmonary function. Vomiting, abdominal cramps, and diarrhea can also occur. Excessive cholinergic effects may be counteracted with atropine (see section on Treatment of Acetylcholinesterase Inhibitor Poisoning). Physostigmine at toxic doses or administered rapidly IV can cause seizures.

e. The duration of action of physostigmine is only 1 to 2 hours, whereas tricyclics persist over 24 hours. Therefore, the patient must be monitored and repeated doses administered as necessary.

SALICYLATE INTOXICATION

Background

1. Salicylates are the medications that most frequently produce clinically significant intoxication. The most common source is aspirin, but Na salicylate and oil of wintergreen are also common causes.

a. Adult aspirin tablets contain 325 mg of aspirin, whereas low-dose (formerly children's aspirin) tablets contain 81 mg. Some so-called "extra strength aspirin tablets" contain as much as 750 mg.

b. Oil of wintergreen contains methyl salicylate in a concentration of about 0.7 g/mL. It is highly toxic, and 1 or 2 teaspoons can be a fatal dose for a small child.

2. The toxic dose of salicylate is about 250 mg/kg in a healthy person. Lower doses of both methyl salicylate and aspirin can be intoxicating in a person who is dehydrated or in renal failure.

Pathophysiology

1. Salicylates are well absorbed from the GI tract, over 50% of a therapeutic dose being absorbed within 1 hour of ingestion. Poisoning has occurred from cutaneous absorption of oil of wintergreen.

2. Once absorbed, aspirin is rapidly hydrolyzed to salicylic acid.
3. Salicylic acid is variably bound to albumin. At toxic levels, the serum albumin binding sites are 100% saturated.
4. Salicylic acid is excreted both unchanged and as its glucuronidated product in urine. It has a pK_a of about 3, so it can be "trapped" in the alkaline solution. Thus, alkalinization of the urine can increase salicylic acid excretion by as much as fivefold.

Prognosis

1. CNS abnormalities dominate the clinical picture.
   a. The earliest signs are tinnitus and impaired hearing.
   b. Agitation progressing to delirium, stupor, and coma results from severe intoxication.
   c. Seizures can occur as a direct effect of salicylate toxicity or as a secondary manifestation of hypoglycemia or effective hypocalcemia.
   d. Salicylates in toxic doses stimulate respiration and produce hyperpnea, usually with tachypnea and respiratory alkalosis.
   e. With extremely high doses, respiratory depression occurs.
2. Metabolic derangements
   a. Salicylates interfere with carbohydrate metabolism.
      1) Hypoglycemia may occur in young children.
      2) The brain uses glucose inefficiently and may experience a "relative hypoglycemia" even with a normal blood glucose level.
      3) The organic aciduria, with or without glycosuria, produces an osmotic diuresis, which in turn produces dehydration.
      4) The respiratory alkalosis, when prolonged, has secondary effects on electrolyte metabolism.
         a) There is renal Na and potassium wasting. The hypokalemia renders the metabolic acidosis unresponsive to alkali therapy until the potassium is repleted.
         b) The respiratory alkalosis produces decreased unbound serum calcium levels, which can lead to tetany and seizures.
      5) SIADH has been reported in association with salicylate poisoning.
3. Effects on blood clotting
   a. Salicylate in toxic concentrations exerts an antiprothrombin effect, with

prolongation of the prothrombin time (PT) and diminished factor VII activity.

b. Salicylates interfere with platelet function, even in nontoxic doses.

c. Salicylates are locally irritating to the gastric mucosa and can lead to GI hemorrhage.

Diagnosis

1. Salicylate intoxication occurs frequently in three groups:
   a. Children younger than 5 years, as a result of accidental ingestion
   b. Adolescents and young adults, as a result of intentional ingestion
   c. Unintentional overdose in patients taking salicylates for rheumatic disease
2. The diagnosis is obvious with an adequate history of ingestion; however, it is frequently masked by chronic therapeutic overdose if the physician is unaware that the patient is taking salicylates.
3. The diagnosis is considered in patients with mental status changes, hyperpnea, and respiratory alkalosis, with or without superimposed metabolic acidosis.
4. Serum salicylate levels confirm the diagnosis.
   a. A level higher than 30 mg/dL may produce early symptoms of salicylism; mental changes and hyperpnea occur at levels higher than 40 mg/dL.
   b. With chronic ingestion, blood levels correlate poorly with the clinical status of the patient but nevertheless serve to make or rule out the diagnosis.
5. The ferric chloride test serves as a rapid screening test for the presence of salicylic acid.
   a. A few drops of a 10% solution of ferric chloride are added to 3 to 5 mL of acidified urine. A purple color indicates a positive result. The test is extremely sensitive, but a positive result is not diagnostic of salicylate intoxication.
   b. Ferric chloride reacts only with salicylic acid, not with aspirin. Therefore, it cannot be used to test for the presence of aspirin in gastric contents.
   c. Phenothiazines react with ferric chloride, but they tend to give a pink rather than a purple color.

d. Acetoacetic acid, present in ketosis, will react with ferric chloride. Its presence may be excluded, however, if the urine is boiled and acidified before the ferric chloride is added.

5. The initial laboratory evaluation of a patient with salicylate intoxication should include the following:

a. Serum salicylate level is of prognostic importance and gives a baseline value with which to judge the effects of therapy.

b. Patients with intentional overdoses should have blood or urine (or both) screened for the presence of other toxic substances.

c. Complete blood count (CBC; including platelet count)

d. Stool and gastric contents are tested for the presence of occult blood.

e. Arterial blood gases and pH

f. BUN (or creatinine), electrolytes, calcium, and phosphorus

g. Liver function tests, including aspartate aminotransferase, lactate dehydrogenase (LDH), alkaline phosphatase, total bilirubin, total protein, and albumin levels

h. PT and partial thromboplastin time

i. Chest radiograph

j. ECG, giving particular attention to signs of hypokalemia or hypocalcemia

k. Urinalysis with specific gravity. If the serum Na is low and SIADH is a possibility, urine Na concentration and osmolality are measured.

Treatment

1. Routine emergency measures for the treatment of drug intoxication

a. Protect the airway and support respiration, if necessary.

b. Empty the GI tract of unabsorbed drug.

1) Forced emesis is used if the patient is alert.

2) Gastric lavage is performed after tracheal intubation with a cuffed endotracheal tube if patients are stuporous, in coma, or unable to protect their own airways.

3) Activated charcoal is given as 200 to 300 mL of a thick suspension to bind unabsorbed salicylates.

4) Cathartics are administered after the charcoal has been given.

2. Fluid and electrolyte management is used to treat shock, maintain urine output, and restore electrolyte and acid–base balance.

3. Alkalinization of urine by the infusion of Na bicarbonate hastens the excretion of salicylic acid. However, in practice, the technique has no value.
   a. In elderly patients and those with abnormal heart function, the risks of increased Na load are not justified by the expected benefits of alkalinization of urine.
   b. In patients with metabolic acidosis, the urine cannot be alkalinized except with massive and dangerous quantities of alkali.
   c. In patients with respiratory alkalosis and alkalemia, the administration of alkali is contraindicated.

4. Hypoglycemia
   a. In young children, after blood has been drawn, 50% dextrose in water (D50W) (0.5 mL/kg IV) is administered immediately.
   b. Only glucose-containing fluids are used for maintenance.

5. Hemorrhagic complications
   a. In severe salicylate poisoning, vitamin K 50 mg IV is given after an initial PT has been measured. Vitamin K is repeated as necessary to maintain a normal PT.
   b. If bleeding occurs or if the PT is found to be longer than twice the control value, fresh frozen plasma or concentrates of clotting factors (Konyne) are given.
   c. Platelet transfusion might be required to achieve control of the hemorrhage because the patient's own platelets will have disordered function.
   d. In comatose patients, antacids and histamine antagonists may be given by nasogastric tube in an effort to prevent gastric hemorrhage.

6. Tetany may be treated with the IV infusion of calcium gluconate in 1-g doses, repeated as often as necessary.

7. Seizures
   a. Hypoglycemia and hypocalcemia are treated appropriately. Other metabolic causes of seizures, such as hyponatremia and hypoxia, must also be considered.
   b. Seizures that occur as a direct toxic effect of salicylate are a poor prognostic sign, generally indicating the necessity for hemodialysis to hasten elimination of the salicylate. Diazepam, given IV, or muscle paralysis and respiratory support may be used for the temporary control of seizures until the salicylate level is lowered.

3. Fever can be treated with tepid water baths.
D. Methods to hasten the elimination of salicylates
   a. Forced diuresis is of little benefit, and the patient should not be subjected to a larger fluid load than necessary to achieve a reasonable urine output.
   b. Alkalinization of the urine has no practical use in salicylate poisoning.
   c. Peritoneal dialysis is about as efficient as the normal kidney in eliminating salicylate from the blood. Its primary use is in the setting of renal failure. The addition of albumin to the dialysis solution hastens the elimination of salicylate, but there is no evidence that its benefits outweigh the expense and added complexity of the dialysis.
   d. Hemodialysis is the most efficient means available for the elimination of salicylate. The generally accepted indications for hemodialysis are:
      1) Salicylate level higher than 70 mg/dL or known absorption greater than 5 g/kg
      2) Profound coma with respiratory failure
      3) Severe metabolic acidosis
      4) Renal failure
      5) Failure to respond to conservative therapy

HYPERTHERMIA

Background

Hyperthermia is a common cause of neurologic dysfunction. It is particularly dangerous and may even be lethal in the summer months.

Pathophysiology

I. Rises in body temperature may be caused by excessive heat gain, insufficient heat loss, or both.
2. Excessive heat gain
   a. Exercise
   b. High ambient temperatures
   c. Increased metabolic rate
   d. Release of pyrogen (e.g., by infection)
   e. Neuroleptic malignant syndrome (NMS)

3. Defective heat loss
   a. Excessively warm clothing
   b. Increased humidity
   c. Advanced age
   d. Anticholinergic drugs (e.g., phenothiazines, tricyclic antidepressants)
   e. Sympathetic autonomic failure with decreased or absent sweating caused by:
      1) Elevated body temperatures
      2) Spinal cord transection above T1

Classification

1. Heat cramps: Muscle or abdominal cramps associated with exercise are commonly seen.
2. Heat exhaustion (heat prostration, exertional heat injury) is marked by moderately elevated body temperatures (i.e., 39.5°C to 42.0°C) and a neurologic syndrome characterized by headache, piloerection, hyperventilation, nausea, vomiting, unsteady gait, and confusion. Sweating remains intact in patients with heat exhaustion, so the skin is wet and cool.
3. Heat stroke
   a. When body temperatures rise high enough, CNS mechanisms for control of heat loss might fail. When this occurs, there is a very rapid further rise in body temperature, which is a life-threatening medical emergency.
   b. Such patients might be diaphoretic or have hot, dry skin (sweating having failed) and elevated body temperatures (higher than 41°C, ranging as high as 43°C).
   c. The level of consciousness becomes deranged, often quite suddenly, so patients can deteriorate rapidly from confusion or delirium to deep coma, often with seizures.
   d. Cerebral edema occurs, which can lead to widespread cerebral ischemia and eventually brain death.
   e. Other abnormalities include circulatory failure, disseminated intravascular coagulation, severe dehydration, and hepatic necrosis. Electrolyte abnormalities, most commonly respiratory alkalosis and hypokalemia, are common.

Diagnosis

The diagnosis is made in a patient with compatible history and physical examination and elevated body temperature.

Treatment

1. Heat cramps: Rest and oral electrolyte replacement are usually adequate.
2. Heat exhaustion
   - **a.** Patients should be admitted to the hospital for treatment because some may progress to heat stroke.
   - **b.** Rest and parenteral rehydration are usually adequate to reverse the syndrome.
3. Heat stroke
   - **a.** Surface cooling should be started immediately. The most effective means is to use evaporative cooling by spraying the naked patient with tepid water and using a powerful fan to maintain a flow of air over the patient's body. Less preferably, immersion in ice or cold water may be used.
   - **b.** IV fluids should be administered with care because typically, the patient is normovolemic but has redistributed fluid to peripheral, vasodilated tissues. With cooling, fluid will redistribute and cardiac output will be restored.
   - **c.** A bladder catheter should be placed and urinary output carefully monitored.
   - **d.** Isoproterenol via constant infusion (1 μg/min) may be used to increase cardiac output.
   - **e.** Avoid α-adrenergic drugs (e.g., norepinephrine), which produce vasoconstriction and thus retard heat loss.
   - **f.** Avoid anticholinergic drugs (e.g., atropine), which retard the return of sweating.
   - **g.** Monitoring of ICP using a dural bolt might be necessary if consciousness does not return promptly.
   - **h.** Treat increased ICP as outlined in Chapter 1.
   - **i.** Seizures may be treated with phenytoin or other IV antiepileptic drugs as outlined in Chapter 2.

NEUROLEPTIC MALIGNANT SYNDROME AND SEROTONIN SYNDROME

Background

1. NMS is characterized by hyperthermia, muscle rigidity, and altered mental status.
2. It occurs in patients taking neuroleptic medication or, rarely, in association with withdrawal of L-dopa or other dopaminergic agonists.

Pathophysiology

1. Although a preponderance of reported cases have occurred with the use of potent neuroleptics such as haloperidol, the syndromes have been associated with virtually all dopamine receptor antagonists and dopamine-depleting agents, including newer antipsychosis drugs and selective serotonin reuptake inhibitors (SSRIs).
2. They may occur immediately after the first dose of the drug or in a patient who has been taking them for many years. Many cases are associated with a rapid increase in dose.
3. Life-threatening complications of NMS and serotonin syndrome (SS) include respiratory failure secondary to muscular rigidity and renal failure secondary to myoglobinuria.

Prognosis

1. NMS and SS may be precipitated by dehydration, fever, or environmental exposure to high temperatures in patients taking neuroleptics and SSRIs. These precipitants should be especially avoided in patients taking neuroleptics or dopamine-depleting agents.
2. Withdrawal of dopamine agonists, including carbidopa-L-dopa (Sinemet), should be carried out gradually.
3. If the syndromes are recognized early, the prognosis is excellent. Although mortality rates as high as 15% to 20% are quoted in the literature, it is clear that with adequate supportive care, the mortality is much less.
4. To prevent relapse, the responsible drugs medications must not be

reinstituted until the syndrome has resolved completely. Patients may require sedation with benzodiazepines in the meantime. After resolution of all clinical signs, the drugs may be cautiously reinstituted.

5. NMS and SS are not allergic reactions the drugs to neuroleptics, and the occurrence is not an absolute contraindication to use of the drugs.

Diagnosis

1. Diagnosis is made in a patient on a neuroleptic drug who develops rigidity and hyperthermia.
2. Clinically, SS is associated with hyperreflexia and hyperactive bowel sounds, whereas NMS causes bradyreflexia and normal or decreased bowel sounds. Pupils are also more mydriatic in SS compared to NMS.
3. Laboratory abnormalities may include an elevated serum creatine kinase level, elevated white blood cell (WBC) count, and abnormal liver function tests.
4. The CSF is normal, and the EEG shows a generalized slowing.
5. The computed tomography (CT) scan and MRI findings are normal.

Treatment

1. Immediate withdrawal of all offending medications (including those administered as antiemetics) or dopamine-depleting agents is essential at the earliest sign. In cases associated with withdrawal of dopamine agonists (e.g., L-dopa, bromocriptine), reinstitution of dopaminergic therapy and more gradual withdrawal should be undertaken.
2. The mainstay of management is supportive care.
   - **a.** Rehydration and maintenance of adequate urine flow
   - **b.** Lowering of body temperature with antipyretics, cooling blanket, or tepid water bath as required
   - **c.** Protection of the airway to endotracheal intubation as required
   - **d.** In unusual cases, respirator support with muscular paralysis might be required to maintain ventilation in the face of extreme muscular rigidity.
3. The direct-acting muscle relaxant dantrolene is widely used in severe cases of NMS, although there are no systematic studies documenting its benefit.
   - **a.** Muscle relaxation may facilitate nursing care and aid in lowering body

temperature. In addition, to the extent that muscle rigidity contributes to muscle necrosis and myoglobinuria, muscle relaxation can help prevent renal failure.

b. However, it is clear that muscular rigidity is not the only cause of muscle damage in NMS and that hyperthermia may persist in spite of muscle paralysis.

c. Doses of dantrolene range from 1 to 10 mg/kg/d IV or by nasogastric tube given in four divided doses. Hepatic toxicity occurs with dosages above 10 mg/kg/d.

l. The dopamine agonist bromocriptine has also been widely used and has theoretical support.

a. There are no systemic studies documenting its benefit in NMS.

b. Dosages vary from 2.5 to 10.0 mg IV or by nasogastric tube every 4 to 6 hours.

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19 Infectious Diseases

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MENINGITIS

Background and Pathophysiology

Meningitis is the pathologic term for inflammation of the meninges. This can be divided by meningeal type (pachymeninges vs. leptomeninges); infectious etiologies are much more commonly seen in leptomeningitis, which will be discussed here. Certain vaccines against bacteria have become available to reduce the incidence/severity of meningitis, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*, although none of the current vaccinations covers all strains of the organism that cause meningitis, especially in adults.

Diagnosis

Diagnosis of meningitis is made by presence of abnormal inflammatory cells in the cerebrospinal fluid (CSF), and obtaining spinal fluid is considered an emergency. However, in the setting of known immune compromise, focal neurologic deficit, seizure, or papilledema, computed tomography (CT) scan should precede lumbar puncture to determine procedural safety. Blood cultures drawn prior to initiation of antibiotics can greatly aid in organism identification where CSF Gram stain/culture is unrevealing. Typical CSF findings by organism type can be found in Table 19-1.

Types

Acute

Acute meningitis presents within hours or days and is characterized by the triad of fever, headache, and neck stiffness. However, many will not have all symptoms, and additionally, alteration in mental status is a common accompaniment that does not necessarily imply encephalitis. Most infectious causes of acute meningitis are because of bacteria or viruses. Acute bacterial meningitis is a neurologic emergency that requires immediate intervention for the best outcomes. A list of common etiologies of acute meningitis in adults can be found in Table 19-2.

Subacute/Chronic

Most subacute/chronic meningitidis are caused by fastidious organisms or autoimmune diseases and present over the course of 3 to 6 weeks or longer. A list of infectious etiologies can be found in Table 19-3.

Recurrent

Recurrent meningitis is rare and sometimes difficult to parse from chronic meningitis. Historically, the most common type of relapsing meningitis is caused by herpes simplex virus type 2 (HSV-2).

Table 19-1 Cerebrospinal Fluid Profiles in Meningitis

Diagnosis	Opening Pressure (cm H_2O)	WBC Count (cells/μL)	WBC Differential	Glucose (mg/dL)
Normal	<20	<5 (corrected for RBC)	N/A	50–100 (≥2/3 serum)
Bacterial meningitis	Very high; often >30	Very high; often >1,000	Strong neutrophilic predominance	<40% serum; often very low
Viral/aseptic meningitis	Usually normal	High; teens to hundreds	Strong mononuclear predominance	Usually normal
Fungal/tuberculous meningitis	High to very high	Variably high; teens to hundreds to	Mononuclear or mixed	Low to very low

		thousands		
Chemical	Normal	Variably high; teens to hundreds	Neutrophilic predominance	Normal

WBC, white blood cell; RBC, red blood cell; N/A, not applicable.

Table 19-2 Most Common Etiologies of Acute Meningitis in Previously Healthy Adults Without History of Neurosurgery in the United States

Bacterial (Percentage of Cases)	Viral	Other
Streptococcus pneumoniae (70)	Varicella zoster virus	Chemical (e.g., NSAIDs use)
Neisseria meningitidis (10)	Herpes simplex virus	Fungal (rare)
Streptococcus agalactiae (<10)	Enterovirus	Tuberculosis (rare)
Listeria monocytogenes (<10)	Arboviruses (seasonal/regional)	Autoimmune disease/sarcoidosis
Haemophilus influenzae (<10)		*Borrelia burgdorferi* (seasonal/regional)

NSAIDs, nonsteroidal anti-inflammatory drugs.

Management

Management ultimately depends on the type of meningitis, but because outcomes depend on speed to antimicrobial initiation, early management for adults in developed countries has been standardized and should be initiated without delay upon suspicion of the diagnosis.

1. Dexamethasone (or similar corticosteroid) with or before the first dose of antimicrobials and continued for 4 days unless non-pneumococcal etiology is found, at which point this intervention can be stopped.
2. Third-generation cephalosporin to cover penicillin-sensitive *S. pneumoniae* and also *N. meningitidis*, *Streptococcus agalactiae*, and *H. influenzae*.
3. Vancomycin to cover penicillin-resistant strains of *Streptococcus*.
4. Ampicillin in those over 50 years of age or those with known or suspected immune compromise to cover *Listeria monocytogenes*.

Table 19-3 Most Common Etiologies of Chronic Meningitis in Adults Without History of Neurosurgery

Infectious	Other
Mycobacterium tuberculosis	Meningeal spread of malignancy
Cryptococcus spp.	Autoimmune disease/sarcoidosis
Histoplasma capsulatum	
Coccidioides immitis	
Blastomyces dermatitidis	
Paracoccidioides brasiliensis	
Candida spp.	
Treponema pallidum	
Aspergillus spp.	

5. Acyclovir is recommended, as on presentation, there is significant overlap between HSV encephalitis (HSVE) and acute bacterial meningitis.
6. Source identification.

Treatment is then narrowed based on etiology and continued for 2 weeks. Additional supportive measures such as seizure control, intracranial pressure (ICP) monitoring/intervention, and pain control are often necessary.

Prognosis

Prognosis depends greatly on speed to initiation of definitive antimicrobials for acute bacterial meningitis, although sequelae are common. Viral etiologies in the immune competent have an excellent prognosis for full recovery. Tuberculous, fungal, and parasitic etiologies have varying outcomes.

ENCEPHALITIS

Background and Pathophysiology

Encephalitis is defined pathologically as inflammation of the brain parenchyma in the presence of neurologic dysfunction. It can be of infectious or noninfectious nature. Epidemiology studies show that in the United States, the

etiology is most commonly unknown, but for known entities, most common causes identified are viral, with HSV generally dominating, although West Nile virus incidence periodically exceeds HSV. Other infections, especially viruses and mycoplasma, can trigger an immune-mediated encephalitis without direct central nervous system (CNS) infection, for example, acute disseminated encephalomyelitis.

Diagnosis

The International Encephalitis Consortium proposed diagnostic criteria for encephalitis that are divided into major and minor criteria (diagnosis requirements can be found in Table 19-4).

1. Major: At least 24 hours of decreased or altered level of consciousness, lethargy, or personality change requiring medical attention.

Table 19-4 Requirements for Confirmed, Probable, or Possible Diagnosis of Acute Encephalitis

Confirmed	Probable	Possible
Major criteria	Major criteria	Major criteria
At least three minor criteria	At least three minor criteria	Two minor criteria
At least one of the following: • Pathologic evidence of encephalitis • Serologic, microbiologic, or pathologic evidence of acute infection with organism associated with encephalitis • Laboratory evidence of autoimmune disease associated with encephalitis		

Table 19-5 Chief Diagnostic Considerations in Encephalitis by Area of Cerebral Involvement

Location of Involvement	Diagnostic Considerations
Hippocampus/medial temporal lobe	HSV, HHV-6, paraneoplastic
Anterior temporal lobe/orbitofrontal cortex	HSV, *Naegleria fowleri*
Thalamus/basal ganglia	Respiratory viruses, arboviruses

Rhombencephalon	*Listeria monocytogenes*, paraneoplastic, enterovirus, VZV
Diffuse cortical	Rabies

HSV, herpes simplex virus; HHV, human herpesvirus; VZV, varicella zoster virus.

2. Minor
   a. Fever to 100.4°F or greater within 72 hours of presentation
   b. Unexplained/new seizure
   c. New focal neurologic deficit
   d. CSF pleocytosis of >4 cells/mm^3
   e. Neuroimaging suggestive of encephalitis
   f. Electroencephalogram (EEG) consistent with encephalitis

Identification of infectious etiologies depends largely on demographics, immune status, travel/exposure/vaccine history, and season of presentation, although there may be overlap. Characteristic imaging findings by disease entity can be found in Table 19-5.

Types

1. HSVE: Most commonly identified sporadic encephalitis in the United States and most commonly caused by HSV-1. Immune status is not relevant, and infection can be primary or reactivation. Usually seen in those between ages 61 and 64 years with a notable relative hiatus between the ages of 20 and 50 years. HSV polymerase chain reaction (PCR) of CSF is highly sensitive even after several days on treatment have passed.
2. Varicella zoster virus (VZV): CNS manifestations of VZV are protean, but encephalitis is among them. Other infectious manifestations include meningitis, cranial neuritis, myeloradiculitis, and vasculitis. Intrathecal VZV immunoglobulin G (IgG) production or DNA detection is diagnostic.
3. Enterovirus: More commonly associated with meningitis, this group of viruses can also cause an encephalitis and/or poliomyelitis. Diagnosis is by detection of viral RNA from CSF in the correct setting.
4. Arboviral: These are viruses carried by mosquitoes or ticks, and specific viruses vary by location (Table 19-6). The most common arboviral encephalitis in the United States is West Nile virus, which has been reported from all 48 contiguous states with incidence ranging from 0.13 up to 1 case

per 100,000 since 2002. Diagnosis is by presence of CSF immunoglobulin M (IgM), appropriate serologic evolution over time, or PCR on CSF (where available).

5. Rabies: Common cause of encephalitis in Africa but extremely rare in the United States. Worldwide exposure to infected dogs is the source of human transmission, but in the United States, infected bats are most commonly the vectors.

Table 19-6 Worldwide Distribution of the Most Common Encephalitis Viruses

Virus	Endemic Location	Vector
Japanese encephalitis virus	East Asia	Mosquito
West Nile virus	United States, East Africa, Middle East	Mosquito
Tick-borne encephalitis virus	Europe, Russia, Asia	Tick
Eastern equine encephalitis virus	Northeast United States	Mosquito
Western equine encephalitis virus	Western United States	Mosquito
Venezuelan encephalitis virus	Central America, Northern South America	Mosquito
Powassan virus	Great Lakes, Northeast United States	Tick
La Crosse virus	Eastern United States	Mosquito
Colorado tick fever virus	Western United States	Tick
St. Louis encephalitis virus	United States	Mosquito
Murray Valley encephalitis virus	Australia	Mosquito

6. Other: Less commonly, bacteria, parasites, spirochetes, fungi, and other viruses have been implicated in encephalitis. A listing can be found in Table 19-7.

Management

1. General: Management of seizures, severely increased ICP, and cardiopulmonary compromise vary depending on severity of disease. Reduction of inflammation with immune modulation, especially corticosteroids, is often implemented, as well.
2. HSV, VZV: 14 to 21 days of acyclovir 10 mg/kg every 8 hours (10 to 15

mg/kg for VZV) with adequate hydration and renal monitoring. Adjunctive corticosteroids are sometimes used with severe concomitant inflammation, but there is no strong data as yet for this to be standard. In some instances of severe edema, hemicraniectomy may be a management consideration.

Table 19-7 Infectious Causes of Encephalitis

Viruses	Bacteria	Other
Herpes family	*Listeria monocytogenes*	*Naegleria fowleri*
Arboviruses	*Tropheryma whippelii*	*Trypanosoma brucei gambiense*
Enteroviruses	*Borrelia burgdorferi* (rare)	*Aspergillus* spp.
Rabies	*Bartonella henselae*	*Taenia solium*
Mumps	*Brucella* spp.	*Balamuthia mandrillaris*
Measles	*Francisella tularensis*	*Toxoplasma gondii*
Adenovirus	*Nocardia asteroides*	*Cryptococcus* spp.

3. Rabies: Vaccine is available for impending high-risk situations, and postexposure prophylaxis can be given immediately after a bite from an infected animal. Management is otherwise supportive.
4. Other: Specific antimicrobials are implemented depending on the disease entity identified.

Prognosis

Prognosis for HSVE depends on time to initiation of acyclovir, but permanent neurologic sequelae (memory loss, personality changes, seizures) are common. Treatment for less than 14 days carries a high risk of relapse. Nearly 50% of patients are rehospitalized within 1 year, usually for seizure. More recently, HSVE has been recognized to trigger anti-*N*-methyl D-aspartate (NMDA) receptor encephalitis. Rabies encephalitis is almost universally fatal. For most arboviruses, about half of survivors have permanent neurologic damage. Other encephalitides have varying prognosis.

BACTERIAL BRAIN ABSCESS

Background and Pathophysiology

Bacterial brain abscess begins as localized cerebritis that encapsulates and grows, accumulating pus (which manifests as diffusion restriction by magnetic resonance imaging [MRI]). Abscess sources can be because of hematogenous spread of a more proximal infection (especially endocarditis), direct extension of a localized infection (especially otitis, mastoiditis, or sinonasal infection), or by penetrating trauma.

Diagnosis

Seizure, headache, and focal deficits are common presenting symptoms, and neuroimaging (preferably MRI with gadolinium) showing a rim-enhancing lesion with strong internal diffusion restriction in the correct clinical setting (fever, bacteremia, infective endocarditis [IE]) should raise suspicion. Blood and/or aspirate cultures recover the organism in about 70% of cases. Lumbar puncture is of limited utility and may lead to clinical worsening.

Types

Bacterial abscesses can be monomicrobial or polymicrobial, but even in the latter, one organism often dominates. The most commonly recovered organisms are staphylococcal or streptococcal species. Gut flora and slower growing organisms, such as *Propionibacterium acnes*, *Actinomyces*, and *Nocardia asteroides*, are much less frequent culprits. Abscesses are more commonly single than multiple. Nonbacterial abscesses should also be considered in the differential diagnosis, especially in the immune compromised.

Management

Prompt surgical intervention can be both diagnostic and therapeutic, and once the patient has been stabilized from a cardiopulmonary perspective, this should be pursued. Initial antibiotic coverage is usually broad spectrum to cover both gram-positive and gram-negative organisms (usually vancomycin with third-generation cephalosporin or meropenem), with added anaerobic coverage (metronidazole) where anaerobes are suspected. This subsequently should be narrowed based on culture data. Seizure should be considered where not overt and managed accordingly.

Prognosis

Untreated brain abscesses are almost uniformly fatal, and rupture into the ventricular system also carries a high mortality rate. With prompt and appropriate management, however, complete recovery can be achieved.

SPINAL EPIDURAL ABSCESS

Background and Pathophysiology

The spinal epidural space contains the venous plexus and fat to support the spinal cord, but this provides a rich culture medium for bacteria. Abscesses most commonly occur from hematogenous spread but also can be because of direct extension of a discitis/osteomyelitis. Risk factors include diabetes, intravenous (IV) drug use, endocarditis, trauma, and HIV infection. Clinically, spinal epidural abscess (SEA) starts as fever and back/radicular pain and progresses to focal neurologic deficits.

Diagnosis

Contrast-enhanced MRI diagnoses the abscess, and blood and/or surgical specimen cultures identify the organism.

Types

Most hematogenously, spread abscesses start in the dorsal epidural space because this is where the venous plexus and epidural fat are typically most prominent. About 50% occur in the thoracic spine (which is not a typical location for chronic back pain), with about 35% occurring in the lumbosacral spine and the remaining 15% originating at the cervical level. However, as the lesion grows, it can become both circumferential and longitudinal.

Management

Immediate surgical management, including laminectomy and drainage, is imperative. Broad-spectrum antibiotics to cover staphylococcal, streptococcal, and gram-negative species (vancomycin with third-generation cephalosporin) should be initiated and subsequently narrowed based on culture data. Typical

course is for 6 weeks.

Prognosis

Complete recovery is possible if surgical intervention occurs within 24 to 36 hours of any onset of focal neurologic deficit. Permanent damage ensues beyond this window, and death occurs in some 5%. Presurgical functionality is the most important predictor of outcome.

NEUROLOGIC COMPLICATIONS OF INFECTIVE ENDOCARDITIS

Background and Pathophysiology

Neurologic sequelae of IE are common, with ischemic stroke topping the list of complications. The most common organism overall is *Staphylococcus aureus*, although any etiology of IE can produce neurologic disease.

Diagnosis

Duke criteria for diagnosing endocarditis are used for cardiac disease, and neurologic sequelae are diagnosed by imaging (MRI brain/spine for stroke, abscess, or microhemorrhage; noncontrast head CT for macrohemorrhage; conventional angiogram for infectious intracranial aneurysm (IIA); lumbar puncture for meningitis). Embolism from the infected valve is greatly increased when the vegetation is >1.0 cm.

Types

1. Stroke: Can be silent or symptomatic and occurs in around 50% of patients
2. Intracranial hemorrhage: Resulting from hemorrhagic conversion of stroke, rupture of IIA, or spontaneous (likely relating to microhemorrhages)
3. Bacterial brain abscess: Can be solitary or multiple
4. IIA: Most commonly seen in distal branches of middle cerebral artery (MCA) territory; magnetic resonance angiography (MRA) and computed tomography angiography (CTA) are often of inadequate resolution

5. Meningitis (discussed earlier)
6. SEA (discussed earlier)

Management

Management varies by type of complication. Stroke management differs in this setting insofar as IE is a relative contraindication for IV tissue plasminogen activator (tPA) use; furthermore, antiplatelet therapy and anticoagulation should be avoided except in extenuating circumstances (e.g., mechanical mitral valve) in the acute setting because the risk of hemorrhage is very high. Timing of valve repair/replacement surgery in the setting of neurologic complication has not been well studied, but overall, only large ischemic strokes and hemorrhages will require a conversation on delaying this intervention. IIA management includes prolonged antibiotics and serial imaging, with surgical intervention required where antibiotics fail. Brain and spinal abscess and meningitis are managed as described in respective sections.

Prognosis

Prognosis varies by severity of cardiac and neurologic disease. Risk of embolization is greatly reduced after 7 days of appropriate antibiotics. Any instance of macrohemorrhage carries high mortality.

LYME DISEASE

Background and Pathophysiology

Lyme disease is caused by *Borrelia burgdorferi*, a spirochete carried by the tick vector *Ixodes scapularis*. It is seen from spring to early fall in endemic areas of the Unite States (Northeast and upper Midwest) and Europe. Sufficient exposure to an infected nymph is required for transmission of the organism; this does not occur with bites of less than 24 hours. Common sites of infection include the popliteal fossa, axilla, groin, and back, and a characteristic rash (erythema migrans) is diagnostic but not always present/detected. Neurologic involvement typically occurs several weeks after initial exposure.

Diagnosis

Lyme is diagnosed by the characteristic rash in someone with a history of exposure or by Western blot demonstrating antibodies to the spirochete. Nervous system Lyme is often a clinical diagnosis in the setting of systemic Lyme. CSF antibodies or Lyme PCR are specific but insensitive.

Types

1. Meningitis: Typically a lymphocytic pleocytosis with normal glucose and elevated protein
2. Radiculitis: Acute to subacute onset of severe radicular pain, with or without associated weakness and sensory loss
3. Cranial neuropathy: Most commonly cranial nerve (CN) VII; can be bilateral

Management

Management of systemic Lyme, including facial palsy, is with 2 weeks of doxycycline 100 mg twice daily. In the United States, radiculitis, multiple CN palsies, and meningitis are treated with ceftriaxone 2 g IV daily for 28 days.

Prognosis

Prognosis of acute symptoms is excellent as is overall prognosis, although many will complain of lingering nonspecific symptoms, for which management is supportive. There is no evidence that prolonged or repeat antibiotic courses in the absence of reexposure are beneficial.

NEUROCYSTICERCOSIS

Background and Pathophysiology

Cysticercosis is caused by the pork tapeworm *Taenia solium*. Ingestion of undercooked pork containing cysts results in intestinal disease (called taeniasis) but not in neurologic disease. It is ingestion by fecal/oral route of the larvae, which then burrow across the intestinal lining and disseminate to eyes,

muscle, and brain/spinal cord, that results in cysticercosis. Neurocysticercosis (NCC) is one of the leading causes of epilepsy worldwide, and most commonly the presenting symptom is seizure, although for some forms, presentation relates to obstruction of CSF flow.

Diagnosis

Diagnostic criteria can be found in Table 19-8. Definitive diagnosis is made by any one absolute criterion or by two major and one minor plus one epidemiologic criterion. Probable diagnosis is made by one major plus two minor criteria, one major plus one minor and one epidemiologic criterion, or three minor plus one epidemiologic criterion.

Types

1. Parenchymal cysts: Can be solitary (more common in India) or multiple (more common in Central/South America and China)
2. Extraparenchymal cysts: Found in the subarachnoid spaces and ventricles, frequently in absence of parenchymal disease
3. Cysticercosis encephalitis: Innumerable parenchymal cysts that presents as encephalopathy

Management

There are four stages of cysticercosis, with the final stage being calcific. This stage is considered nonviable and does not require antiparasitics. For viable disease, with the exception of cysticercosis encephalitis, antiparasitic treatment (usually albendazole 15 mg/kg/d divided and/or praziquantel 20 mg/kg/d divided for at least 1 to 2 weeks, with dual therapy favored for multiple cysts) with adjunctive corticosteroids is warranted. There can be an intense inflammatory reaction to the breakdown of the cysts, and in some scenarios of extraparenchymal disease, particularly for intraventricular cysts, surgical extraction (taking care not to rupture the cyst) is first line. Shunting may also be necessary. For cysticercosis encephalitis, shunting and steroids are the management of choice.

Table 19-8 Proposed Criteria for the Diagnosis of

Neurocysticercosis			
Absolute	**Major**	**Minor**	**Epidemiologic**
Cystic lesion demonstrating scolex on neuroimaging	Highly suggestive cystic lesions on neuroimaging	Compatible cystic lesions on neuroimaging	Travel to or residence in endemic areas
Direct visualization of parasites on funduscopic exam	Serology demonstrating cysticercus antibodies	Clinical manifestations compatible with NCC	Demonstration of close contact with taeniasis
Pathologic evidence on biopsy	Resolution of lesions after antiparasitic therapy	Detection of cysticercus antibodies or antigen in CSF	
	Spontaneous resolution of cystic lesions compatible with NCC	Cysticercosis outside the CNS	

NCC, neurocysticercosis; CSF, cerebrospinal fluid; CNS, central nervous system.

Prognosis

The natural history of NCC is involution and death of the cyst over years. This often results in residual calcification. Antiparasitics hasten resolution and reduce sequelae of disease, but long-term management of ongoing epilepsy is commonly required.

NEUROSYPHILIS

Background and Pathophysiology

Syphilis incidence waxes and wanes, with a recent increase in the United States, particularly among men who have sex with men. Syphilis is commonly seen as a coinfection with HIV, although the previously typical neurologic presentations of tabes dorsalis and paralytic dementia are still rare. Statistics on contemporary neurologic presentations are lacking, although the observed shift is thought related in part to widespread use of antimicrobials (which partially treat the disease).

Diagnosis

Neurosyphilis can be asymptomatic, and presentations compatible with the diagnosis may also have alternative explanations. With a serum rapid plasma reagin (RPR) titer of 1:32 or greater, or coinfection with HIV, CSF evaluation is warranted. Venereal Disease Research Laboratory (VDRL) positivity in CSF is highly specific but highly insensitive; any unexplained elevation in protein or pleocytosis should prompt treatment.

Types

Strokes centered around the proximal MCA branches, chronic memory loss, vision loss, and myelopathy are the most common presentations in the antibiotic era.

Management

IV penicillin G 4 million units every 4 hours for 14 days is standard treatment for neurosyphilis. Desensitization is required in the event of penicillin allergy.

Prognosis

Chronic damage incurred by syphilis often does not reverse, although improvements can be made with aggressive rehabilitation.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Background and Pathophysiology

Progressive multifocal leukoencephalopathy (PML) is a demyelinating viral infection of oligodendrocytes by the John Cunningham virus (JCV). The vast majority of cases are seen as a result of immune compromise because of HIV, but it was first identified in the setting of lymphoproliferative disorders. Furthermore, with widespread use of immune-modulating agents (most notoriously the multiple sclerosis drug natalizumab), PML has become a dreaded complication of the treatment of autoimmune disease (Table 19-9).

PML is a reactivation disease, meaning that the virus remains quiescent in the body until the appropriate circumstances arise, including immune compromise and genetic mutation, allowing the virus to cause disease in the brain. The virus is ubiquitous throughout the world, and most of population is initially exposed during childhood or early adulthood. Antibodies to the virus can be detected in those who have been exposed, which impacts risk stratification. See Table 19-10 for risk stratification in the setting of natalizumab use.

Table 19-9 Predisposing Factors for Progressive Multifocal Leukoencephalopathy

Diseases	Therapies
HIV (CD4 <200)	Natalizumab
Lymphoproliferative disease	Other biologic agents (rituximab, efalizumab, infliximab, adalimumab, etanercept, brentuximab, ruxolitinib)
Myeloproliferative disease	Bone marrow/solid organ transplant
Carcinoma	Corticosteroids
Sarcoidosis[a]	Mycophenolate mofetil
Systemic lupus erythematosus[a]	Dimethyl fumarate
Rheumatoid arthritis[a]	Cancer chemotherapy regimens (especially cyclophosphamide)
Tuberculosis	

[a]Reports almost invariably confounded by history of exposure to therapies that also predispose to progressive multifocal leukoencephalopathy.

CD4, cluster of differentiation 4.

Table 19-10 Likelihood of Developing Progressive Multifocal Leukoencephalopathy in the Setting of Natalizumab Treatment for Multiple Sclerosis by Risk Factor

Characteristic	Risk
JCV antibody negative	<1:10,000
JCV antibody positive only	1:2,000
JCV antibody and prior immune suppression	1:625

JCV antibody and >24 months of treatment	1:200
JCV antibody, >24 months treatment, and prior immune suppression	1:90

JCV, John Cunningham virus.

Diagnosis

In the correct clinical setting, characteristic MRI findings (Table 19-11) along with detection of JCV DNA in the CSF are diagnostic. Although previously the gold standard, biopsy is now reserved for unclear cases.

Management

No proven therapies specific to JCV have proven effective. In general, immune restoration and supportive therapy are the current management strategies for all with PML. Because natalizumab has a long half-life, plasmapheresis is often necessary to remove the drug and expedite immune restoration.

Table 19-11 Magnetic Resonance Imaging (MRI) Findings in Progressive Multifocal Leukoencephalopathy (PML)

MRI Characteristic	Finding in PML Lesions
Location	Multifocal/confluent subcortical white matter abutting cortical ribbon
	Middle cerebellar peduncle extending into pons and cerebellar white matter
Mass effect	None
T_2/FLAIR	Hyperintense
T_1	Hypointense
Presence of lesional gadolinium enhancement	15% (HIV), 35% (natalizumab), 50% (IRIS)
Diffusion restriction	Variable; leading edge of lesion if present

FLAIR, fluid-attenuated inversion recovery; IRIS, immune reconstitution inflammatory syndrome.

Prognosis

Prognosis depends on degree of immune compromise and severity of disease.

Historically, those with PML related to HIV have had very poor outcomes, but for those in whom immune restoration is achieved, survival has improved, although has not been systematically evaluated. In natalizumab-related PML, survival rates have been reported at about 85%. Many, however, will have residual neurologic deficit.

HIV

Background and Pathophysiology

Neurologic complications of HIV can be divided by immune status and relationship to the virus (direct vs. indirect vs. opportunistic/neoplastic vs. treatment complication). Because HIV both invades the CNS within days of initial infection and results in chronic immune activation, controlled infection systemically results in eradication of opportunistic CNS infections but does not completely eliminate other CNS complications. Notably, HIV infects glial and immune cells, and therefore, neuronal damage is caused by secondary effects on neurons.

Diagnosis

Diagnosis of HIV in general is by detection of serum antibodies and/or by plasma RNA burden. Quantification of RNA from the CSF is also available albeit not Clinical Laboratory Improvement Amendments (CLIA)-certified. Many of the CNS complications in controlled HIV infection, however, are diagnosed clinically. HIV-associated neurocognitive disorders (HAND) have research-related diagnostic criteria and subcategories that can be found in Table 19-12.

Types

A listing of common complications can be found in Table 19-13. HAND prevalence has remained stable to slightly increased from the era of uncontrolled infection to that of complete plasma viral suppression, but the subtype of neurocognitive deficits has shifted toward less severe forms.

Table 19-12 Diagnoses Falling Under HIV-Associated Neurocognitive Disorder (HAND) Umbrella

HAND Subcategory	Diagnostic Criteria
Asymptomatic neurocognitive impairment (ANI)	One standard deviation (SD) below mean in two domains by neuropsychological testing without functional impairment
Minor neurocognitive disorder (MND)	One SD below mean in two domains with mild functional impairment
HIV-associated dementia (HAD)	One SD below mean in two domains with marked functional impairment

Table 19-13 Common Neurologic Complications of HIV Infection Stratified by Disease Severity

Controlled HIV	Uncontrolled HIV
Memory loss (minor)	Memory loss (dominated by dementia)
Peripheral neuropathy	Distal sensory polyneuropathy
CSF escape encephalomyelitis	Vacuolar myelopathy
Cerebrovascular disease	Toxoplasmosis (CD4 <100)
	AIDP/CIDP
	Cranial neuropathy
	Inflammatory myopathy
	Lymphoproliferative neuropathy
	PML (CD4 <200)
	Cryptococcal meningitis (CD4 <200)
	EBV-related primary CNS lymphoma (CD4 <100)
	CMV retinitis (CD4 <50)

CSF, cerebrospinal fluid; CD4, cluster of differentiation 4; AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; PML, progressive multifocal leukoencephalopathy; EBV, Epstein–Barr virus; CNS, central nervous system; CMV, cytomegalovirus.

Management

Treatment of CNS opportunistic infections can be found in Table 19-14. The

most important management strategy for any complication of HIV infection is viral suppression and immune restoration. For many complications, specific therapies are lacking. With robust response to antiretroviral therapy (ART), patients are at risk for immune reconstitution inflammatory syndrome (IRIS). Treatment is based on continuing immune restoration and supportive care. In some circumstances (e.g., cryptococcal meningitis), specific antimicrobials are initiated prior to ART to reduce antigen burden; some experts recommend corticosteroids adjunctively but controlled studies are lacking.

Prognosis

Prognosis varies by complication type. For controlled individuals with cognitive deficits of any etiology (unless medication-related), most will suffer indolent disease. For those with complications relating to severe immune suppression, immune restoration and specific treatment of opportunistic infection results in prolonged survival with varying degrees of permanent sequelae.

TUBERCULOSIS

Background and Pathophysiology

Mycobacterium tuberculosis is one of the most common infections worldwide. Neurologic symptoms usually arise secondary to pulmonary disease but can occur in isolation.

Table 19-14 Management of Central Nervous System Opportunistic Infections in AIDS

Opportunistic Infection	First-Line Therapy (70 kg)	Notes
Toxoplasmosis	Initial: pyrimethamine 200 mg × 1 followed by pyrimethamine 75 mg p.o. daily plus sulfadiazine 1,500 mg p.o. q6h plus leucovorin 10–25 mg p.o. daily × 6 wk Maintenance: pyrimethamine 25–50 mg p.o. daily plus sulfadiazine	Corticosteroids are occasionally required to treat severe mass effect.

	2,000–4,000 mg p.o. daily (divided) plus leucovorin 10–25 mg p.o. daily until CD4 >200 × 6 mo	
Cryptococcal meningitis	Induction: liposomal amphotericin B 3–4 mg/kg IV daily plus flucytosine 25 mg/kg p.o. four times daily × 2 wk Consolidation: fluconazole 400 mg p.o. daily × ≥8 wk Maintenance: fluconazole 200 mg p.o. daily × ≥1 y; can discontinue thereafter if CD4 ≥100 cells/μL and HIV RNA is suppressed × ≥3 mo and patient is asymptomatic	Serial lumbar punctures and/or CSF diversion may be required to manage elevated intracranial pressure.
Progressive multifocal leukoencephalopathy (PML)	Immune restoration with combination antiretroviral therapy	No effective antiviral therapy currently available
Cytomegalovirus retinitis	One to four intravitreal injections of ganciclovir 2 mg or foscarnet 2.4 mg over 7–10 d with 900 mg p.o. valganciclovir twice daily for 14–21 d	No defined therapies or duration exist for CMV ventriculoencephalitis or sacral radiculitis

CD4, cluster of differentiation 4; CSF, cerebrospinal fluid; CMV, cytomegalovirus.

Diagnosis

Interferon gamma release assay (IGRA) or tuberculin skin testing (TST) is used to detect *M. tuberculosis* infection, although TST has the disadvantage of giving false-positive results in the setting of prior bacillus Calmette–Guérin (BCG) vaccination. This is not necessarily specific for neurologic disease, however. CNS tuberculomas, which present as slow growing rim-enhancing lesions on MRI (often with disproportion between clinical symptoms and imaging) require biopsy unless unsafe to do so, in which case empiric treatment and serial imaging help to make the diagnosis in retrospect. Evaluation of CSF for tuberculosis meningitis (TBM) often demonstrates mixed or lymphocytic pleocytosis with low glucose and high protein. TB culture from the site of involvement is often tedious and insensitive. Organism detection by PCR or staining for acid–fast bacilli is also of low sensitivity. Specificity, however, is high for all of these approaches.

Types

1. Pott disease: Osteomyelitis often in the thoracic spine given proximity to the

pleura; this can grow to cause compression on the spinal cord and myelopathy.

2. TBM: Most commonly basilar and thought because of hematogenous spread via the circle of Willis. Cranial neuropathies often accompany typical meningeal symptoms.
3. Tuberculoma: Focal abscess that can be solitary or multiple; this is a rare presentation.

Management

Quadruple therapy is the standard therapy for active TB (Table 19-15). Drug resistance is an emerging problem but is overall rare in the setting of neurologic disease. Surgical spine stabilization should be considered in severe cases of Pott disease.

Prognosis

Prognosis varies, but overall, mortality for TBM is about 30%. Most neurologic morbidity or mortality occurs in the setting of missed and/or late diagnosis.

Table 19-15 Recommended Treatment of Drug Susceptible Central Nervous System Tuberculosis Infection

Phase	Regimen	Notes
Intensive (2 mo)	Isoniazid 300 mg p.o. daily (with pyridoxine 25 mg p.o. daily) + Rifampin 600 mg p.o. daily + Pyrazinamide 15–30 mg/kg p.o. daily + Ethambutol 15–25 mg/kg p.o. daily	1. Concomitantly administer dexamethasone (0.3–0.4 mg/kg/d) × 4–6 wk followed by slow taper over 6–8 wk. 2. Monitor for liver toxicity. 3. Direct observation required 5–7 d/wk.
Continuation (7–10 mo)	Isoniazid 300 mg p.o. daily (with pyridoxine 25 mg p.o. daily) + Rifampin 600 mg p.o. daily	1. Monitor for liver toxicity. 2. Direct observation required 5–7 d/wk.

PRION DISEASES

Background and Pathophysiology

The prion protein is encoded by the PRNP gene and is naturally occurring in the human brain. Its distortion leads to an infective particle that propagates through the brain. Although brains affected by prion disease are contagious in the correct setting, only a small fraction of prion diseases actually originate by infectious means. Eighty-five percent affect the elderly population and occur sporadically, and about 10% are familial. Less than 5% are acquired through exposure to infected material, and this exposure is usually via infected brain tissue. There have been cases linked to blood transfusions, albeit extremely rarely. Overall population incidence is about 1/1,000,000.

Diagnosis

Clinically, a rapidly progressive (<2 years) dementing illness presents, although in familial cases, the time course can be longer. Patients develop myoclonus, cerebellar ataxia, hyperreflexia, and subsequently progress to akinetic mutism. Definitive diagnosis is made by pathologic identification of spongiform changes most frequently in the deep gray structures and cerebellum; genetic sequencing of the prion protein from tissue reveals the specific type. Probable diagnosis can be made in the setting of the correct clinical scenario coupled with the following: typical MRI findings of diffusion restriction throughout the cortical ribbon and within the basal ganglia and sometimes the thalamus, suggestive EEG, detection of 14-3-3 protein in CSF. Extreme elevations of CSF tau protein are also common, and a recent assay to detect prions within the CSF is also available, although its utility is currently being determined.

Types

1. Sporadic
   a. Sporadic Creutzfeldt–Jakob Disease (sCJD) is the most common, and its pathophysiologic trigger is unknown.
   b. Sporadic fatal insomnia
2. Familial: May present at younger ages and may have prolonged courses; all

have autosomal dominant inheritance.

a. Familial CJD (fCJD): Most common of familial prion diseases
b. Gerstmann–Straüssler–Scheinker disease: Extremely rare
c. Familial fatal insomnia: Extremely rare

3. Acquired

a. Variant CJD (vCJD): Acquired from consumption of cattle affected by bovine spongiform encephalopathy (mad cow disease); exposures were linked to husbandry practices in the 1970s and 1980s that since have been changed; notably only affected individuals with a specific PRNP genotype.
b. Iatrogenic CJD (iCJD): Extremely rare; caused by consumption of cadaveric thyroid hormone (a historic practice), dural and corneal transplant, or exposure to contaminated neurosurgical instruments previously used on CJD patients.
c. Kuru: A historic disease relating to cultural practice of human brain consumption among the Fore tribe in Papua New Guinea.

Management

Management is supportive; there is no treatment or cure for prion diseases. For familial forms, extensive genetic counseling of the patient and core family members is imperative.

Prognosis

Prion diseases are universally fatal.

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Drug Index

Generic names are boldface in main entries. *Trade names* of drugs are in italics. **DRUG CLASSES** appear in bold capital letters with the drugs that fall in that class listed as official names under the class heading.

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