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Brain Abscess and Meningitis

Subarachnoid Hemorrhage: Timing Problems

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Obituary

In deep sorrow, the neurosurgeons of Germany gathered in Erlangen on November 17, 1980 to take

Prof. Dr. med. Wolfgang SCHIEFER

to his final resting place. He died of a heart attack in the midst of his clinical work on November 11, 1980. On January 20, 1981 he would have looked back on 62 years of life – a life which was so strongly influenced by his profession that he did not simply practice it, he was completely absorbed by it.

Following his graduation in medicine and his doctoral thesis, he began his career in medicine in 1946 under the great physician and surgeon, Wilhelm TÖNNIS, the founder of German neurosurgery, who at that time was at the Knappschaftskrankenhaus in

WOLFGANG SCHIEFER

Bochum-Langendreer. In preparation for his neurosurgical training, SCHIEFER studied neuropathology at the Max-Planck-Institut für Hirnforschung under K. J. ZÜLCH and the physiology of cerebral circulation at the Physiologisches Institut of the University of Cologne under Max SCHNEIDER.

When TÖNNIS was appointed to the chair of neurosurgery at the University of Cologne, SCHIEFER assumed much of the responsibility of building the new neurosurgical hospital there. Since this building was an enlargement of the Nervenklinik in Cologne, this architectual concept led to the development of Germany's first *Nervenzentrum* under the direction of Wilhelm TÖNNIS and Werner SCHEID.

The fact that the two Colognians, Wolfgang SCHIEFER and Hans-Heinrich WIECK, built such a magnificent Kopfklinik (for neurology, psychiatry, neurosurgery, and opthalmology) in Erlangen is the manifestation of this fruitful and constructive idea passed on to generations of teachers and students.

From 1951 to 1958, Wolfgang SCHIEFER was an assistant and later the Oberarzt of TÖNNIS in Cologne. In 1957, SCHIEFER wrote his Habilitationsarbeit on the subject *Die Bedeutung der Serienangiographie für die Erforschung des Hirnkreislaufs* (The Importance of Serial Angiography for the Study of the Cerebral Circulation) for which he received the Prize of the Niederrheinische Chirurgen Vereinigung. In 1959 his book *Zirkulationsstörungen des Gehirns im Serienangiogramm* (Circulatory Disturbances of the Brain in Serial Angiography), written in collaboration with TÖNNIS, was published. This book has lost nothing of its importance in the course of time, because it is the result of solid clinical basic research and is based on an angiographic technique which is still of the highest standard. His later research was also devoted to the development and application of new diagnostic methods. SCHIEFER's publications include 111 papers, 6 books, and 16 handbook chapters.

In 1967 he organized the international symposium „Echo-Encephalographie" in Erlangen and the book *Klinische Echo-Encephalographie* (Clinical Echoencephalography), which he published together with Ekkehard KAZNER, is a standard reference text in this field. And it is not surprising that the „Internationales Symposium zur Koordinierung der neurologischen Wissenschaften" (International Symposium for the Coordination of Neurosciences) has already been held in Erlangen twice. In 1975 the topic of this symposium was spinal space-occupying lesions and in 1979, it was neurotraumatology. Numerous papers on infectious diseases of the central nervous system and on brain abscesses are the groundwork for a recently concluded handbook chapter written with Stefan KUNZE.

All his professional and scientific work had a strong clinical bent, because contact with the patient and a genuine feeling of responsibility toward his patients always had priority for him. Although he deeply sympathized with the fate of his patients, he still succeeded in giving them strong moral support. In his students and in his staff he created not only enthusiasm for the task of helping others, but also the optimism which is often necessary in the field of neurosurgery.

Wolfgang SCHIEFER's death also left a large gap in the Deutsche Gesellschaft für Neurochirurgie. From 1970 to 1974, he was the secretary of this society and from 1974 to

1976, he was its vice-president. He declined the position of president which was then offered to him, because he wished to devote all his energy to the construction of the new Kopfklinik.

The Thirty-First Annual Meeting of the Deutsche Gesellschaft für Neurochirurgie in May 1980, held in Erlangen, which Wolfgang SCHIEFER as congress president, organized and planned in an exemplary manner, will remain unforgettable because it was filled with his warm-hearted, endearing spirit from beginning to end.

In Erlangen Wolfgang SCHIEFER established and developed the discipline of neurosurgery. The milestones of his involvement in this development are as follows:

On March 1st, 1958, he became the head of the Neurochirurgische Abteilung der Chirurgischen Universitätsklinik.

On December 20, 1963, he was named *außerplanmäßiger Professor*. On April 16, 1965 he was appointed to the newly created chair of neurosurgery.

In 1968, he decided not to accept the position as head of the department, which his teacher Wilhelm TÖNNIS had vacated. Students and residents thanked him for this decision to remain in close contact with them with a torchlight procession.

In the spring of 1978, the Department of Neurosurgery moved into one of the most modern neurosurgical hospitals in Germany.

For him the fulfillment of these responsibilities was not merely a duty, it was the content of his life. The Neurochirurgische Universitätsklinik Erlangen was not only the instrument for the highest development of his medical skill, it was also his most valuable possession – his home – and those who worked with him were his family members.

Although the new university laws define the tasks of a professor quite differently – and although these laws rule our hospitals by way of the administrations – future generations will, nevertheless, do well to remember that not such laws, but rather men like Wolfgang SCHIEFER, who are the reason for the fame and good reputation of German universities abroad.

WOLFGANG SCHIEFER, we thank you!

Prof. Dr. H. P. JENSEN

President of the
Deutsche Gesellschaft für Neurochirurgie

Introduction

W. SCHIEFER

The 31st annual meeting of the Deutsche Gesellschaft für Neurochirurgie was held in Erlangen on May 1 – 4,1980. The numerous participants obviously enjoyed the opportunity to become acquainted with the attractive city of gardens, lecture theatres and workshops surrounded by a lovely countryside and a historic environment. The program included a visit to the neighboring city of Nürnberg, to the old Reichsstadt Regensburg and an opening ceremony in the orangerie of the Erlangen palace, where the "Bamberger Ensemble für alte Musik" presented interesting and little-known early music.

The annual meeting was held in the newly-built "Kopfklinik" of the University of Erlangen-Nürnberg, which houses the departments of neurosurgery, neurology and ophthalmology. As far as possible, many functions of this hospital were centralized because this has economic advantages and saves personell. Other functional units, such as the operating theatres, the intensive care units, research laboratories and units specific to the individual disciplines remained decentralized and independent. This concept has proved to be a happy solution.

At the membership meeting of the Deutsche Gesellschaft für Neurochirurgie, Prof. Dr. K. J. Zülch of Cologne was made an honorary member of this society, of which he is a founding member.

In the choice of scientific topics for this 31st annual meeting, we were guided by the thought that problems should be discussed which had not been the theme of recent neurosurgical meetings or symposia, or problems that merited further discussion. The first chief topic was "Brain Abscess and Meningitis" from a neurosurgeon's point of view, while the second chief topic dealt with the "Timing Problems in the Diagnosis and Treatment of Subarachnoid Hemorrhage".

Even in the age of antibiotics, brain abscesses continue to present numerous problems. The influence of the antibiotics has altered the underlying disease and the clinical course in many cases, but the actual number of brain abscesses has not decreased. The continuously changing spectrum of causative organisms and their rapid development of resistance against antibiotics constantly present new problems. Up-to-date information from clinical microbiology, as well as on symptomatology and clinical picture, including computer tomography, was discussed. In addition to the antibiotics, research and clinical evidence has shown that dexamethasone is of decisive importance for successful treatment today. Animal experiments on the penetrability of newer antibiotics into the CSF as well as into brain substance, as determined by survival rates, provide valuable data in the choice of antibiotic therapy.

The second chief topic of the meeting was the course of treatment to be followed at the time of a subarachnoid hemorrhage and subsequently. It would be irresponsible to pretend that the problems of aneurysm treatment have all been solved. There are such wide gaps between the data of the various neurosurgical centres in Germany as well as abroad that a clear classification of clinical states and patterns of treatment are necessary. The optimism of modern aneurysm treatment directs attention more to treatment successes than to failures. Sensational medical reports are of less importance than the cautious and reflected evaluation of the possibilities and the limitations, however. The careful analysis of the failures and of undesirable side effects of medical practice is an indispensible ingredient of scientific medicine and a basic prerequisite for further progress.

Almost all the leading German-speaking neurosurgeons participated in the final round table discussion on the topic "Timing Problems in the Diagnosis and Treatment of Subarachnoid Hemorrhage". Despite some incertitude, a distinct trend towards earlier operations evolved, with the goal of escaping the danger of deadly re-bleeding. This is particularly true for patients in stage I, who have not had a loss of consciousness, where the computer tomogram shows no signs of cisternal tamponade, and where the angiogram fails to reveal angiospasm. There is less certainty about the timing of operations in patients with an initial loss of consciousness and with signs of hemorrhage in the computer tomogram. Operation was recommended after the 10th day in these cases. Patients in stage III and IV cannot undergo operation at an early date. Extensive discussion was devoted to the positive aspects of antifibrinolytic therapy. Because of the great interest in this topic, the auditorium remained filled to the end of the meeting.

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Brain Abscess and Meningitis

Brain Abscess and Acute Purulent Meningitis: Recent Developments in Clinical Microbiology

W. H. TRAUB

The purpose of this brief review is to mention some of the more recent developments in clinical microbiology with respect to brain abscesses and acute bacterial meningitides. Much of the relevant material has been condensed into tables.

Brain Abscess

Brain abscesses may arise as a complication of several illnesses (3, 21, 26, 35, 45). The various modes of pathogenesis of this infectious syndrome are shown in Table 1, including cryptic dental sepsis (32). The most common underlying illnesses are summarized in Table 2. Some of the salient clinical features, diagnostic methods, some of the pertinent differential diagnoses, and the bacteriological workup of brain abscess material, are listed in Table 3. The causative microorganisms are shown in Table 4. It should be stressed that the proportion of anaerobic bacteria isolated from brain abscesses appears to be a reflection of the quality of anaerobic culture techniques of given bacteriology laboratories. The surgical and adjunct chemotherapy of brain abscesses are stated in Table 5. Chemotherapeutic information, regarding *Nocardia asteroides* is given in Table 6 (15, 22, 54, 76). It must be emphasized that *N. asteroides* have been discerned as well (59). Although the majority of strains are susceptible to sulfonamides, such as sulfadiazine and sulfisoxazole, this microorganism appears to be resistant against cotrimoxazole (trimethoprim + sulfamethoxazole). With respect to chemotherapy for anaerobic bacteria, several points require emphasis. First, as summarized by FINEGOLD (21), chloramphenicol achieves ready penetration of the blood-brain-barrier (Table 7).

Table 1. Brain abscesses: pathogenesis

1. Penetrating head injuries Neurosurgery (endogenous/exogenous infection)
2. Extension of infectious processes (direct, retrograde) Usually solitary abscesses Infections of the middle ear, mastoid, paranasal sinuses Chronic otitis media, mastoiditis - temporal, cerebellar frontal, sphenoidal sinusitis - frontal, temporal
3. "Metastatic" brain abscesses (usually multiple) Lung abscesses, pneumonitias, empyema, bronchiectases - frontal, parietal, occipital rarely temporal, cerebellar Congenital heart malformations (right-left-shunts) - cerebellar Acute bacterial endocarditis - miliary abscesses

Table 2. Brain abscesses: underlying illnesses. Modified from (21, 26, 32)

Chronic otitis media
Mastoiditis
Sinusitis
Pulmonary infections (bronchiectases, abscesses, empyema, pneumonia)
Congenital heart malformations (right-left-shunts)
Bacterial endocarditis
Septicemia
Facial, scalp infections
Tonsillitis
Trauma
Surgery, neurosurgery
Rarely: dental septicemia
Criminal (septic) abortion

Table 3. Brain abscesses: clinical features, diagnosis

Clinical features:
Low grade fever (not with encapsulated abscesses)
Neutrophilic granulocytosis
Symptoms and signs of tumors
Headaches, confusion, stupor
Generalized or focal convulsions
Nausea, vomiting
Focal motor, sensory or speech defects
Papilledema (advanced stages, 50%)
Diagnosis:
Non-characteristic cerebrospinal fluid abnormalities
Slight increase in CSF pressure
Low grade pleocytosis (25 to 300 cells/mm^3)
Protein slightly elevated
Glucose usually normal
CSF cultures usually negative
X-ray studies (mastoid, paranasal sinuses)
EEG (slow waves, 3/sec)
Echoencephalography
Ventriculography (parietal)
Scintigraphy (Technetium 99 m)
Arteriography (temporal)
Computerized axial tomography (CAT scans)
Differential diagnoses:
Subdural abscess, subdural empyema, extradural abscess, cerebral thrombophlebitis, focal embolic encephalopathy, mycotic aneurysm, brain tumor, necrotizing viral encephalitis, ischemic infarction, acute necrotizing hemorrhagic encephalopathy
Definitive laboratory diagnosis:
Neurosurgical tissue, exsudate
Gram-stain
Modified ZIEHL-NIELSEN stain *(Nocardia asteroides)*
Cultures: aerobic *and* anaerobic
Antibiograms, MIC and MBC determinations

Table 4. Brain abscesses: microbiology. Modified from (21)

I. Anaerobic bacteria: 11-35-89% (various literature statements)

Bacteroides fragilis
Other Bacteroides Sp.
Fusobacterium Sp. (F. necrophorum)
Peptostreptococci
Peptococci
Microaerophilic streptococci
Actinomyces israelii
Other gram-positive, non-spore-forming bacteria
Clostridium Sp.

II. Facultative anaerobic-aerobic bacteria:

Staphylococcus aureus
Streptococcus pneumoniae
Alpha-hemolytic streptococci
Haemophilus influenzae
Haemophilus aphrophilus
Other gram-negative rods: enterobacteriaceae
pseudomonadaceae
Nocardia asteroides
Neisseria meningitidis

III. Additional microorganisms:

Mycobacterium tuberculosis
Fungi, e.g., cladosporium Sp.
Entamoeba histolytica

Table 5. Brain abscesses: therapy (mortality = 25-40%). Modified from (30)

1. Neurosurgical drainage/excision

2. Chemotherapy: early onset, high dosage, long-term

Chloramphenicol (succinate) intravenous
50 - 60 mg/kg/day
All anaerobic bacteria, N. meningitidis,
streptococci, H. influenzae, staphylococci

Penicillin G intravenous
200 - 300 mg/kg/day (= 320 - 480,000 IE)
Anaerobic bacteria (with the exception of
B. fragilis, some Fusobacterium Sp.)
N. meningitidis, group A B-hemolytic
Streptococci, alpha-hemolytic streptococci,
Haemophilus aphrophilus

Penicillinase-resistant penicillin, e.g. nafcillin
200 - 250 mg/kg/day intravenous
Staphylococcus aureus
S. epidermidis (combination chemotherapy necessary)

Table 6. Nocardia asteroides. Based on (15, 22, 59, 54, 76)

Underlying illness +/- corticosteroids, immunosuppression, cytotoxic chemotherapy
Rarely trauma
Nosocomial infections possible
Primary infections: 15-40%

Chemotherapy:

Penicillinase - inactivates penicillin G
Additional resistance mechanism: some strains resistant against ampicillin and carbenicillin
Resistant against co-trimoxazole

N. asteroides usually susceptible to:
sulfonamides (sulfadiazine, sulfisoxazole)
Minocycline
Ampicillin + erythromycin
Triple sulfonamides + ampicillin

Table 7. Activity, pharmacokinetics of antimicrobial drugs against anaerobic bacteria (central nervous system). Based on (21)

Antimocrobial drug	Toxicity	Passage of blood-brain barrier	Alteration of bacterial normal flora	Administration local	Administration parenteral	Bactericidal activity
Penicillin	(+)	Good	Minimal	+	+	+++
Linomycin	++	Poor	Marked	+	+	(+)
Clindamycin	++	Poor	Marked	+	+	++
Metronidazole	(+)	? good	? minimal	+	-	++++
Chloramphenicol	+++	Excellent	Minimal	+	+	-
Tetracyclin	(+)	Good	Minimal	+	+	-
Erythromycin	(+)	? good	? minimal	+	+	-
Vanocomycin	+++	Poor		-	+	+++

The future role of metronidazole for the chemotherapy of brain abscesses (3) needs to be established through additional clinical studies. The state of the art regarding the currently available armamentarium of antimicrobial drugs (70) against anaerobic bacteria is summarized in Table 8; cefoxitin and co-trimoxazole appear to be promising drugs (71, 81), apart from metronidazole, although the latter drug appears to be less active against Gram-positive, non-spore-forming anaerobic bacteria (45). As shown in Table 9, a variety of anaerobic bacteria, notably *Bacteroides fragilis* and *B. melaninogenicus*, produce β-lactamases, which hydrolyze benzyl penicillin and related drugs (52, 53, 64, 77). The β-lactamase of *B. fragilis* is susceptible to clavulanic acid as determined recently by WISE (80). These β-lactamase-producing microorganisms are readily detectable with a rapid test for bacterial β-lactamase (Table 10), utilizing the semisynthetic cephalosporin (Glaxo) Nitrocefin (11). It should be added that resistance (R-) plasmids are being detected at an increasing rate among gram-negative, non-spore-forming, anaerobic bacteria; for instance, MANCINI and BEHME (42) have

Table 8. Antibiotic susceptibility of anaerobic bacteria. Modified from (45)

Microorganism	Penicillin	Lincomycin	Clindamycin	Metronidazole	Chloramphenicol	Tetracycline	Erythromycin	Vancomycin	Carbenicillin
Microaerophilic and anaerobic cocci	++++	+++	+++	++	+++	++	++/+++	++/+++	+++
Bacteroides fragilis	+	+/++	+++[a]	+++	+++	+/++	+	+	++/+++
B. melaninogenicus	++++[b]	+++	+++	+++	+++	+++	++	+	+++
Fusobacterium varium	+++[b]	++	++/+++	+++	+++	++/+++	+	+	+++
Other Fusobacterium Sp.	++++	+++	+++	+++	+++	++/+++	+	+	+++
Eubacterium, Actinomyces	++++	++/+++	++/+++[a]	+/++	+++	++	++/+++	?+++	?+++
Clostridium perfringens	+++[b]	+/++	+++[a]	+++	+++[b]	++	+/++	+++	+++[b]
Other Clostridium Sp.	++/+++	+	++	?+++	+++[a]	++	++/+++	?+++[b]	+++[b]

[a] Rarely resistant
[b] Few strains resistant

Addendum:
(81): Trimethoprim-sulfamethoxazole (1:19) active against 85% of 144 anaerobic isolates; effective against 100% (45) isolates of *B. fragilis*.
(71): Cefoxitin (≥ 32 µg/ml) inhibited 100% of *B. melaninogenicus*, *Fusobacterium Sp.*, anaerobic cocci, *C. perfringens* isolates.
91% of *B. fragilis*, 98% of other *Bacteroides Sp.*,
96% of non-spore-forming Gram-positive bacteria,
64% of other *Clostridium Sp.*.

Table 9. β-lactamases of anaerobic bacteria

Bacteroides fragilis[a]	Penicillin MIC (μg/ml)
Highly resistant	128 - 512
Slightly resistant	8 - 16
Sensitive, no β-lactamase	0.125
Sensitive, weak β-lactamase	2
(MW of β-lactamases 29-31.000 and 43.000 Daltons)	
B. melaninogenicus[b]	0.8
B. oralis[c]	
Clostridium ramosum[d]	
C. clostridiiformis[d]	

[a] (53). [b] (52). [c] (64). [d] (77).

Table 10. Rapid slide test for β-lactamases of anaerobic bacteria. Modified from (11).

1 drop of 500 μg/ml cephalosporin 87/112 (Nitrocefin/Glaxo)
+ 1 loopful of bacteria (from Brucella blood agar),

15 min: positive: red = penicillin G MIC 0,78 μg/ml
negative: yellow.

Microorganism	n	MIC penicillin G 0.78 μg/ml	β-lactamase Nitrocefin	jodometric
B. melaninogenicus	46	25	25	25
B. fragilis	78	77	70	0
Other Bacteroides Sp.	21	11	10	0
Fusobacterium Sp.	25	0	0	0

Addendum: This test is suitable for the detection of β-lactamases of clinical isolates of *Staphylococcus aureus* and *Haemophilus influenzae*.

succeeded in transferring in vitro antibiotic resistance against β-lactam antibiotics, tetracyclines, and chloramphenicol from *B. fragilis* to *Escherichia coli* through bacterial conjugation, an alarming finding. Furthermore, a strain of *B. fragilis* was recently found to produce a constitutive chloramphenicol acetyltransferase (12).

Acute Purulent Meningitis

The causative bacteria of a large series of meningitis cases are listed in Table 11. The most common pathogens were *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae* (48), confirming previous findings (23, 72). Of these, *S. pneumoniae* is encountered most frequently in post-traumatic bacterial meningitis (27). Conventional and more recent laboratory methods for the diagnosis of bacterial meningitides (2) are listed in Table 12, in particular methods for the detection of bacterial capsular antigens, such as

Table 11. Acute purulent bacterial meningitis.
Mortality, United Kingdom, 1974 (CDC-MMWR, 20.9.1975)

Microorganism	No. of positive cultures	Deaths	%
N. meningitidis	1091	74	7
H. influenzae	342	13	4
S. pneumoniae	288	51	18
Other streptococci	69	20	29
E. coli	81	22	27
Staphylococci	79	5	6
M. tuberculosis	30	4	13
L. monocytogenes	15	7	47
P. aeruginosa	11	1	9
P. morganii	10	1	10
K. pneumoniae	8	2	25
Salmonella Sp.	4	1	25
Other species	8	6	75
Total	2036	207	10

Table 12. Acute, purulent, bacterial meningitis[a,b]
Laboratory diagnosis: 30-50% of cases pre-treated

A. *Blood* specimen - culture

B. *Cerebrospinal fluid* specimen:
Lumbar puncture (occipital, ventricular puncture)
Aseptic technique, 3 sterile tubes
Caution: inoculation of bacteria into CSF compartment[c]

1. *Hematology laboratory:*
Cell count (pleocytosis)
% neutrophilic granulocytes/mononuclear cells

2. *Clinical chemistry laboratory:*
Protein (> 80 mg/dl)
Glucose (< 45 mg/dl)
Lactate (> 35 mg/dl)[d], including pre-treated cases
Conventional or gas-liquid chromatography methods
Caution: CNS-necroses, tumors

3. *Bacteriology laboratory:*
Pleocytosis: Tyndall "snowy" effect (bedside test)[e]
$= \geq 20$ cells/mm^3

a) *Conventional* procedures:
Gram-stain of sediment
Aerobic and anaerobic cultures
Identification: biochemical tests
Antibiogram - direct, followed by standardized antibiogram
MIC- and MBC-determination ("tolerance")

b) *Detection of capsular bacterial antigens*
Latex agglutination
Countercurrent immunoelectrophoresis
Coagglutination (S. aureus, protein A)

ELISA (enzyme-linked immunosorbent assay)
Limulus endotoxin assay (Gram-negative bacteria)

[a] (30). [b] (60). [c] (24). [d] (1, 10, 13, 20, 25, 65). [e] (68).

latex agglutination (37, 73, 79), countercurrent immunoelectrophoresis (73, 79), coagglutination (*Staphylococcus aureus*, Protein A; 73), and the enzyme-linked immunosorbent assay (ELISA; 9, 29), as well as the Limulus assay for the detection of Gram-negative bacterial lipopolysaccharides (36, 61). One word of caution regarding lumbar punctures seems appropriate. FISCHER et al. (24) observed 4 bacteremic pediatric patients who developed meningitis after lumbar puncture, a finding that was verified in experimental laboratory animals. Lactate measurements in cerebrospinal fluid (CSF) specimens serve as a sensitive indicator of acute purulent meningitis, especially so in pretreated cases (1, 10, 13, 20, 25). Recently, SIMON and ABELE (68) drew attention to a very simple bedside diagnostic test with respect to estimating CSF pleocytosis via notation of the presence ($\geq$ 20 cells/mm^3) or absence of scattered light by suspended particles (= cells). Also, MOORE and ROSS (47) observed three pediatric patients with acute symptoms of meningeal irritation, whose CSF revealed either no or only minimal abnormalities; two of the 3 uncentrifuged CSF specimens revealed no bacteria. In this context, many cases of acute bacterial meningitis reveal concomitant bacteremia, as emphasized by SWARTZ and DODGE (72); therefore, a blood specimen should be submitted along with every CSF specimen to the bacteriology laboratory (Table 13). Some additional pitfalls regarding the procurement and bacteriological processing of CSF specimens, notably those of exogenous or endogenous contamination (19, 78) and errors in the interpretation of Gram-stained smears (60), are listed in Table 14. Tables 15-18 depict results obtained with various laboratory methods designed for the detection of bacterial capsular antigens in body fluids, in this case CSF specimens. Evidently, latex agglutination is somewhat more sensitive than countercurrent immunoelectrophoresis (CIE); coagglutination in turn proved more sensitive than latex agglutination (Table 16). However, the ELISA method appears most promising in this regard (Table 17), in that it is far more sensitive than either of the former methods (9, 29). For instance, the ELISA assay was 25-fold more sensitive than CIE in the detection of pneumococcal capsular polysaccharide (29). BEUVERY et al. (9) stressed some of the inherent advantages of the ELISA technique as contrasted with radioimmunoassays (Table 17). The Limulus assay for Gram-negative bacterial lipopolysaccharides is capable of detecting ng amounts of endotoxin. Various investigators attested to the specificity of this method, as summarized by JORGENSEN and LEE (36) and shown in Table 18.

For presumptive chemotherapy, i.e., prior to availability of laboratory antibiograms, HOEPRICH (30) recommends specific antimicrobial drugs of first and second choices, respectively, given the patient's age (Table 19) or underlying clinical problem (Table 20). Following receipt of the results of antimicrobial susceptibility tests, HOEPRICH (30) advises use of those drugs that are listed in Table 21. Drugs and relevant dosages for the intrathecal route of administration are listed in Table 22, as based on the recommendations of SIMON and STILLE (67).

With respect to hydrocephalus-shunt infections by staphylococci, SCHOENBAUM et al. (65) noted that these occurred in 27% of 289 hydrocephalic patients during a 10-year observation period. *Staphylococcus epidermidis* and *S. aureus* accounted for one-half and one-quarter of these infections, respectively. As pointed out also by ARCHER (4) and LOWY et al. (41), removal of the infected shunt in conjunction with administration of systemic antibiotics constituted effective therapy. Given the notorious multiple antibiotic resistance of *S. epidermidis* isolates, the combination of either gentamycin + vancomycin or rifampin + vancomycin currently is recommended for this particular microorganism.

Table 13. Incidence of positive Gram stains and cerebrospinal fluid cultures. Modified from (72)

Microorganism	Positive Gram stain (%)	Positive CSF culture (%)	Positive blood culture (%)	Negative Gram stain, positive CSF culture (%)	Falsely interpreted Gram stains, positive CSF cultures (%)
S. pneumoniae	77	91	56	14	2
H. influenzae	67	96	79	16	13
N. meningitidis	54	87	33	38	0

Table 14. Bacteriological work-up of CSF specimens: pitfalls

1. Poor skin desinfection (lumbar puncture): contamination through bacteria of normal skin flora: staphylococci, *Propionibacterium acnes*
2. Contamination through aerosols from personnel: bacteria from normal flora of oropharynx, skin, etc.
3. Contamination of commercial lumbar puncture kits through nonviable bacteria - false positive Gram stains[a]
4. Faulty cleansing of glass slides, storage in contaminated ethanol[b]
5. Erroneous interpretation of stain precipitates, artifacts (use of stabilized, commercial stain reagents)[c]
6. Gram stain variability of *Neisseria meningitidis* in early stages of meningitis (differential diagnosis: staphylococci)

[a] (78). [b] (19). [c] (60).

Table 15. Detection of bacterial capsular antigens through latex agglutination (Latex) and countercurrent immunoelectrophoresis (CIE). From (79).

Microorganism	No. of examined CSF specimens	Positive (%) Latex	CIE	Gram stain or culture
N. meningitidis	126	88	89	79
S. pneumoniae	87	82	98	67
H. influenzae	16	94	88	69
Unproven meningitis, controls	162	0	0	0

Table 16. Detection of bacterial capsular antigens in CSF specimens through latex agglutination (Latex). From (73)
Countercurrent immunoelectrophoresis (CIE)
Coagglutination (*Staph. aureus* Protein A; Co-aggl.)

Microorganism	No. of positive/examined CSF specimens		
	Co-aggl.	Latex	CIE
H. influenzae	58/63	32/37	49/65
S. pneumoniae	3/5	2/4	1/5
N. meningitidis	2/6	1/5	1/6
Group B streptococci	0+10	0/10	0/10

Table 17. Detection of bacterial capsular antigens through enzyme-linked immunosorbent assay (ELISA) and countercurrent immunoelectrophoresis (CIE). From (9)

Microorganism	No. of examined CSF specimens	Positive specimens	
		CIE	ELISA
H. influenzae	1	1	1
S. pneumoniae	10	8	10
N. meningitidis	8	6	7
Controls	3	1	0

Advantages of ELISA:
More sensitive than CIE
Independent of electric charge of capsular antigens
Almost as sensitive as RIA
Cheaper than RIA
Lyophilized anti-capsular antigen sera can be stored (125J-tagged sera must be prepared every 3 weeks)

Table 18. Limulus endotoxin assay: gram-negative bacterial meningitides amoebocytelysate + ng amounts of lipopolysaccharide-coagulation. From (36)

Investigators	No. of patients with positive CSF cultures	No. of patients with Gram-negative bacteria in CSF	No. of positive Limulus assays
BERMAN et al., 1976	107	86	86
DYSON and CASSADY, 1976	10	6	6
McCRACKEN and SORFF, 1976	94	84	60
NACHUM et al., 1973	43	38	38
ROSS et al., 1975	51	38	37
TUAZON et al., 1977	14	8	8
JORGENSEN and LEE, 1978	74	61	61

Table 19. Suspected acute bacterial meningitis: presumptive chemotherapy. Modified from (30)

Age	Chemotherapy (intravenous) 1. choice	2. choice	Comments
Newborns, premature babies	Ampicillin 50 mg/kg 30 min followed by 400 mg/kg/day	Chloramphenicol (succinate) -25 mg/kg 30 min followed by 25-100 mg/kg/day -7th day of age: -25 mg/kg/day	Often polymicrobial meningitides (5-15%)
2 months - 5 years	Ampicillin 50 mg/kg 30 min followed by -300 mg/kg/day	Chloramphenicol (succinate) -25 mg/kg 30 min followed by -100 mg/kg/day	-7 days following defervescence; often extralepto-meningeal infections
5 - 40 years	Penicillin G 50 mg/kg 30 min followed by -150 mg/kg/day = 240,000 IE/kg day	Chloramphenicol (succinate) -25 mg/kg 30 min followed by -60-75 mg/kg/day	Ditto
> 40 years	Penicillin G Ditto	Chloramphenicol (succinate) Ditto	Ditto

Table 20. Suspected acute bacterial meningitis: presumptive chemotherapy. Modified from (30)

Clinical	Chemotherapy (intravenous) 1. choice	2. choice	Comments
Extension of intracranial infections	Penicillin G -50 mg/kg 30 min followed by -150 mg/kg/day	Chloramphenicol (succinate) -25 mg/kg 30 min -60-75 mg/kg/day	During and for at least 1 week after neurosurgery
Skull fractures	Penicillin G Ditto	Chloramphenicol (succinate) Ditto	Neurosurgical repair of defect, otherwise relapses
Penetrating injuries, shunt-prostheses, endocarditis, leukemias, lymphomas	Penicillinase-resistant penicillin, e.g., nafcillin 50 mg/kg 30 min followed by -200 mg/kg/day	Chloramphenicol (succinate) Ditto	Removal of foreign bodies; *S. epidermidis* may require either gentamicin + vancomycin or rifampin + vancomycin

Table 21. Chemotherapy of etiologically proven acute bacterial meningitis. Modified from (30)

Microorganism	Antimicrobial drug (intravenous) 1. choice	2. choice	Comments
N. meningitidis S. pneumoniae Streptococci of serogroups A,B,C,G	Penicillin G	Chloramphenicol (succinate) or gentamicin intraventricular (Ommaya reservoir in newborns, premature infants)	Pen G + gentamicin for streptococci of serogroup B; -7 days after defervescence; -21 days in newborns and premature infants
H. influenzae	Ampicillin caution: β-lactamase	Chloramphenicol (succinate)	Initially ampicillin + chloramphenicol, prior to antibiogram
S. aureus	Penicillinase-resistant penicillin, e.g., nafcillin	Erythromycin or chloramphenicol (succinate)	If penicillin G-sensitive, Pen G; if methicillin-resistant, vancomycin intrathecally
E. coli	Ampicillin	Carbenicillin or chloramphenicol (succinate)	Or gentamicin intrathecally
P. aeruginosa	Gentamicin iv and intrathecally + carbenicillin	Polymyxin B iv and intrathecally	Gentamicin and polymyxin B penetrate blood-brain barrier poorly

Table 22. Intrathecal administration of antimicrobial drugs (once per day): dosages. Modified from (67)

Drug	Children	Adults
Penicillin G	Newborns (2 weeks) 2,500 IE Infants 2,500-5,000 IE Children (2.-6. year) 5,000 IE School children 5,000-8,000 IE	10,000 IE
Ampicillin	5-10 mg	10-20 (-40) mg
Carbenicillin	Children (≤ 2. year) 5-10 mg Children (above age 2 yr.) 10-20 mg	40 mg
Oxacillin	5-10 mg	10-20 mg
Polymyxin B	2 mg	5 mg
Gentamicin for intrathecal application	0.5-1 mg	5 mg
Amphotericin B		10 mg prednisolone intralumbar, then 0.5 mg amphotericin after dilution with CSF in syringe; repeat treatment 2-3 days later

Recently, SKINNER et al. (69) observed 9 cases of shunt or post-neurosurgical infections due to *Propionibacterium acnes*, a member of the normal flora of the skin and scalp; the isolates proved susceptible to the majority of conventionally employed antimicrobial drugs, including penicillins and tetracyclines, but resistant against metronidazole. Also, BASSETT et al. (7) observed infection of a HOLTER shunt by *Pseudomonas cepacia* as a consequence of contaminated chlorhexidine.

Recently, the phenomenon of bacterial tolerance of antibiotics, which inhibit bacterial cell wall synthesis, such as penicillins, cephalosporins, and vancomycin, was described by SABATH et al. (63) for isolates of *S. aureus* (Table 23), by TOMASZ and co-workers (74, 75) for pneumococci, by KIM et al. (38) for β-hemolytic streptococci of serogroup B, and by PULLIAM et al. (57) for alpha-hemolytic streptococci. Briefly, these microorganisms exhibit low minimal inhibitory concentrations (MIC's) toward the above named drugs, i.e., these bacteria appear susceptible as determined with conventional susceptibility tests (agar diffusion and agar dilution tests). However, these microorganisms are not killed by these drugs, i.e., the minimal bactericidal concentrations (MBC's) of these drugs are significantly higher than their MIC's (Table 23). This tolerance phenomenon meanwhile has been found to be of alarming clinical relevance. For example, ROZENBERG-ARSKA et al. (62) found that 8 of 15 clinical isolates of *S. aureus*, that had been recovered from septicemic patients, proved tolerant for penicillin and cephalosporins. The combinations of either gentamicin + cloxacillin or gentamicin + cephalothin proved synergistically active against these penicillin-tolerant strains. DENNY et al. (16), observed 20 severe *S. aureus* infections. Half of the patients received non-bactericidal chemotherapy and 40% of the patients died. In contrast, those patients, who received bactericidally active drug combinations (gentamicin + a penicillin), survived.

Table 23. Penicillin (cephalosporin, vancomycin) tolerance. Modified from (63)
Staph. aureus (blood, bone, sputum specimens)
Nafcillin MIC's = 0.1-0.4 μg/ml; MBC's = 50-200 μg/ml
Cross-tolerance for cephalosporins and vancomycin
Sensitive to: rifampin, cycloserin

Characteristics	Type of penicillin-resistance		
	β-lactamases	Intrinsic	Tolerance
Minimal inhibitory concentrations	Very high	High	Normal
Minimal bactericidal concentrations	Very high	High	High
Valid only for β-lactam antibiotics	+	+	-
Phenotypic expression	99.9%	10^{-5}	10^{-2}
Growth of bacterial cells	Rapid	Slow	Rapid
Stability of resistance	+	+	-
Hospital incidence (USA)	80-90%	1-8%	44%
Clinical significance	+	+	+
Phage types	Various	Few	Various

Lately, an increasing number of observations attest to the worldwide decreased penicillin susceptibility of *Streptococcus pneumoniae* (Table 24), in that various clinical isolates of pneumococci were not inhibited by $\leq$ 0.1 µg/ml of penicillin G (17, 28, 44, 46, 49, 55, 56). Most alarming was a strain of capsular serotype 19A which caused two epidemics in Johannesburg and Durban in South Africa (33); there were 3 cases of meningitis, 10 cases of pneumonia, and 2 cases of pneumonia with empyema. Eight of the children died, including the three with meningitis. This strain of *S. pneumoniae* was resistant against all antibiotics except rifampin and fusidic acid. The resistance mechanism requires further elucidation, although it appears not to be mediated by R-plasmids (58).

An ever increasing number of clinical isolates of *Haemophilus influenzae* (Table 25) are resistant against ampicillin (14, 31, 66). In the majority of cases, this resistance was found to be mediated by a β-lactamase coded for by R-plasmids; molecular biology studies of this resistance mechanism by ELWELL et al. (18) and by JAHN et al. (34) indicated that the β-lactamase gene was a transposon. On the other hand, BELL and PLOWMAN (8) found that the so-called intrinsic ampicillin resistance of *H. influenzae* is due to a different, as yet unidentified mechanism. Lately, several clinical isolates of *H. influenzae*, that had been recovered in various states of the USA and in the Netherlands (6, 39, 43, 50, 51), were found to be resistant against chloramphenicol. Van KLINGEREN et al. (39) noted a conjugative R-plasmid (chloramphenicol, tetracycline resistance) in their Dutch isolate of *H. influenzae*.

Finally, two British groups of investigators (Table 26) submitted preliminary evidence indicating that clinical exudates inactivated penicillins and cephalosporins. BARNES and WATERWORTH (5) hypothesized that the responsible enzyme in empyema fluid was derived from neutrophilic granulocytes, whereas DE LOUVOIS and HURLEY (40) thought this enzyme to be a cell-associated amidase.

Taken together, these findings serve to emphasize a number of points: Laboratories should be equipped and trained to perform quantitative broth dilution antibiotic susceptibility tests, i.e., to determine both MIC's *and* MBC's of penicillins, cephalosporins and vancomycin for staphylococci, streptococci and possibly pneumococci, that had been isolated from serious, life-threatening infections. Furthermore, carefully standardized sensitivity studies appear warranted for pneumococci, in order to detect slight decreases in penicillin susceptibility and safeguard against potentially disastrous chemotherapeutic consequences. The same applies, of course, for clinical isolates of *H. influenzae*. In view of the latest developments in the field of bacterial resistance against antimicrobial drugs, clinicians and clinical microbiologists alike are tempted to ask: "What next?"

Table 24. Reduced penicillin G susceptibility of Streptococcus pneumoniae. Wild type strains susceptible to 0.015 - 0.03 µg/ml Pen G

Investigators	Serotype	Pen G MIC's (µg/ml)	Geographic region	Incidence
CDC-MMWR, 1979	68	0.25	USA	Single strain
DIXON, 1977		0.1-0.9	Canada	2.4%
HANSMAN et al., 1974		0.1-1.0	Australia	12%
MODDE, 1978		> 0.1	Switzerland	3%
PABST and NIGRIN, 1979		1.9	England	Single strain
PERLINO and BURLEIGH, 1979		0.4-1.6	USA	2 strains
MEERS and MATTHEWS, 1978		0.25 Chlor 20 µg/ml Tc 20 µg/ml	England	Single strain
JACOBS et al., 1978	19A	1-4 µg/ml	South Africa	2 epidemics
ROBINS-BROWN et al., 1979		This strain was *resistant* against: ampicillin, cephalothin, tetracycline, chloramphenicol, clindamycin, erythromycin, trimethoprim. This strain was *susceptible* to: fusidic acid, rifampin; no β-lactamases discernible. This strain produced a chloramphenicol acetyltransferase; R-plasmids not discernible.		

Table 25. Ampicillin-resistance of Haemophilus influenzae. From (31)

	Haemophilus influenzae		
	Type b	Other serotypes	Nontypable
No.	34	29	889
Resistant against: Ampicillin	4[a]	1[a]	10[a]
Chloramphenicol	0	0	2
Tetracycline	2	0	24
Trimethoprim	1	0	1

[a] Positive for β-lactamase.

Table 26. Inactivation of penicillin by clinical exudates

BARNES and WATERWORTH, 1977 (5):
Empyema (diabetic patient), group B streptococci, penicillin therapy ineffective
After 2 weeks of chemotherapy, the exudate fluid contained no active penicillin
Exudate + penicillin - penicillin inactivated, also ampicillin, methicillin, and carbenicillin
Exudate inactivated 7 cephalosporins as well: cephaloridine, cephalothin, cefuroxim, cephazolin, cefatrizin, cephalexin, and cephradine
Hypothetical enzyme derived from neutrophilic granulocytes?
De LOUVOIS and HURLEY, 1977 (40):
4 of 22 clinical exudates inactivated up to 90% of added penicillins within 1 hour in vitro, but not streptomycin and fusidic acid
Hypothetical enzyme = cell-associated amidase?

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Symptomatology and Diagnosis of Brain Abscesses

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The symptoms of brain abscesses are due to two main characteristics, infection and space-occupation. This symptomatology varies greatly according to the mode of infection, the localization and the stage of the abscess.

General signs of an infection may be very discrete or absent. As early as 1893 McEWEN pointed out that the brain abscess may occur without any fever at all, and hardly ever with prolonged periods of fever. The same is true for other general signs of an infection. The most reliable indicator appears to be the blood sedimentation rate.

The degree to which an abscess exerts a space-occupying effect is variable and depends on the stage of development. In the latent phase after edema has receded, there may be no volume displacement at all, especially if there is liquefaction of brain tissue (MERREM, 1963) or brain atrophy due to a primary head injury (TÖNNIS, 1948) which compensates the space-occupying effect of the absecc. In the manifestation stage the infection recurs and the increasing edema leads to a continual rise in intracranial pressure.

Headache is the earliest and most constant symptom of the brain abscess, less common are *vomiting* and *dizziness*. Papilledema occurs in half of the cases.

Disturbances in consciousness occur in almost all patients with brain abscess. Depending on the amount of raised intracranial pressure, every level of disturbances in consciousness from sleepiness to deep coma may be found. Perforation of the abscess into the ventricular system leads to the terminal stage more commonly than increasing intracranial pressure, however. Sudden severe headache and nuchal rigidity are typically followed by a sudden rise in temperature.

The local symptoms will not be discussed here because these depend on the localization of the abscess and these correspond to those of other space-occupying lesions.

Epileptic seizures, including Jackson as well as grand-mal seizures are common in patients with brain abscess. Almost every second patient has such seizures in the course of his disease.

The perfect diagnosis of brain abscess based on the neurological findings alone is not possible. They generally permit only a probable diagnosis.

Therefore the use of modern methods of diagnosis and neuroradiological procedures are all the more important. Even if a single method of investigation does not lead to the correct diagnosis, the combined re-

sults of different procedures allows the exact diagnosis of the localization and type of lesion in almost all cases.

There is no pathognomonic *CSF finding* for a brain abscess. The chemical composition is usually altered, but the results of this investigation are multifarious. As in all cases of space-occupying lesions, the lumbar puncture of a patient with a brain abscess is not without danger. CAREY et al. (1972) reported eight deaths following a lumbar puncture. In 5 of these cases, the authors found a direct correlation with the lumbar puncture, this corresponds to 8% of all those who had undergone this examination.

The changes in the chemical composition of the CSF are dependent on the stage of development of the abscess, on the virulence of the pathogenic organism, the resistance level of the patient and on the localization of the abscess, especially in its relation to the meninges or the ependymal lining of the ventricles. The closer the abscess lies to the CSF spaces, the more likely a pleocytosis will be found. BONNAL et al. (1960) however, found a normal cell count of the CSF in 63 of 208 patients with brain abscess. ZÜLCH (1964) has also pointed out that changes in the CSF are often missing in cases of chronic brain abscess and that a raised cell count is even rarer than an elevation in the protein level.

X-rays of the skull continue to remain the most important non-invasive method of investigation for the demonstration of a possible cause of an intracranial infection. For inflammatory diseases of the nasal sinuses, the pyramids, osteomyelitis of the skull as well as open head injuries are causes of brain abscess in more than half or the cases. For the detection of the abscess itself, the plain X-ray of the skull is of less importance. Important is the detection of foreign bodies or bony fragments within the skull. An X-ray of a 55-year-old man showed a metal foreign body in the right temporo-basal region. A traumatic brain abscess developed in the left frontal region however, as the computer tomogram showed (Fig. 1). Obviously very small, radiologically non-visible foreign bodies such as pieces of clothing or hair lead to an infection more easily than metal particles which may be in themselves bactericidal.

The *electroencephalographic findings* in cases of brain abscess generally are the same as those of rapidly growing brain tumors. Circumscribed delta or subdelta waves make it possible to determine the side of the lesion in 75-90% of the cases, the exact diagnosis of the localization is possible in about 50-60% of the patients. The development of the brain abscess with increasing capsule formation and the recession of the inflammatory changes may be recognized by the gradual normalization of the generalized alterations and the delineation of a focus.

A greater accuracy in the detection of brain abscesses is achieved with *brain scintigraphy*. SUWANWELA et al. (1971) reported on a series of 162 cases in the literature and 18 cases of his own. 163 of the 180 abscesses were demonstrated by means of isotope diagnosis, that is 90,6%. Experimental studies have shown that the abscess contents possess a far lower activity than normal surrounding brain tissue, but the activity in the abscess capsule lies 1,5-5 times higher and is therefore adequate for scintigraphic demonstration. Because of alterations in the capillary permeability of the brain tissue in the immediate vicinity of the abscess, there is considerable accumulation of activity. Grouping the various stages of abscess development with the corresponding scintigraphic findings, three types emerge: In the phase of circumscribed inflammation of the brain tissue, the scinti-

gram shows an irregular, spotty activity. In the second stage of liquefaction and marked inflammatory reaction, a homogeneous, more or less clearly demarcated zone of increased activity is seen. In the chronic abscess stage mit a well-formed capsule and only slight inflammatory reaction, a typical ring-shaped zone of increased activity appears with a central area of less activity as observed in some cases of glioblastoma with central necrosis. This finding is seen in about 1/4 of the cases of brain abscess.

The diagnosis with *computer tomography* is based on a more or less circumscribed area of decreased density. Without the injection of contrast medium a fine ring structure is seen only occasionally. Once contrast medium has been given, the majority of the cases show a marked ring of increased density (Table 1). As a result one sees a round or oval, usually clearly demarcated ring-shaped structure of increased density with a central zone of decreased density. This ring-structure is typically uniformly thick and has smooth contours inside and outside. Peripheral to this ring-shaped abscess capsule, there is often an extensive zone of decreased density due to the surrounding edema. Rarely one may see an accumulation of gas within the abscess capsule.

Treatment with steroids may influence the tomographic finding in cases of brain abscess, in respect to the extent of the edema as well as the demonstration of the abscess capsule, as is described for brain tumors. Computer tomography also influences the treatment of brain abscess and seems to favor puncture treatment alone, since control examinations are easy to carry out and recurrences recognized immediately.

The question whether computer tomography has a favorable influence on the results of treatment of brain abscesses has often been set. From 1958-1979 120 patients with brain abscesses were treated in our department (Table 2). The total mortality was 32,5%. Of the 23 patients treated since the introduction of computer tomography, only 17,4% died. Excluding other influences on the results of treatment as far as possible and taking only the last 23 patients treated before the introduction of computer tomography, a mortality of 30,4% is found. Despite the fact that these figures indicate the beneficial effect of improved diagnostic measures, it is impossible to differentiate clearly between the effect of these diagnostic measures and modern treatment (use of dexamethason in suitable cases, more effective antibiotics).

The differential diagnosis of an "abscess" in the CT must include all cystic tumors or glioblastomas with central necrosis as well as metastases. However the ring structure of these lesions is rarely so smooth and regular as that of the brain abscess. SCHMITT (1979) has reported on the pathological-anatomical aspect of brain abscesses who were mistaken for glioblastomas and treated with radiotherapy. If there is the slightest doubt about the diagnosis of glioblastomas, the diagnosis should be clarified with a biopsy. Occasionally brain infarcts and intracerebral hematomas in a certain phase of their development may lead to a ring-shaped structure with a central zone of decreased density after the injection of contrast medium. The rim of increased density is not so regular and smooth as in the case of an abscess however.

Even today an *angiogram* is performed in addition to the CT except in emergencies. According to HEEP (1949), the most important signs include a vascular blush due to the abscess capsule and its immediate vicinity. This circular contrast medium shape with a central avascular

Table 1. Computer tomographic findings with brain abscesses

Author	Year	No. of patients	Ring structure with contrast medium	Hypodense area only	Other
PAXTON and AMBROSE	1974	6	3	3	-
SCHIEFER and HUK	1976	10	8	2	-
CLAVERIA et al.	1976	26	24	-	2 not diagnosed
NEW et al.	1976	7	6	-	1 knot-shaped
LOTT et al.	1977	8	7	-	1 not diagnosed
JOUBERT and STEPHANOW	1977	23	21	2	-
NIELSEN and GYLDENSTEDT	1977	22	18	4	-
STEINHOFF et al.	1977	26	19	-	4 knot-shaped 3 mixed
STEVENS et al.	1978	25	25	-	-
Total		153	131	11	11

Table 2. Influence of computer tomography on the treatment results of brain abscesses

	No. of cases	Deaths	%
1958-1979	120	39	32.5
Before CT	97	35	36.1
Last 23 cases before CT	23	7	30.4
With CT	23	4	17.4

zone is almost pathognomonic for the brain abscess. Occasionally however, similar findings may be observed in cases of brain metastasis and glioblastoma. The data on the incidence of such typical abscess pictures in the angiogram range from approximately 6% to almost 50% (TÖNNIS and SCHIEFER, 1959; NIELSEN and HALABURT, 1976).

Pneumoencephalography does not play a role for the diagnosis of brain abscesses any more.

Central ventriculography for the diagnosis of cerebellar abscesses has also lost in importance and is no longer performed in every case. The findings correspond to those of other lesions in this localization.

Of all diagnostic measures, only the *puncture of the abscess* makes it possible to set the diagnosis with certainty if it is performed successfully. The abscess contents obtained by this puncture may be sent for histological and bacteriological examination. This diagnostic method leads directly into the treatment process. However, such a puncture is not always successful even in cases of abscess by extension where the source of the infection is known. Especially in cases of small, unfavourably situated infections, computer-directed biopsies, as Dr. HUK has developed in our department, can greatly simplify this procedure. Figure 1a, b shows the computer tomogram during a puncture of a left frontobasal brain abscess. The instillation of contrast medium into the abscess cavity after successful puncture has lost in importance. Follow-up studies are better performed in the computer tomograph where most contrast media lead to undesirable artefacts.

The diagnosis of brain abscesses belongs to the most difficult problems of neurologists and neurosurgeons. BRONISCH (1947) emphasized that the diagnostic considerations should not be centered on a single symptom and not on a cross-section of the clinical course, but rather on the accumulation of indices and their total evaluation as well as on the history, clinical course and findings in a longitudinal analysis.

The most important criteria leading to the diagnosis of brain abscess are:

1. The history indicates a head injury either recently or some time ago, or certain infections such as chronic bronchitis, bronchiectases, otitis media, chronic sinusitis or a cyanotic congenital cardiac malformation is reported
2. General signs of an infection such as fever, leucocytosis, and raised erythrocyte sedimentation rate
3. Signs of raised intracranial pressure
4. Localizing cerebral symptoms
5. Positive findings in the diagnostic methods of investigation especially brain scintigraphy and CT as well as the abscess puncture.

All these criteria will only rarely be fulfilled and in a series of cases only the abscess puncture will allow the differentiation from other space-occupying lesions.

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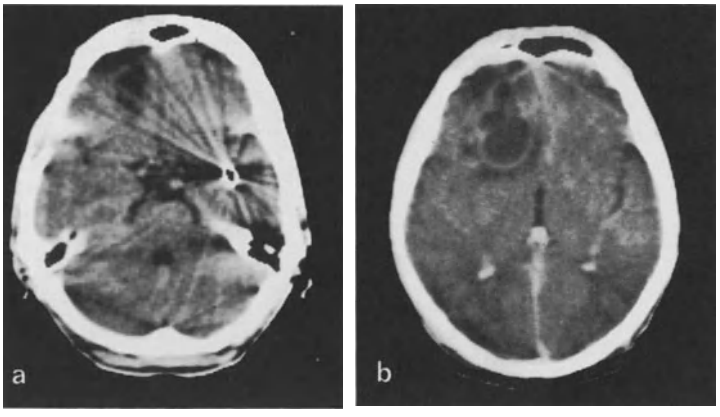

Fig. 1. a The computer tomogram of a 55-year-old male shows artefacts due to a metal foreign body in the middle cerebral fossa on the right. b This section of the same computer tomogram demonstrates a large frontal brain abscess on the left in the same patient

Development of Brain Abscesses – Computerized Tomogram Compared with Morphological Studies

H. C. NAHSER, L. GERHARD, R. FLOSSDORF, and H.-E. CLAR

Introduction

The basic factors for a successful treatment of brain abscesses are a diagnosis as early as possible and the knowledge of the exact localisation as well as of the course and stage of tissue reactions. For that purpose the detailed correlation between changes in Computer-Tomography (CT) and their underlying morphological changes is most important.

Material and Approach

Our CT investigations were performed with a Siretom 2000. The diameter of each slice was 1 cm. In all cases contrast medium (Rayvist 300 or Urografin 70%) was given in a dose of one to one and a half ml per kg. According to the method described by BOCK et al. (1978), CT levels were compared with horizontal brain sections of precisely the same level. These brain sections were embedded in paraffin and histological investigations were carried out in serial sections focusing on regions of special interest and using H.E. and Van GIESON stain. In this way CT findings and their underlying gross anatomy as well as the microscopic changes of 21 patients with brain abscess were studied.

Results

Small, non-confluent hyperdense areas are the first CT findings in the beginning of brain abscesses which can be correlated with diffuse or irregular spots of inflammation (encephalitis) and marked edema. Light microscopy exhibits early disturbances of the blood-brain barrier with dilatation and swelling of vessel walls, penetrations of neutrophil leucocytes and increasing number of macrophages. The occurrence of small haemorrhages is dependent on a number of factors, including toxic damage to vessel walls by some microorganism - mainly streptococci and fungi or immunological factors. In the CT these haemorrhages are marked by spotted enhancement.

The transition to stage II (Table 1) appears in the CT as confluent hypodense zones with an indistinct but detectable accentuation of the borderline. In this stage, extension and intensity of edema is at its largest. After the injection of contrast media, diffuse spotted enhancement of the center and striped enhancement of the border becomes visible. In gross anatomy liquefaction , demarcation of tissue necrosis and an expanding perifocal oedema will be seen. Petechial haemorrhages are still visible in this stage. Light microscopy exhibits the increasing growth of granulation tissue and proliferation of glia cells. Small vessels have increased in number, demonstrate swelling of vascular walls and endothelial nuclei. They are mainly responsible

Table 1. Development of brain abscess

	Stage I	Stage II	Stage III
CT	Focal hypodensity	Hypodense area irregular borderline	Ring enhancement Perifocal hypodensity
	Punctiform hyperdense foci		
Macro	Diffuse inflammation Diffuse oedema	Demarcation Liquefaction Irregular border, perifocal oedema	Capsule Perifocal oedema
	Petechial hemorrhage		
Micro	Early vascular reaction Polymorphonuclear cell response	Formation of granulation tissue Glial prolieration	Collagen formation of granulation tissue Formation of glial fibres
	2nd week	3rd week	6th week

for the spotted and accentuated enhancement of the borders in CT after contrast.

A case with an unusual complication should be mentioned here. In a patient with a left-sided loculated abscess extending into the overlying subarachnoid space, there developed an extensive subdural empyema confined to the left hemisphere. The sickle-like subdural empyema is visible after contrast medium had been given. It reveals a hyperdense membrane with a central hypodense area correlated with the purulent fluid of the empyema. The wall of the loculated abscess exhibited different portions according to its stage. There was still young proliferating granulation tissues as well as early perivascular production of collagen, which indicates at least six-week-old tissue reaction. At the level of the temporal pole, the CT shows a semicircular abscess membrane of stage III opening into the temporal white matter with no distinct borderline but with marked irregular hypodensity. This correlates morphologically with a semicircular abscess wall, stage II-III at the temporal pole but also with an active infection deep in the temporal white matter. In loculated abscesses the wall very frequently exhibits portions of different age. This may be interpreted as a proof for decreased resistance in the development of loculated abscesses. Another example with different development and different age of the inflammatory process can be demonstrated in a patient with lethal infection by streptococci (Figs. 1 and 2). The spread progressed here through the white matter but not through the better vascularized cortex. The pronounced perifocal edema surrounding abscess A (stage II) in the occipital white matter should be underlined. It differs quite definitely from the older abscess B (stage III) with less perifocal edema. Another case (progressed stage III) demonstrated a large fronto-polar abscess, which was remarkably reduced in size by puncture. This explains the difference in size between CT and gross anatomy. The midline has also shifted back close to its normal position after puncture. But the extensive perifocal edema in the frontoparietal white matter is not affected and the right lateral ventricle appears still compressed. After prolonged compression, morphological

changes may occur in the tissue which cannot be simply cured by the reduction of the compression. A sudden decrease in the compression may even lead to an increase in edema or the danger of hemorrhage. In the same case a perforation of the tip of the abscess into the ventricular cavity was observed. This is explained by a much more extensive abscess capsule containing more collagen at the lateral sides than at the side adjacent to the ventricle. The rupture occurred in the weaker part of the abscess membrane close to the ventricular wall. The inflammation spread to the ependymal and subependymal layers producing new granulation tissue in the ventricular wall similar in its histology to the abscess membrane already described. The CT therefore showed increased density of the wall of the ventricular cavity after the application of contrast medium. Under light microscopy the oldest and most solid portions of the abscess capsule in this case possess many collagen fibers somewhat parallel and orientated in a circular fashion may sometimes exhibit hyalinization. In the center of the abscess, necrotic amorphous material is mixed with polynuclear leucocytes. In the capsule one finds mainly phagocytes and a few lymphocytes and plasma cells. The border between the abscess wall with its collagen fibers and the surrounding brain tissue is a clear cut line in comparison to the earlier stages. This is another factor contributing to the strong accentuation of the ring structures in the CT of old abscess capsules.

Discussion

The investigated cases with their CT findings can be correlated with their underlying morphological substrate. This includes gross anatomy as well as the microscopic substrate. As has been shown in Table 1, it is possible to extend the purely morphological staging to the CT findings by our method. Our analysis of the CT and of the underlying morphological substrate provide some explanations for detailed phenomena in the CT as well. The staging, however, is an approach to a dynamic biological process influenced by many factors. The most important among them are immunity and the different properties of the microorganisms. The delicate balance of this process can change in different directions during the development of an abscess. This gives each brain abscess an individual course. If this fact is kept in mind, the staging and its correlated interpretation of CT and morphology should be a useful tool for the clinical practice. This approach avoids the unspecifity of isolated CT findings. Only the correlation of clinical and morphological data gives distinct interpretations of the CT changes occurring during the development of brain abscesses.

Conclusion

A combined computer tomogram and morphological staging of brain abscesses is presented which can be used in clinical diagnosis and follow-up.

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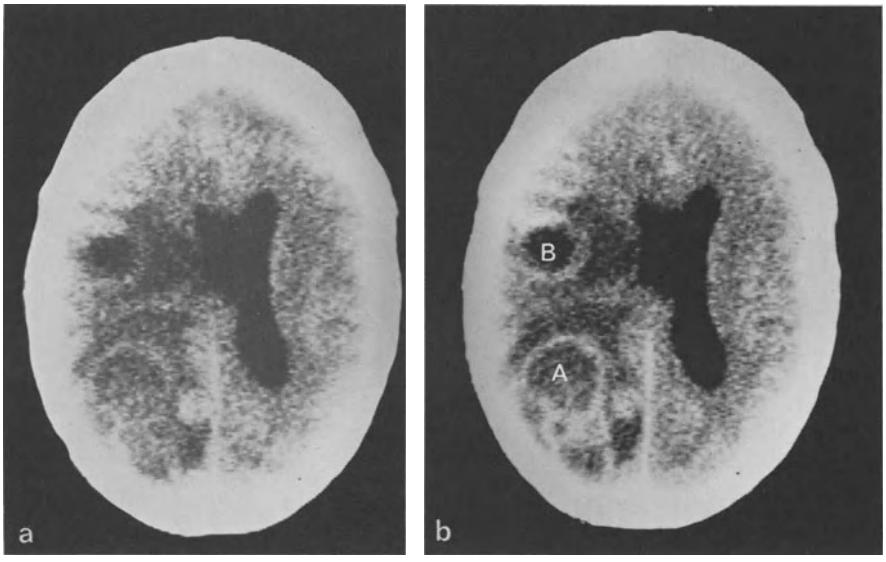

Fig. 1. a CT with ring structures. b CT after contrast medium demonstrating abscess A and abscess B

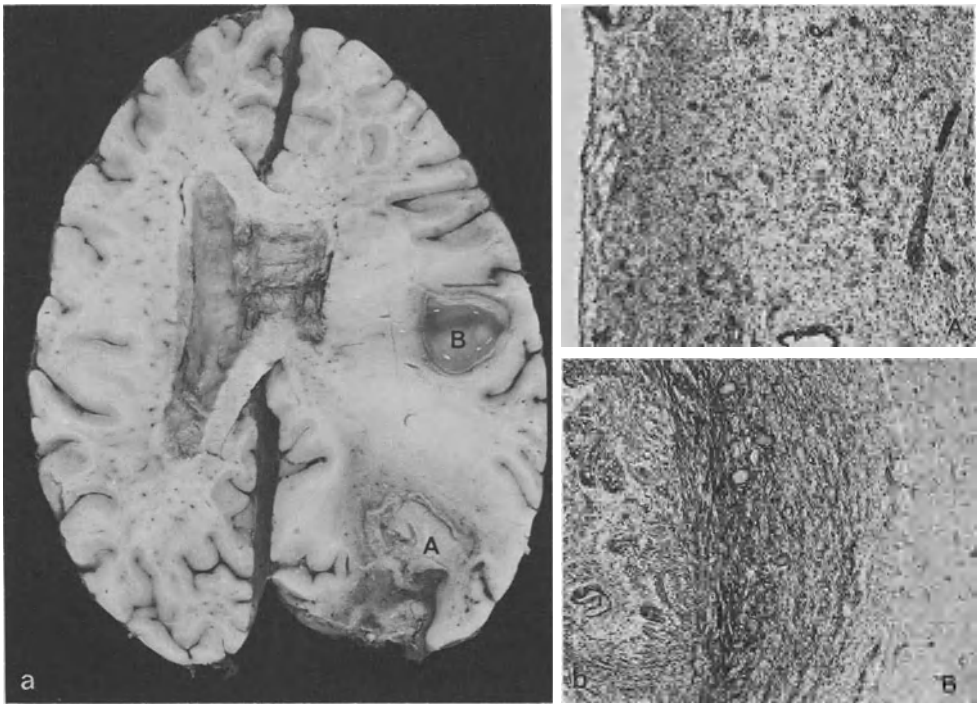

Fig. 2. a Horizontal brain section at the level of Fig. 1 exhibiting 2 abscesses of different age. In b the microscopic picture of both abscesses, demonstrating growing granulation tissue in A (stage II) and the well-delineated collagenous wall in B (stage III)

The Determination of Absorption Values as an Aid in Computer Tomographic Differentation Between Cerebral Abscess and Glioblastoma

W. MAUERSBERGER

The ring structure is a frequent, but completely non-specific, image in the computer tomogram. In a survey by KAZNER et al. on 2,581 intracranial tumors and space-occupying processes, a ring was observed in 86% of all cerebral abscesses and in 54% of the glioblastomas. It is thus understandable that differential diagnosis of the two clinical syndromes in the computer tomogram can present considerable difficulties, especially if adequate additional clinical data are not available (Fig. 1).

While it is possible in virtually every case to detect an intracranial, growing and displacing process in the computer tomogram, differential diagnosis frequently presents considerable difficulties. Thus, STEINHOFF et al. were able to make a precise differential diagnosis only in 69.8% of the 295 glioblastomas which they investigated. In this context, it should be taken into account that the 206 cases for which an accurate preoperative diagnosis was made included 41 cases of recurrence.

However, if therapeutic procedures are to be instigated, an accurate preoperative diagnosis is essential (5).

The question thus arisis as to whether quantitative analysis of the computer tomographic findings could provide further data which would permit further differentiation of the two clinical syndromes (2, 8).

It must be taken into account that the determination of the individual density values is the actual basis of computer tomography and that the computer tomographic image which has been familiar hitherto merely constitutes the transference of these density values to a grey shade scale. The transverse layer image can, however, reproduce only a very small section of the data stored during scanning. The reasons for this are, on the one hand, the fact that the sensitivity and linearity of the film material for optical image reproduction are limited and, on the other hand, the fact that the human eye is not able to differentiate between more than 15-20 different shades of grey, although the HOUNSFIELD scale comprises 2,000 density values (4). For this reason, the numerical values determined by densitometry can be far more accurate than the optical impression, which is relative depending on the grey rating which can be arbitrarily chosen. The significance which this method will attain in the future cannot yet be estimated, since the requisite basic principles are still largely to be worked out (1, 2, 6).

Material and Method

A total of 9 cerebral abscesses and 23 glioblastomas of the ring or garland type were examined. All of the investigations were carried

out using a tube power of 140 KV and 28 mA and with a scanning time of 64 seconds.

A representative layer was then selected on the video display unit, in order to determine the following areas, both in the native scan and after the administration of a contrast medium (50 ml of Telebrix administered intravenously, or 1 ml/kg of body weight).

1. Total area of the tumour or abscess
2. Peripheral active part of the tumour or abscess capsule
3. The central, necrotic part of the tumour or the contents of the abscess.

The areas selected for investigation were marked on the video display unit with a light pen, in order subsequently to determine the following values in each case:
average value, modal value, minimum and maximum and number of measurement points (Fig. 2).

Results

The results of the investigations carried out before administration of the contrast medium are given in Table 1.

Table 1. Density values - Native scan

	Abscess	Glioblastoma
	Whole abscess	Whole tumour
$\bar{x}$	15.9 HU	26.6 HU
$S\bar{x}$	2.84	1.32
S	6.97	4.8
	Capsule	Solid tumour tissue
$\bar{x}$	15.2	28.9
$S\bar{x}$	3.58	1.41
S	8.77	5.05
	Pus	Necrotic tumour tissue
$\bar{x}$	10.98	23.2
$S\bar{x}$	2.98	2.47
S	8.45	5.8

$\bar{x}$, mean value; $S\bar{x}$, standard error; S, standard deviation.

The average value for the total abscess was 15.9 H.U., with a standard deviation of 6.97. For the glioblastoma, this value was 26.6 H.U. with a standard deviation of 4.8.

The average value for the abscess capsule was 15.2 H.U., with a standard deviation of 8.77, and was thus likewise markedly below the value for the solid part of the tumour (average value = 28.9 H.U.; standard deviation = 5.0). The values for the contents of the abscess and for the necrotic part of the tumour also displayed marked differences (average value for the pus = 10.98 H.U.; standard deviation = 8.45;

average value for the necrotic tumour tissue = 23.2 H.U.; standard deviation = 7.8).

Distinct differences in density still exist after the administration of the contrast medium (Table 2); thus, the average value for the total abscess was 22.85 H.U. with a standard deviation of 6.42 and for the glioblastoma the average value was 34.55 H.U. with a standard deviation of 4.71, the glioblastoma values thus being markedly above those for the abscess. The abscess capsule had an average value of 31.35 H.U. with a standard deviation of 6.6, whilst the values for the solid part of the tumour were distinctly higher, being 38.6. H.U. (standard deviation = 4.9). After administration of the contrast medium, the pus contents of the abscess gave an average value of 12.94 H.U. with a standard deviation of 6.3 and the necrotic part of the tumour gave an average value of 22.89 H.U. with a standard deviation of 5.19.

Table 2. Density values - after enhancement

	Abscess	Glioblastoma
	Whole abscess	Whole tumour
$\bar{x}$	22.85 HU	34.55 HU
$S\bar{x}$	2.13	0.96
S	6.42	4.71
	Capsule	Solid tumour tissue
$\bar{x}$	31.35	38.6
$S\bar{x}$	2.20	1.0
S	6.60	4.9
	Pus	Necrotic tumour tissue
$\bar{x}$	12.94	22.89
$S\bar{x}$	2.1	1.1
S	6.3	5.19

$\bar{x}$, mean value; $S\bar{x}$, standard error; S, standard deviation.

Discussion

On the basis of the experience gained from this example, densitometry represents an enrichment of computer tomographic diagnosis. The prerequisite is precise calibration of the apparatus, so that the values determined actually also agree with the values on the HOUNSFIELD scale assigned to the apparatus. The deviation found when calibrating the zero point as part of the monthly maintenance on our equipment was never greater than 3 H.U., so that the cases summarized in this article are comparable.

With regard to the observed differences in the densities of the total tumour area and of the abscess, both in the native scan and after the administration of the contrast medium, it must be taken into account that the proportion of solid tumour tissue relative to the total mass of the tumour was, at 2.6 : 1, distinctly greater than the same ratio in the case of the abscesses, for which it was 1 : 1. However, since

considerable problems arise with regard to differential diagnosis, in particular in the case of those glioblastomas which have only a narrow active tumour border, this is not necessarily an acceptable criterion.

Since the abscess capsule is in general only a narrow border of tissue, precise limitation of this area is difficult and it is certainly possible that both portions of the perifocal oedema and of the contents of the abscess are also included in the determination, so that the differences in density observed between these values and those for the solid tumour tissue of the glioblastoma can likewise be utilised only with reservations.

The situation is different with regard to the comparison of the density values for the contents of the abscess and for the necrotic part of the tumour. Delimitation of these from the peripheral parts of the tissue presents no technical difficulties on the video display unit and is also not affected by portions of tissue with considerable differences in density. The low density values of the pus are due to fatty degeneration of the decaying leucocytes (6). Since fat has negative absorption values, the density of the pus will be lower the further this process has progressed. In addition, the formation of a seropurulent exudate results in a further decrease in the density of the contents of the abscess. Depending on the degree of maturation of the abscess, its density value will vary, so that it cannot be expected that a single characteristic and specific density value can be cited; however, it is possible to indicate more or less typical absorption zones, which can be of value as supplementary data to the computer tomographic diagnosis.

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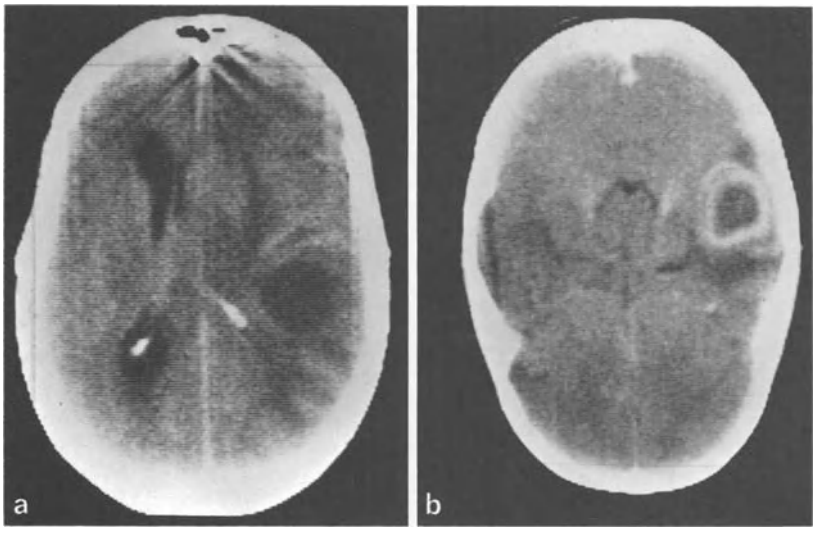

Fig. 1a, b. Distinction between abscess and glioblastomas by the computer tomographic picture is not always possible. a temporal otogenic abscess; b temporal glioblastoma

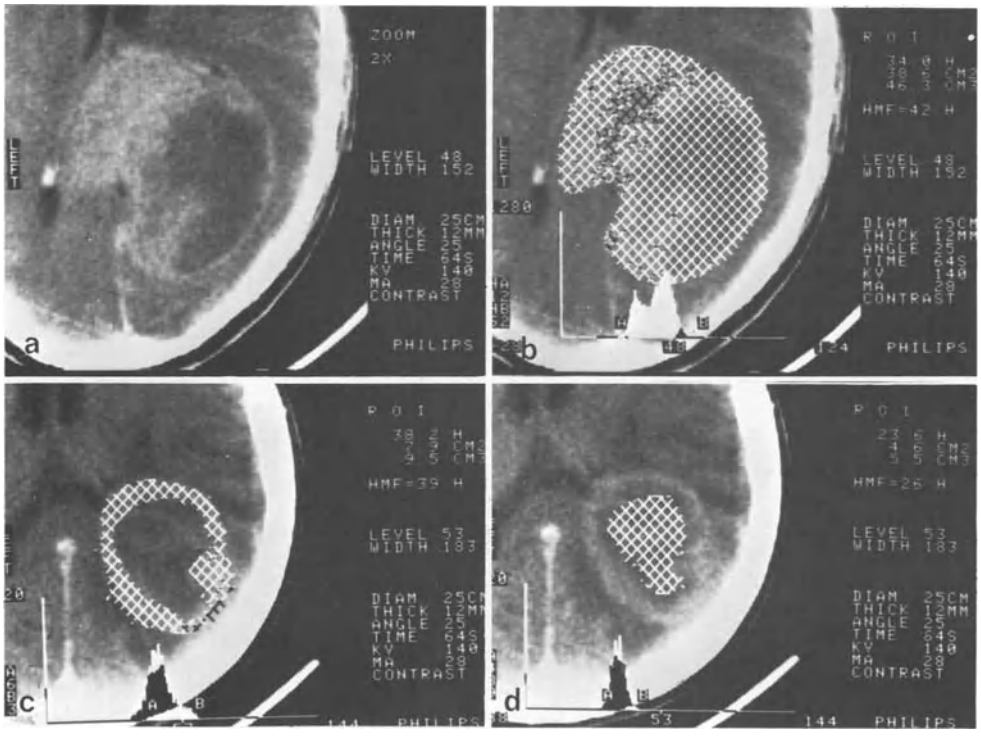

Fig. 2a-d. Quantitative analysis was performed for: a whole tumour area; b solid tumour tissue; d necrotic tissue

Therapy of Brain Abscess

TH. WALLENFANG, H. J. REULEN, and K. SCHÜRMANN

Despite all the advances in diagnosis and therapy, brain abscess still constitutes a clinical picture which has to be taken seriously today. It is interesting that there has been no decisive change in the mortality since the introduction of antibiotics between 1946 and 1950 and despite their intensive further development up to the present day. In the literature, the mortality is quoted to range from 30-45% (1, 2, 4, 5), which was consistent with our own results up to a few years ago. However, today the analysis of our clinical material justifies our hope that this mortality can be lowered with the correct treatment strategy if consideration is given to the various factors which are crucial for the prognosis.

The first important prognostic factor is the state of preoperative consciousness. In our group of 110 cases, the mortality increased markedly with the deterioration in the state of consciousness (alert, somnolent, soporous and comatose). The second important prognostic factor is the condition of the abscess, whether it is acute or chronic (Fig. 1). Thus the mortality of patients with an acute abscess was markedly higher in all four states of consciousness than in the patients with a chronic abscess. Even in the patients with clear consciousness in stage I, the mortality of the acute abscess was 25%. Finally, our own and other results (1, 2, 5, 7) show that the localization plays a role, i.e. an abscess located in the midbrain or multiple abscesses had a very much more unfavorable prognosis than the solitary hemisphere abscesses. Today, computerized tomography (6) is able to provide important information with regard to the localization and the state of the abscess (acute or chronic). The more rapid diagnostic investigation which is made possible by this method of investigation and the resulting earlier instigation of therapy brings the mortality even further down.

In an effort to lower the mortality decisively, an attempt should be made on the one hand to achieve an improvement in the state of consciousness by reducing cerebral edema (8) and intracranial pressure, on the other hand, the infectious process should be converted from an acute to a chronic stage. For this reason, dexamethasone[1] (4x4 up to 3x8 mg daily) has therefore been employed since 1972 in addition to the antibiotics for treatment of cerebral edema in 53 patients. This group was compared with a group of 52 patients (mainly up to 1972 but in some cases also afterwards) who were treated exclusively with antibiotics.

Results

The influence of treatment with dexamethasone on the state of consciousness before a possible operation was investigated. The indivi-

1 Decadron (MSF Sharp + Dohme, Munich).

dual alteration in the state of consciousness of all patients with and without steroid pretreatment is shown in Fig. 2a, b. In the group treated with dexamethasone as well as antibiotics, there were 18 patients with completely clear consciousness without deterioration. Out of the 19 patients who were admitted in stage II (somnolent), 15 improved to stage I and of the patients in stage III (soporous) five improved to stage I and four to stage II. Three patients remained in the soporous state, and only one patient with multiple abscesses deteriorated. On the other hand, only a few patients receiving antibiotic therapy alone improved: three patients improved from stage II and three patients improved from stage III to the next better state of consciousness. Of the eleven patients who were awake, ten remained in the same state and one deteriorated. In stage II, 17 patients showed no alteration of the state of consciousness, 10 deteriorated and in stage III, 17 showed no alteration of the state of consciousness, 10 deteriorated and in stage III 3 remained in the same state of consciousness and one deteriorated. The patients admitted in deep coma had a poor prognosis with and without steroid therapy.

If the results for the various states of consciousness are summarized, the positive effect of steroid treatment in combination with antibiotics becomes especially evident. In the combination therapy, 47% of the patients improved with regard to their state of consciousness, 51% showed no alteration, and only 2% of the patients deteriorated. On the other hand, with antibiotic therapy alone, only 13% improved, 66% showed no change and 23% even deteriorated. The favorable effect of dexamethasone could be observed not only in the solitary abscesses, but also in cases of multiple abscesses when they were localized only supratentorially. In the whole group of 110 patients, there were ten patients with multiple abscesses, five patients were treated before 1972 exclusively with antibiotics and died. Three of the other five patients with multiple brain abscesses survived under combination therapy. An improvement of the state of consciousness to stage I or II respectively could be attained by the use of dexamethasone (Fig. 2a). In these three cases, the abscesses were situated in the hemispheres, while the other two patients, who died, had supra- and infratentorial abscesses.

Antibiotherapy still constitutes the basis of preoperative treatment. Antibiotics with a broad spectrum should be given in adequately high doses and administered postoperatively for a period of time up to a few weeks. Thus for example three of our patients deteriorated because antibiotics had been discontinued too early. Our animal experimental studies confirm this experience made clinically. We were able to demonstrate bacteria capable of proliferation in the encapsulated abscess up to the 20th day by means of electron microscopic investigations. The activity of these bacteria increased again when the resistance of the animals was reduced or an adequate level of active antibiotic substance was not attained in the brain tissue (8). The analysis of our study shows that time, necessary for antibiotic therapy, is gained by the combination therapy (antibiotics and steroids) because of the improvement of the preoperative state of consciousness. With the gain in time and the control of the cerebral infection, the chances of encapsulation of the abscess increase, which results in a further improvement of the prognosis.

The significance of this pretreatment with a combination of antibiotics and steroids was also shown by the results of surgery. If the operation was performed under combination therapy, the mortality of acute abscesses could be reduced to 47% and of chronic abscesses to 10%. The operation was very much more unfavorable under antibiotic protection alone:

the mortality was then 89% in the acute abscess stage and 30% in chronic abscess stage (Table 1). The mortality was also markedly lower in the group which was treated conservatively when steroids were employed. The impression might now arise that the low mortality of the steroid group is attributable to the better preoperative state of consciousness. However, it was shown that with the same state of consciousness and with the same mode of surgical treatment the mortality was always lower under the combination therapy.

With regard to the surgical procedure, the analysis of our cases showed that of the abscess primary excision and secondary excision following aspiration of the contents give rise to equally good results (3, 7) (Table 2). Aspiration alone should remain reserved for those cases in which the abscess is situated in functionally important brain areas. In the acute abscess, one should wait if possible until a capsule has been formed under the combination of antibiotics and low dose steroids.

In the steroid therapy of the brain abscess, two dangers must be pointed out, however. Advantageous as the use of dexamethasone in addition to antibiotics has proved to be for controlling inflammatory edema and gaining time for capsule formation, it is dangerous to apply steroids alone in a disturbed state of consciousness, e.g. when the diagnosis is not correct. Three patients with brain abscesses were thought to have glioblastomas and were treated exclusively with dexamethasone. They died in a very short time (Fig. 3). A further danger of steroid therapy results from too high doses and from extended treatment periods. An activation of the cerebral infection was not observed in our patients with dexamethasone and antibiotics. Nevertheless, there is danger of delayed capsule formation when steroid therapy is administered at too high a dose and for too long a time. In animal experimental investigations on cats with a brain abscess in the white matter of the hemisphere, an antiphlogistic effect of dexamethasone was demonstrated after a 13-day combination therapy: this was manifested in a delayed development and in a lack of firmness of the capsule. If a reduction of the inflammatory edema has been achieved by the employment of dexamethasone, which is manifested in an improvement of the state of consciousness, it is recommended to reduce steroid therapy to a minimal dose.

Table 1. Relationship between the mortality and different forms of therapy with and without dexamethasone and operation

	Acute abscess		Chronic abscess		Total	
	n	mortality	n	mortality	n	mortality
Antibiotic + operation	9	8 (88,8%)	37	11 (29,7%)	46	19 (41,3%)
Antibiotics + dexamethasone + operation	15	7 (46,7%)	30	3 (10%)	45	10 (22,2%)
Antibiotics	2	1 (50%)	1	1 (100%)	3	2 (66,6%)
Antibiotics + dexamethasone	8 1	1 (12,5%) 1 (after LP)	4	1 (25%)	13	3 (23,1%)

Table 2. Results of various surgical procedures in patients with acute and chronic brain abscess

	Total	Discharged	Mortality	Acute abscess	Mortality	Chronic abscess	Mortality
Aspiration	28	14	14 (50%)	9	7 (77,8%)	19	7 (58,3%)
Primary Excision	45	35	10 (22,2%)	10	6 (60%)	36	4 (11,1%)
Aspiration + secondary excision	18	14	4 (22,2%)	5	2 (40%)	13	2 (15,4%)

Summary

The prognosis of the brain abscess is determined today less by the infection than by the inflammatory brain edema. By additional therapy with dexamethasone besides the antibiotics, an improvement of the state of consciousness is attained by reduction of the inflammatory edema. Time is thereby gained for a specific and sufficiently long antibiotic therapy. The chances that a capsule will be formed around the abscess increase with the gain in time. If the operation of a chronic abscess was performed under a combination therapy, a mortality of 10% could be achieved. Primary excision and secondary excision after prior aspiration led to equally good results. The therapy with steroids is dangerous if the diagnosis is not correct, when the abscess is mistaken for a glioblastoma and when dexamethasone is administered for too long and at too high a dose because of the antiphlogistic effect.

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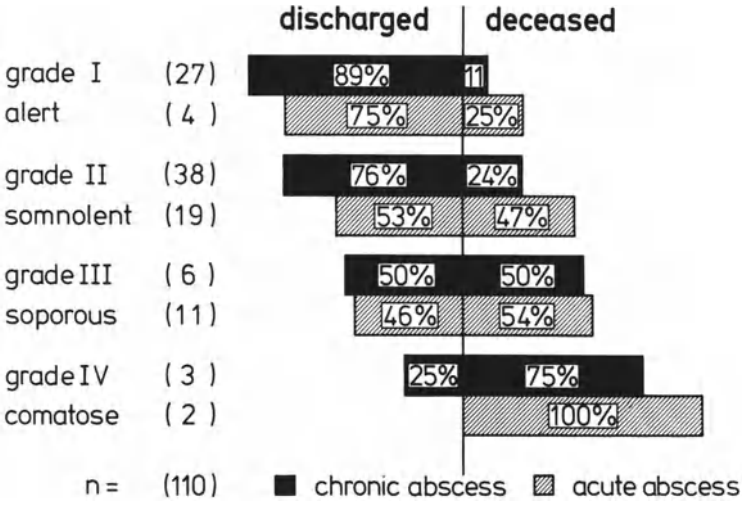

Fig. 1. Relationship between the mortality of acute and chronic brain abscess and the level of consciousness (grades I-IV) on admission to hospital

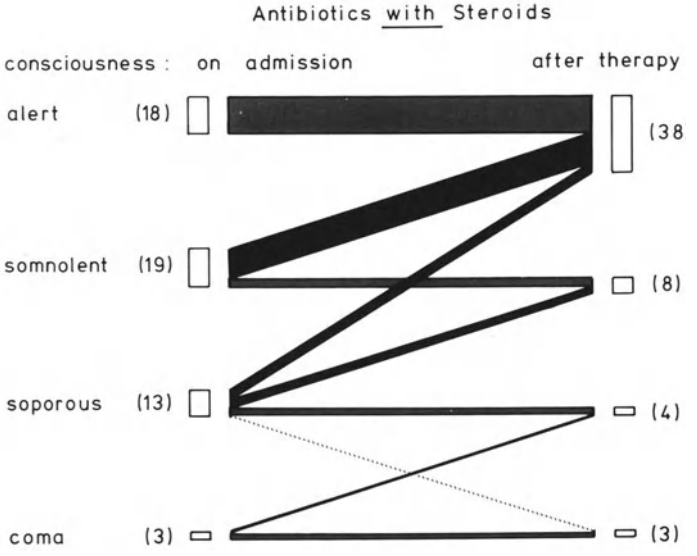

Fig. 2. a The alterations in the state of consciousness under treatment with antibiotics in combination with steroids. 47% of the patients show an improvement and only 2% show a deterioration of consciousness

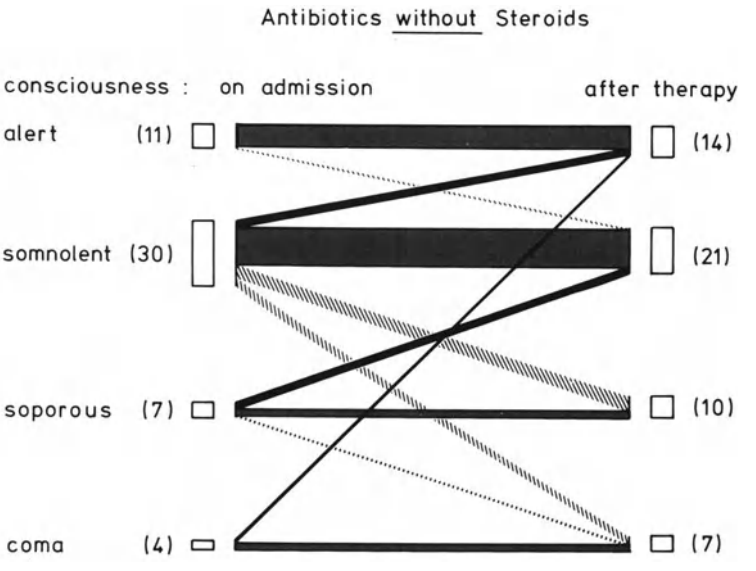

Fig. 2. b The changes of consciousness under treatment with antibiotics alone and without steroids. Only 13% of the patients show an improvement, but 23% show a deterioration of consciousness

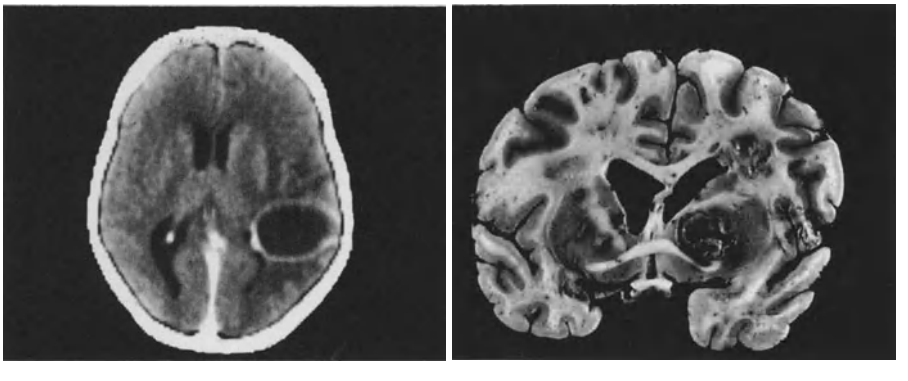

Fig. 3. The solitary brain abscess in the CT scan was thought to be a glioblastoma. In another patient who was thought to have a brain tumor, multiple brain abscess were seen at autopsy after therapy with dexamethasone alone

34 Years Therapeutic Experience with Brain Abscesses

S. TIYAWORABUN, A. WANIS, N. NICOLA, and H. U. THAL

Despite the introduction of surgical procedures into the treatment of brain abscess by MacEWEN in 1893, the application of antimicrobial agents by JOOMA in 1951 and the advance in the development of neuro-radiological techniques, brain abscess has still continued to be a challenging lesion, which carries a distressingly high mortality rate ranging between 30-60% (1, 4, 5, 6, 7, 9, 10, 14). With the aid of computerized tomography (CT), this lesion could be promptly and accurately diagnosed, treated and its course of surgical treatment be easily followed up. Thus, the mortality rate could now be further reduced to around 10-20% (7).

The purpose of the present communication is to attempt to review and analyse our own results in the treatment of brain abscesses in the past 34 years in a community with a population of around 1 million and to draw conclusions as to how the mortality rate can be reduced through establishing the general rules applying to the treatment of all cases of intracranial abscess.

Material and Approach

During the past 34 years, from 1946-1979, 154 brain abscesses were seen at the Neurosurgical Department of the University Teaching Hospital Düsseldorf. 122 patients were male and 43 patients were female. The ratio of male to female was 4:1. 51.7% of the patients were in the first 3 decades of life with the peak in the 2nd and 5th decade. The latter was influenced by patients, who were between 30-50 years old, and who suffered from late traumatic abscess after the world war injuries. The youngest patient of this series was 5 months old and the eldest patient was 71 years old (Fig. 1).

The correlation of the age-group, sex, localisation as well as side difference to the etiologies of the entity were shown in Tables 1 and 2.

Immediately after establishing the diagnosis with the aid of neuro-radiological examinations and/or microbiological laboratory proof, penicillin and broad spectrum antibiotics were given systematically. Osmolar dehydrating agents and steroids were given in cases with clinical signs and neuro-radiological findings of space-occupying lesions. Bacteriological examination of pus, cerebro-spinal fluid and blood were carried out in all cases receiving surgical treatment. Follow-up studies were obtained in 62 of 106 survivors with a time interval ranging from 6-24 months. They were evaluated for their general, emotional and mental status, without formal psychometric studies, specific neurological defect and seizures.

Table 1. Correlation of the age-group and sex to the etiologies of the brain abscesses

Age (years)	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	Total	(%)
No. of patients	n=19	n=32	n=29	n=15	n=31	n=17	n=8	n=3	n=154	
Etiologies (male/female)										
Trauma									32/0	20.8
early abscess	1/0	3/0	3/0	-	1/0	-	-	-	8/0	5.2
late abscess	-	-	1/0	7/0	15/0	1/0	-	-	24/0	15.6
Direct extension									44/17	39.6
otogenic	2/0	11/4	11/3	0/3	3/2	2/2	2/0	-	31/14	29.2
rhinogenic	-	4/1	4/1	1/1	3/0	-	-	1/0	13/3	10.4
Heamatogenous metastatic									38/10	31.2
thoracogenic	-	-	3/0	-	50/	3/2	2/1	1/0	14/3	11/1
congenital heart disease	11/2	3/0	-	-	-	-	-	-	14/2	10.4
soft tissues of the head[a]	2/0	1/0	1/1	2/0	-	0/1	-	0/1	6/3	5.8
other metastatic[b]	-	1/0	-	-	1/1	2/1	-	-	4/2	3.9
Cryptogenic	1/0	3/1	0/1	0/1	-	2/1	2/1	-	8/5	8.4

[a] Tonsillectomy 4; perimandibular abscess 3; eye phlegmon after dacryocystitis 1; upper lip carbuncle 1.
[b] Renal abscess 1; pelvic abscess 3; thigh abscess 1; foot abscess 1.

Table 2. Correlation of the localisation, side difference to the etiologies of the brain abscesses

Localisation	Frontal	Tempo-ral	Pari-etal	Occip-ital	Basal ganglia	Supra-tent. multip.	Cere-bellum	Brain-stem	Pituit-ary	Total
Etiologies (right/left)										
Trauma	7/10	2/3	4/5	1/0	-	-	-	-	-	14/18
Direct extension										38/22
otogenic	-	19/11	-	-	-	1/0	10/4	-	-	30/15
rhinogenic	7/6	1/1	-	-	-	-	-	-	1	8/7
Haematogenous metastatic										27/20
thoracogenic	3/1	-	0/3	3/2	1/0	1/0	2/0	1	-	10/6
congenital heart diseases	3/4	1/1	0/2	1/0	1/0	3/0	-	-	-	9/7
soft tissues of the head	1/1	2/1	2/2	-	-	-	-	-	-	5/4
other metastatic	-	2/1	1/1	0/1	-	-	-	-	-	3/3
Cryptogenic	1/3	0/2	1/1	1/2	-	1/0	1	-	-	4/8
Total n =	47	47	22	11	2	6	17	1	1	83/68
%	30.5	30.5	14.3	7.2	1.3	3.9	11.1	0.6	0.6	

Discussion

Despite the advances in the development of antimicrobial agents and the treatment of the source of infection of a brain abscess, our observation showed no decrease in the incidence.

The ratio of male to female, as reported in the literature, ranged from 1:2-1:4, and over 50% of the patients were in the first 3 decades of life (1, 5, 7, 10, 11). This was probably influenced by the factor that trauma, direct extension and congenital heart disease had been found mostly in these decades and favour male patients (5, 10). The incidence of the source of infections seen in our series (Table 1) were nearly similar to those reported in the recent literature except that there is a lower incidence of late traumatic abscesses in recent years. The patients suffering from late traumatic abscess in our series had a silent period ranging from 10 months to 33 years, while those of early traumatic abscess ranged from 4 days to 4 weeks. Foreign bodies were found in 12 cases of patients with late traumatic abscess and most were bone fragments. In 5 cases, fistulas were formed from scar in the brain tissue. These were observed only in male patients and found mostly in the frontal and parietal lobes. In the group due to direct extension, 3/4 of the abscesses were due to otogenous infection, males being affected significantly more than females, right more than left and located mostly in the temporal lobe and cerebellum. Those of rhinogenous origin had no side differences, but were found mostly in male patients and in the frontal lobe. These may be due to the anatomical distribution of the venous system drainage in that region. Haematogenous metastatic cases comprised 1/3 of the cases and about 2/3 of them was thoracogenic in origin, males affected significantly more than females. These abscesses were located mostly in the parietal and frontal lobe. Cryptogenic abscesses had also been found in about 8% of the cases, without any significant side, site and sex difference.

69.8% of the patients were treated by aspiration. Among these 50%, 25.8% and 23.7% of the patients were needled once, twice and three times. 38.10% of these patients had to undergo secondary excision because aspiration was not successful. 28.8% of the cases were treated with primary excision. In addition to those who underwent secondary excision, 55.4% of the cases had been treated with surgical excision. The mortality rate of the patients with aspiration was 22.7% and those of excision was 14.3%. The total mortality rate of the surgically treated patients was 23.7% and those of the sum total was 31.2%. 15 patients in this series arrived at our department in the stage of brain death. In 1973 Le BEAU et al. (9) reported a mortality of 50-70% of those treated by piecemeal excision and 70-100% treated by aspiration and 25-28% of those treated by excision in the subacute cases. The results of surgical excision of brain abscesses had shown a clear-cut superiority to those treated with aspiration ± drainage (1, 2, 3, 5, 9, 12). The feasibility of primary surgical removal of brain abscess was that in acute cases it provides prompt internal decompression and thus prevents the space-occupying effect with the risk of herniation of the brain. It also permits careful inspection of the abscess cavity and does not miss some loculi in multilobulated abscess. Thirdly, the lesion which remains after surgical operation results in a lower incidence of seizures in comparison to the capsular scar left after surgical aspiration (5). The recurrence or acute exacerbation of the chronic cases as seen in 38.1% of the patients treated with aspiration in our series can also be omitted. Lastly, this method shortens the length of illness and hospitalization of the patients. However, after the introduction of CT monitoring with the aid of

Table 3. Complications after surgical treatment of brain abscesses

Operative methods:	Aspiration ± drainage		Excision (primary + secondary)		Total	
Complications	n = 97	(%)	n = 77	(%)	n = 39	(%)
1. Meningitis		20.6		13.0		21.6
2. Osteomyelitis of the skull		2.1		7.8		5.8
3. Introduction of purulent material into the ventricular system		6.2		1.3		5.0
4. Iatrogenic inoculation		4.1		-		2.9
5. Encephalitic herniation of the brain		-		5.2		2.9

Table 4. Neurological sequelae of the 62 patients followed up from 6 months to 2 years after the operation

	Aspiration ± drainage		Excision		Total	
	n = 36	(%)	n = 26	(%)	n = 62	(%)
1. Seizures		44.5		38.5		42.0
2. Mental disorders		14.0		58.0		32.3
3. Hemiparesis		16.7		38.5		25.8
4. Visual defects		13.9		27.0		20.0
5. Dysphasia		5.6		15.4		9.7
6. Cerebellar symptoms		22.2		53.8		35.5
7. No defects		30.5		42.0		35.5

anti-edematous drugs and strong antibiotics therapy, we feel that brain abscesses could be treated by initial burrhole aspiration, so that the space-occupying effect could be decreased, and the spread of infection reasonably checked. CT monitoring provides the possibility of further treatment (namely surgical extirpation) should the need arise. Figure 4 illustrates this view.

The mortality rate of the brain abscess as related to localisation was shown in Fig. 3. In fact, this was influenced by the duration of the process, mode of entry, methods of operative procedures, vital function of the region, drug therapy, general condition as well as host resistance of the patients. The mortality rates of the brain abscesses in relation to the etiologies were as follows: trauma 28.1%, direct extension 27.9%, haematogenous metastatic 41.7% and cryptogenic 15.4%. The mortality rate in the group of haematogenous metastatic was nearly double that seen in other groups. This was chiefly so in cases where the primary focus was not amenable to therapy.

The complications after surgical treatment of brain abscess was shown in Table 3. Postoperative meningitis, the introduction of the purulent material into the ventricular system and iatrogenic inoculation of the abscess into the surrounding brain tissue were predominantly found in cases that were treated with aspiration. Osteomyelitis of the skull and encephalitic herniation of the brain were seen predominantly in cases, who had undergone surgical excision.

The neurological sequelae of the 62 patients followed up for 6 months to 24 months postoperatively are shown in Table 4. This incidence was also recorded by CAREY et al. (2) and NORTHCROFT and WYKE et al. (13). The incidence of epilepsy in our series cannot be accurately estimated because of the limitation of the interval of follow-up, since epilepsy may develop years later (1, 5, 14). 15% of the surgically treated patients had suffered seizures preoperatively and were not included in the result seen in Table 4. 35.5% of the patients had no neurological defects.

In summary, it could be said that in encapsulated supra- and infratentorial brain abscesses, deep-seated brain abscesses in the basal ganglia or brainstem, or in poor risk patients with encapsulated, or polylobulated, or multiple brain abscesses, surgical apsiration should be advocated. Our indications for surgical excision of brain abscesses were: after failure of surgical aspirations, brain abscess after trauma with foreign bodies in or around the abscess, a combination of brain abscess with epi- or subdural empyema, encapsulated polylobulated or multiple brain abscesses and finally after the failure of operative drainage or aspiration of the brain abscess by the ENT specialists.

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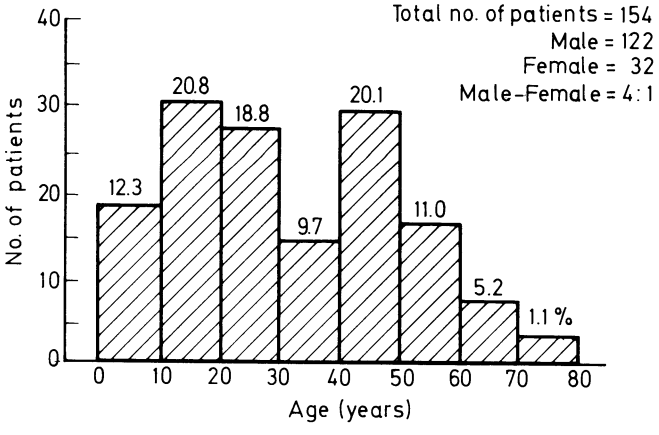

Fig. 1. Age distribution and sex ratio of 154 patients in this series

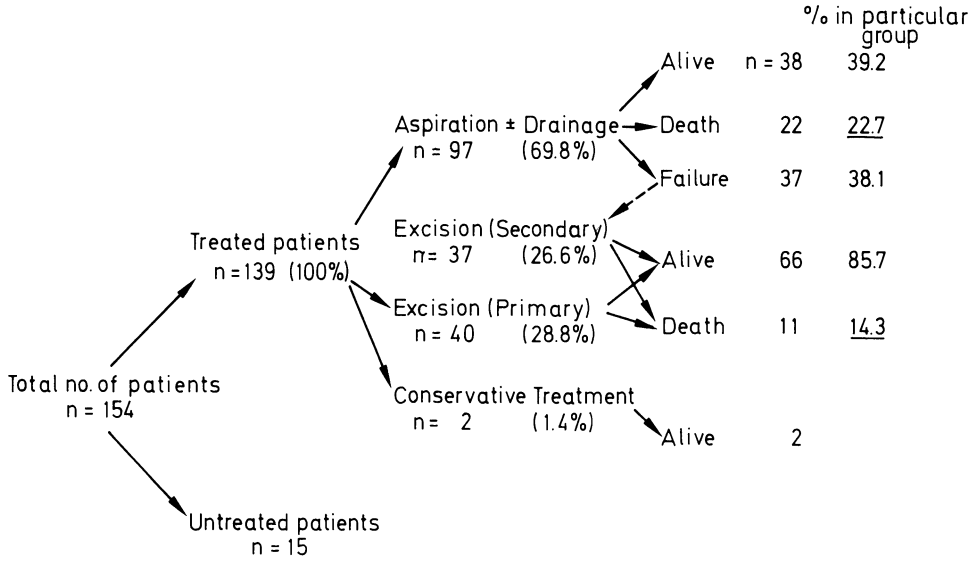

Fig. 2. The outcome of the 154 patients with brain abscesses in this series. Total mortality rate of all patients: 31.2%; total mortality rate of the surgically treated patients: 23.7%

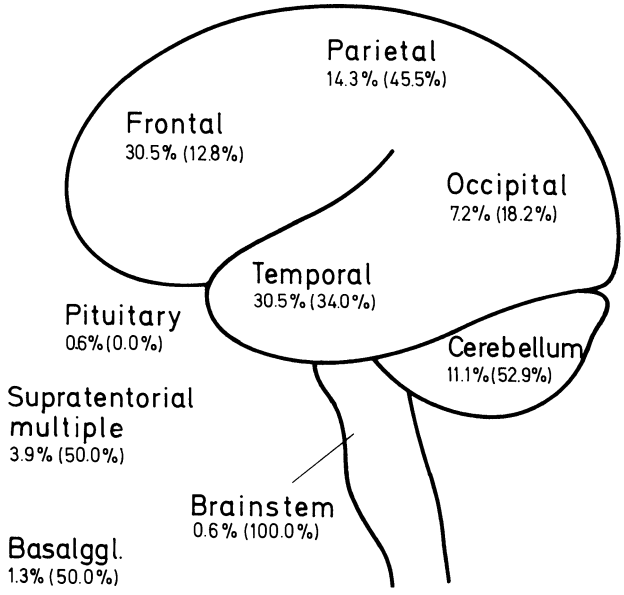

Fig. 3. The incidence of brain abscesses by site and their mortality rates, in ( ), of the present series

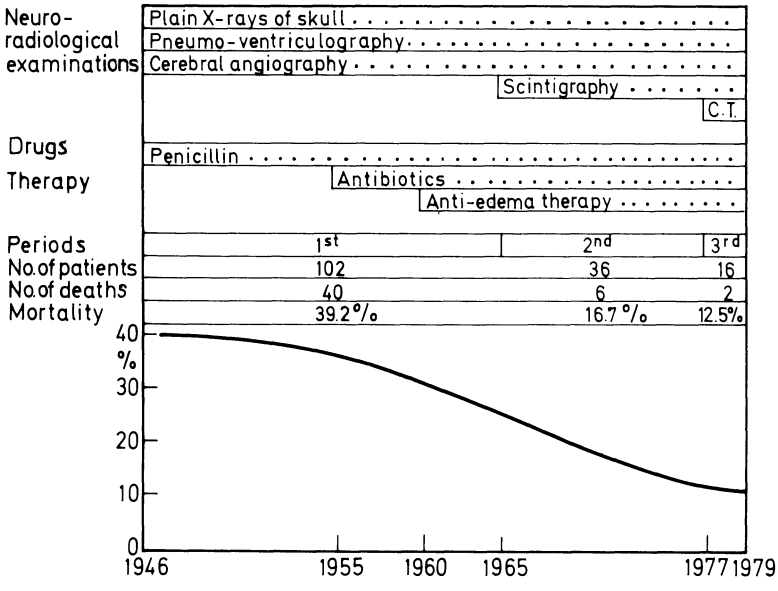

Fig. 4. The mortality rate of the patients in 3 consecutive periods in relation to the development of drug therapy and neuro-radiological examinations

Surgical Treatment of Brain Abscesses with Special Consideration of Acute and Subacute Abscesses

G. PENDL, H. SCHUSTER, A. PERNECZKY, and W. KOOS

Introduction

Treatment of intracranial abscesses has become somewhat more successful since the introduction of antibiotic therapy, although surgery of acute brain abscesses still has a high rate of mortality. On the basis of experience gained with 167 intracranial abscesses, the method of choice in the surgical approach to the various stages of development in brain abscesses is to be demonstrated.

Material and Results

Over a period of 22 years 167 cases of intracranial abscesses were encountered, 115 of which occurred in children and adolescents and 52 in adults. These cases were divided into three groups: acute abscesses (18, 4), subacute abscesses (22%) and chronic cases (60%). Four methods of surgical treatment of brain abscesses were applied over the said period of time:

- aspiration by burr hole (9%)
- aspiration and drainage by craniotomy (12%)
- total extirpation by craniotomy (62%)
- sponge drainage (17%).

There is no doubt that with a few exceptions the method of choice for the largest group of brain abscesses - chronic and encapsulated abscesses - is total extirpation; the mortality rate in this group was 9.5%.

The major therapeutic problem occurs in the group of acute brain abscesses (18%), in which demarcation to the surrounding brain tissue has not yet been established. Yet, subacute abscesses, in which only a thin and fragile cellular formation has developed around the necrotic centre, accounting for 22% of all brain abscesses, also had a poor prognosis when total extirpation was attempted. Further propagation of brain tissue infection to surrounding structures, especially to the ventricular system, led to severe complications, such as meningoencephalitis and ventriculitis.

In cases of acute brain abscesses we have to distinguish two phases of development, which can easily be differentiated by computerized tomography:

- the acute stage or more or less localized encephalitis without central necrosis and
- the stage of the acute abscess with central necrosis of brain tissue without signs of a glious membrane, but with marked perifocal edema, which is often responsible for alarming brain pressure signs;

particular attention is to be devoted to this group of patients in the present paper.

In cases of very acute stages with diffuse purulent encephalitis we are very cautious as far as surgical therapy is concerned. On the one hand, not all of the affected brain area can be removed, and on the other hand, the borderline between infected and non-infected but edematous brain areas is so indistinct, that aspiration might also destroy affected but viable brain tissue. Internal decompression by puncture cannot be achieved either and instillation of a contrast medium and of antibiotics in adequate amounts for diagnostic and therapeutic purposes is not possible. Conservative antibiotic and antiedematous measures, as well as constant observation of the development of the clinical signs and symptoms with repeated checks by CT produce the best results in early acute brain abscesses.

In cases of fresh and acute abscesses with central necrosis without a membranous borderline we achieved fairly good results by means of the open sponge drainage method (Fig. 1-3), while neither puncture nor aspiration or drainage alone produced similarly satisfactory results.

With regard to mortality, the four different methods of treatment produced the following results in 67 cases of acute and subacute brain abscesses:

Acute abscesses:

- aspiration	100%
- craniotomy and drainage	50%
- total extirpation	50%
- sponge drainage	0%

Subacute abscesses:

- aspiration	66%
- total extirpation	50%
- craniotomy and drainage	33%
- sponge drainage	19%

Discussion

The original method of open sponge drainage was developed by SACHS, DAVIDOFF, HORRAX, ADSON and CRAIG, whereas the method applied by us is based on PEIPER and TÖNNIS; the latter had used it in cases of acute intracranial abscesses and infected gun shot wounds during the Second World War (KRÜGER).

The objectives of the method are the following (Fig. 1-3):

1. The so-called inner immobilisation of the brain after successful evacuation of the necrotic centre of the abscess and
2. prevention of outer and inner brain herniation during the edematous phase, i.e. prevention of outer herniation through the opening of the craniotomy and of inner herniation of edematous brain tissue into the abscess cavity by the inserted sponge (Fig. 1);
3. prevention of propagation of the infection into perifocal edematous and disintegrated brain tissue and into subarachnoid and ventricular areas;
4. sealing of a possible passage to a ventricle;
5. prevention of the formation of a retention cyst and encapsulation of further abscess formations;

6. cleansing of the abscess cavity by daily lavage and withdrawal of secretion by suction (Fig. 1 and 2);
7. Gradual formation of a capsule-like cavity wall, which by and by yields to the normal pressure of the brain tissue, so that subsequent gradual shrinking of the abscess cavity occurs (Fig. 2 and 3); experience has shown that the perifocal edema disappears completely within a few days if this method of treatment is applied; neurological signs, which are largely due to this edema, also disappear.

The method of open sponge drainage has also proved successful in cases of subacute brain abscesses with only thin capsules and also in certain cases of chronic brain abscesses located in the basal areas of the brain.

Summary

In spite of antibiotic therapy, the surgical management of brain abscesses still presents considerable problems, depending on the stage of the disease (acute, subacute, chronic). Based on 22 years of experience with 167 patients, the procedures applied in cases of acute and subacute abscesses with "acute" clinical conditions and the favourable results to be obtained by sponge drainage are reviewed.

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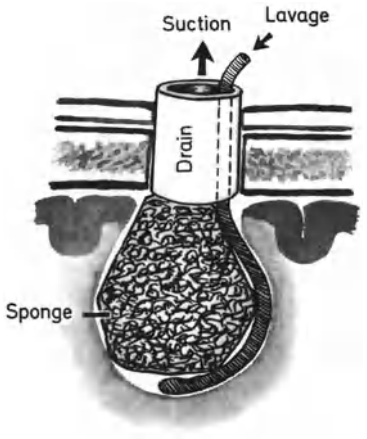

Fig. 1. Insertion of a sponge into the cavity of the abscess to prevent so-called inner prolaps of the surrounding brain tissue and to permit drainage and suction of the secretion and the possibility of daily antibiotic lavage

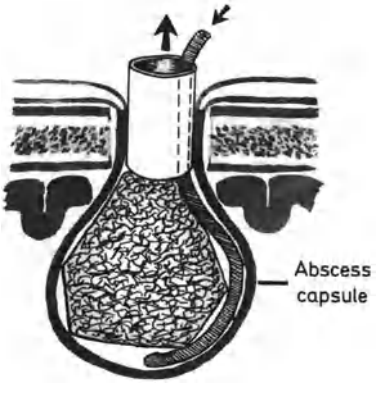

Fig. 2. Formation of a capsule after cleaning of the abscess cavity

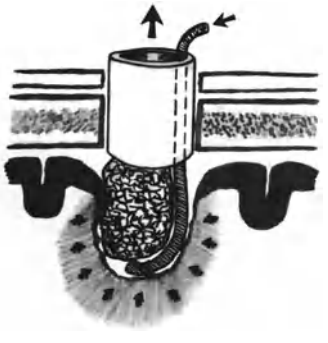

Fig. 3. Reduction of the size of the abscess cavity now well encapsulated by gradual reduction of sponge drainage and by tissue pressure of the surrounding brain structures until complete removal of the drainage system after 1-4 weeks

Difficulties in the Differential Diagnosis of Brain Abscesses

N. KLUG and I. D. ELLAMS

134 patients with brain abscesses were treated in the Neurosurgical Department of the University of Gießen in the period from 1950-1979.

For age and sex distribution see Fig. 1. The male sex dominated in all the age groups.

The aetiological distribution was as follows: otogenic - 27 cases, sinusitis - 19 cases, 26 cases of haematologic aetiology, 20 post-traumatic cases and in 17 cases iatrogenic. The aetiology could not be clarified in 25 cases, i.e. 18.9% of all cases.

In 49 cases the abscesses were localized in the frontal region, in 34 - in the temporal, in 19 - in the parietal, in 9 cases in the occipital and in 13 cases the localization was cerebellar. Ten patients had multiple abscesses.

The treatment pattern was as follows: Puncture and aspiration of the abscess was performed in 35 cases, aspiration followed by extirpation at a later date in 58 cases, and primary extirpation in 18 cases. A purely conservative treatment was undertaken in 4 patients in whom multiple abscesses were suspected and later confirmed through the clinical course. In two cases of supratentorial abscess and 2 cases of infratentorial abscesses the pathology was discovered. 19 patients died before any diagnostic or operative measures could be taken. The total mortality within the first three weeks including the patients not operated upon was 33.8%.

The differential diagnosis of brain abscesses with other inflammatory processes or space-occupying lesions is still difficult despite the advances in diagnostic procedure.

Only half of the number of patients demonstrated the classical clinical symptoms: increased intracranial pressure, neurological signs and symptoms, meningeal reaction and general signs of infection. Fever was absent in most cases. According to the literature, increased WBCC is present in 10-63% of the patients (4).

The BSR was normal in 25% or nearly normal in a large proportion of cases.

In one-third of the cases, the lumbar CSF showed an increase in the cell count. The protein content of the CSF is increased in about two-thirds of the cases.

Routine skull X-rays, X-rays of the ethmoid bone and other special X-rays may show destruction of bone or inflammatory changes which can offer valuable diagnostic clues.

In exceptional cases calcifications in the abscess can be demonstrated as in Fig. 2. Sometimes the displacement of the pineal body is seen as proof of midline displacement.

In agreement with the data of the literature we found positive scintigraphic scans in 90% of the patients examined. Angiography is performed now only in cases where CAT does not provide a definite diagnosis. Ventriculography and encephalography are no more considered as indicated. Diagnostic puncture is performed in cases where the differential diagnosis: cystic and central necrotising tumour, multiple lesions and abscesses presents difficulties.

The CAT is certainly an important advancement in the diagnosis of brain abscesses. The typical characteristics of brain abscesses in CAT are: a space-occupying lesion with a central zone of a lesser density, an extensive perifocal oedema, which is not fingershaped and with mass displacement. A ring-like enhancement which is achieved after a contrast medium infusion is probably due to the richness in collagen-tissue of the membrane of the abscess. It is simple to differentiate between encephalitis and abscesses. The CAT allows the recognition of the change from one stage to the other (1, 2, 7, 8, 18).

Accordingly the CAT shows the progress in cases treated conservatively and confirms the diagnosis at the same time.

Difficulties in CAT diagnosis of brain abscess may arise in lesions that show characteristics of brain abscess such as: low central density, perifocal oedema and ringenhancement.

Our observation and the information from the literature show that the differential diagnostic problems occur in cases of cystic tumours, tumours with central necrosis and multiple metastases. The figure shows a CAT of a patient in whom multiple abscesses were mistaken for multiple metastases. In such cases, repeated CT scans with contrast medium injection are of importance.

The typical girland-like enhancement is well known in cases of glioblastoma. Differential diagnostic problems presented by the so-called ring-glioma have been analysed extensively in the past (5, 9, 10, 11, 13, 16, 17).

Haemorrhagic infarction may present as a zone of low central density with ring-enhancement at particular stages (9, 14, 19). In contrast to the ischaemic infarctions the ringenhancement persists for a longer time and is not limited to the grey substance.

The deciding factors in the differential diagnosis of vascular lesions are the history, development, angiography and in cases of infarctions, the distribution pattern of the lesion.

Intracerebral haematoma can also present in CAT as a zone of low density with ring-like enhancement (17, 19).

Out of 13 patients with haematoma followed up by ZIMMERMANN et al., six presented a ringenhancement between the 6th day and 6th week after the haemorrhage. Important for the differential diagnosis is the lack or minimal oedema, and little or no mass displacement. In our series there was a remarkable case of a 45-year-old patient in whom a sterile abscess developed at the site of capsular haemorrhage which occurred 2 months earlier (Fig. 3).

Table 1. Differential diagnosis of brain abscess with ring enhancement in the CT

	Ring enhancement	Space-occupying lesion	Multiple	Edema	Hypodense area	Hyperdense area
Abscess	!	+	++	!	+	-
Cyst. tumor	(+)	+	(-)	+	+	-
Necrot. tumor	(+)	+	(+)	+	+	-
Metastasis	(+)	+	++	!	(+)	(+)
Glioblastoma	!	+	-	!	(+)	(+)
(Haemorrh.-)infarct	(+)	(+)	(+)	(+)	-	(+)
Intracer. haematoma	(+)	(+)	(+)	(+)	(+)	(-)
(Herpes-)encephalitis	-	(+)	(-)	+	+	(-)
Sept. emboli	-	-	(+)	(+)	-	+

- = no; (-) = improbable; (+) = possible; + = yes; ++ = often; ! = marked.

Septic emboli as described by DUNCAN et al. in their CAT studies (3) present a different picture to that of a brain abscess. There is a uniform increase in density after contrast medium injection (Fig. 4). In our series we were able to observe a 12-year-old patient with known mitral valve insufficiency, rheumatic fever and chorea minor 2 years ago. During a new septic attack in this patient, the signs of encephalitis, meningitis and incomplete oculomotor nerve paresis of both sides developed. The diagnosis of septic emboli was confirmed from the history, the clinical presentation, laboratory results and the EEG changes.

The experience with CAT-presentation of mycotic aneurysms is very sparse.

Table 1 shows the summary of the CAT-results of lesions presenting characteristics of brain abscesses and difficulties in the differential diagnosis. CAT differentiation between brain abscess and encephalitis and septic emboli is easy.

If clinical findings, laboratory data and X-ray studies do not permit the immediate differentiation in cases of vascular lesions or multiple lesions as metastases and brain abscesses, repeated CT scans are necessary to ascertain the diagnosis.

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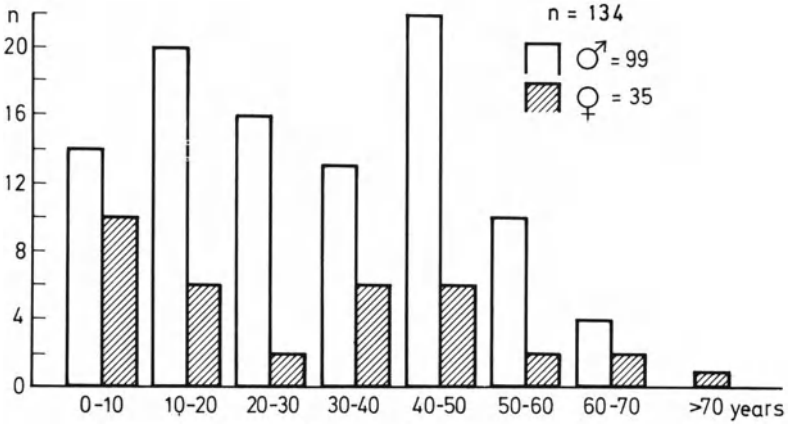

Fig. 1. Age distribution of 134 cases of brain abscesses 1950-1979

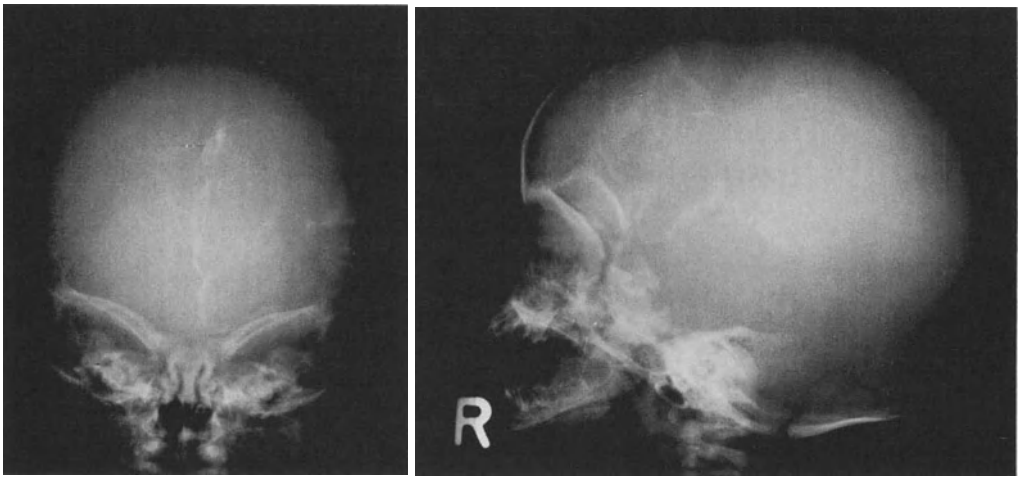

Fig. 2

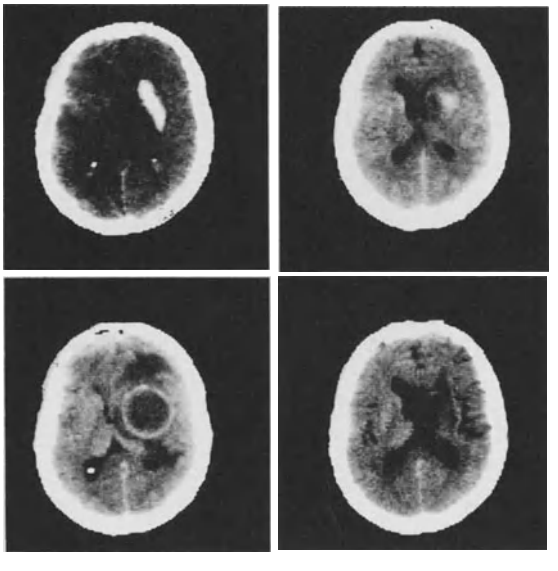

Fig. 3

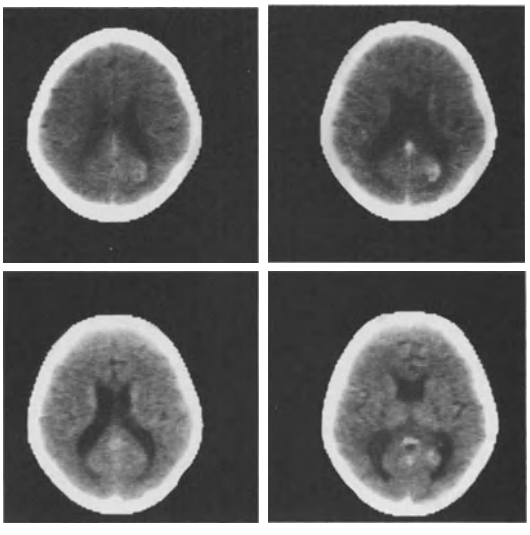

Fig. 4

The Brain Abscess – A Search for Risk Factors

W. ENTZIAN

The prognosis of the brain abscess is limited by a relatively high mortality ranging from 20% and 50% since the use of antibiotics (1, 3). Only a few authors report on very favourable results (4). The question arises, if special risk factors can be identified as the cause of the poor outcome in so many patients. If these were recognized earlier, it would be possible to treat the patients adequately.

Patients

From 1957-1979 75 patients were admitted because of cerebral or cerebellar abscess. The etiology of the abscess, the clinical findings, accompanying diseases specific for brain abscess, microbiological results, therapeutic procedures and final outcome of the patients were correlated. The age of the patients and incidence since 1957 are shown in Fig. 1.

Results

1. The age distribution indicates a tendency to a poor prognosis in patients beyond the 6th decade of life according to our limited number of observations.

2. Concerning etiology, abscesses developing by extension from otogenic or rhinogenic foci represent the largest number and cause a mortality somewhat above average (Table 1).

3. An accompanying meningitis with cell counts above 10 000/3 was followed by a lethal course in all four patients. Among the 31 patients with 15/3-10 000/3 cells in the cisternal CSF, 13 patients (approx. 42%) died. There were lethal courses among the patients with an irritative pleocytosis below 150/3 as well (Table 2).

4. Cerebral and cerebellar abscesses were combined with adjacent subdural empyema in 5 patients (approx. 7% of our patients). Table 3 demonstrates, that this combination occurred in children and young patients below the age of 30 years, that foci were maxillary sinusitis or otitis media, that pus was populated by streptococci and that patients died with one exception. All patients were awake or awakable at the time of admission (Table 3).

5. Multiple abscesses closely adjacent could be excised successfully at craniotomy in two cases. However, a lethal outcome was observed in all other six patients without operation.

Table 1. Abscesses developed by contiguity from an otogenic focus represent the greatest number among our observations and indicate a mortality somewhat above average
Brain abscess: etiology and mortality - 75 patients, 1957-1979, NCH Bonn

Etiology	No. of patients	Mortality	Survivors
Trauma, recently	9	3	6
"Late" abscess from projectile	9	3 } (33%)	6
Extension			
Oto-rhinogenic	26	9 (35%)	17
Osteomyelitis of skull	2	0	2
Metastatic	20	5	15
Cryptogenic	9	3	6
Total	75	23 (31%)	52

Table 2. Abscesses if accompanied by severe meningitis were followed by a fatal outcome. Cell counts below 10 000/3 including pleocytosis below 150/3 may also have a fatal outcome (13/31 = 42%)
Brain abscess: CSF cell counts and mortality. NCH Bonn 1957-1979

	Total	Deaths	Survivors
0 - 15/3	7	0	7
15 - 150/3	14	6 !	8
150 - 1 000/3	6	2	4
1 000 - 10 000/3	11	5	6
10 000/3	4	4	0 !

Table 3. Abscesses combined with subdural empyema could not be treated successfully in 4/5 cases. The combined disease developed from otogenic foci in all patients.
Cerebral and cerebellar abscesses: combination with subdural empyema and mortality - 5/75 patients, 1957-1979, NCH Bonn

Age	Focus	Bact.	CSF cells	On admission	Outcome
♀ 8	Sinusitis maxillary	Strepto-cocci	48/3	Awake	+
♂ 10	Otitis media	Strepto-cocci	132/3	Somnolence	+
♂ 10	Otitis media	Strepto-cocci	?	Somnolence	+
♂ 11	?	No bact.	2 576/3	Awake	Alive
♂ 28	Otitis media	?	1 145/3	Awake	+

6. Streptococci were found more often than Staph. aur. in our patients. The mortality in this group (10/18 = 44%) was above average and by far above the mortality of patients with Staph. aur. (4/16 = 25%). Furthermore Table 4 *(above)* demonstrates a relatively high mortality in the group with "sterile" abscesses and relatively good result in patients with mixed flora. In Table 4 *(below)* a short interval between the onset of cerebral symptoms and diagnosis in patients with streptococci in their abscesses is shown (3.8 weeks) compared with a relatively long interval in patients with Staph. aur. (2.2 months).

Table 4. Streptococci were observed very often, they seemed to cause a faster progress of clinical symptoms and a higher mortality than Staph. aur. did.
Brain abscess: bacteriological findings and mortality - 75 patients, 1957-1979, NCH Bonn

Bacteria	No. of patients	Mortality	Survivors
Streptococci	18	8 (44%)	10
Staph. aur. (17)	16	4 (25%)	11
"No bact."	19	5 (26%)	13
Prot. (3), Bacteroid. (2)			
E. coli (1), Alcalig. (1)			
Eik. corr. (1), Coryneb. (1)			
S. alb. (1), Thetajotam. (1)	6	0	0
No result	16	6	10

Bacteriological findings and acuity (interval primary symptom - operation)

	n	Minimal	Maximal	Average
Streptococci	6	1.5 weeks	6 weeks	3.8 weeks
Staph. aur.	9	2 weeks	6 months	2.2 months

7. Initial clinical symptoms may be further subdivided into light signs (moderate headache, general feeling of being ill) or severe signs of raised intracranial pressure (severe headache, somnolence), neurological deficits (paresis, aphasia, visual field defect) and seizures, focal or generalized. It was found useful to have them arranged according to their combinations observable in the initial phase of the disease, as is demonstrated in Table 5. Those patients, who started with severe signs of raised intracranial pressure, had a more unfavourable prognosis than the average and by far worse than those, whose primary local symptoms dominated long enough until admission into the neurosurgical unit.

8. The results after conservative and operative therapy (tapping or primary excision or both) are collected in Table 6 regardless of the clinical situation. So the numbers contain such patients too, in whom a therapeutic procedure was no longer indicated at the time of admission because of cerebral herniation ("conservative treatment") or therapy was discontinued after abscess aspiration or abscess drainage because of the same reason. Primary excision is followed by less favourable results in supratentorial abscesses than the combined method (secondary excision following primary local therapy by tapping or drainage).

Table 5. Severe headache and/or somnolence may dominate in the initial phase over neurological focal deficits and/or epileptic seizures, which corresponds to a relatively high mortality in our patients
Brain abscess: dominating initial symptoms and mortality

Initial phase signs	No. of patients	Mortality	Survivors
Severe headache or somnolence with or without neurological focal deficits	30	14	16
Severe headache or somnolence with epileptic seizure(s)	22	7 } (40%)	15
Neurological focal deficits with/without light headache	10	2	8
Epileptic seizure(s) with/ without light headache	13	0 } (9%)	13
Total	75	23 (31%)	52

Table 6. The rapid development of cerebral herniation can prevent or interrupt adequate operative therapy of abscesses (line 1 and 2). Primary abscess excision, often performed under unfavourable circumstances, seems to have an above-average mortality. Best survival chance two-step therapy?
Brain abscess: therapy and mortality. NCH Bonn 1957-1979

	No. of patients	Mortality	Survivors
No operation	4	4 (100%)	0
Drainage / aspiration	29	9 (31%)	20
Excision, primary	14	5 (35%)	9
Secondary excision after drainage	20	2 (10%)	18
Infratentorial:			
Drainage	2	2	
Excision, primary	6	1	5
Total	75	23 (31%)	52

9. In the surviving patients, permanent neurological deficits may be correlated to the site of the abscess but not to any other of the factors mentioned, especially not to the kind of therapy chosen (drainage and/or excision). However, it was our policy to avoid excision of the capsule if it was located in dose proximity to the precentral gyrus. Psychic permanent deficiencies seem to correlate with the length of unconsciousness and not with any other factors.

Table 7 demonstrates posttherapeutic epilepsy in 4/12 cases (either first seizure or continuous) if drainage of abscess was chosen as the only form of treatment. 2/32 patients had seizures after excision of capsule.

Recurrence of abscesses following primary excision, drainage and combined procedures were each observed once, so that there seems to be no correlation (3/75 = 4%).

Table 7. Following successful therapy, abscesses may cause epilepsy. Among our observations there is a higher frequency of continuing or newly developing epilepsy, if the capsule remains unexcised after drainage.
Brain abscess: therapy and epilepsy - 75 patients, 1957-1979, NCH Bonn

	Drainage/ aspiration	Abscess excision
Preoperative epilepsy, *continuing*	2	2
Preoperative epilepsy, *discontinuing*	2	10
Postoperative epilepsy, *new*	2	0
No pre-/postoperative epilepsy	6	20
Total	4/12	2/32

Discussion

The clinical course of most of our non-surviving patients with abscesses had become complicated by at least one of some "factors" which appeared to be a risk factor from the beginning or as an additional, accompanying or secondary feature. Because of their frequency they may be considered as specific risk factors. Their unfavourable effect is not equal, the most dangerous ones are mentioned first:

1. Multiple occurrence of abscesses in two hemispheres or in one hemisphere separated widely will probably seldom be treated successfully, even if they are detected by CT.

2. An accompanying meningitis may develop by contiguity from an otogenic putrid focus or from the abscess itself. Or it may develop secondarily to an abscess, if the abscess contaminates the CSF space, or it may be of metastatic origin. If such accompanying meningitis develops very high cell counts in the CSF, the prognosis must be considered to be very poor. According to our experience no abscess-bearing patient with meningitis and a cell count >10000/3 survived.

3. The third most dangerous complicating factor, that may add to a cerebral or cerebellar abscess is an accompanying subdural empyema. In some of our cases it developed by extension from a rhinogenic or otogenic focus, in others it probably developed from the abscess, as the capsule was missing or being developed very poorly as seen

at craniotomy. This morphological problem and the short history of these cases of less than three weeks raises the question, whether the immune defence reaction of these patients (children or younger than 30 years) were deficient or the bacteria were especially aggressive (all examinations done showed streptococci).

4. There were 3 patients with "very large" abscesses of traumatic origin, which had developed within 6 months to 2 years. Only one patient survived the excision of the abscess.

5. An intracerebral phlegmon should be mentioned as another high risk factor from the morphologic point of view. It was found in a number of our autopsies, however it had probably developed secondarily to the above-mentioned risk factors in a final clinical stage and it was not diagnosed clinically in the pre-CT era. Morphological problems are discussed thoroughly by CERVOS-NAVARRO et al.

6. Perifocal edema, sometimes involving both hemispheres is a most serious risk factor but is not analysed in this paper, because most of the patients were treated before the adequate diagnostic help of CT was available.

Other factors were found to occur more often in lethal cases than in the average, but did not have the same fatal effect as the above-mentioned factors:

13/31 patients with abscesses and accompanying meningitis with cell counts between 15/3 and 10 000/3 could not be treated successfully. It is remarkable that there is considerable mortality even among the patients with just an irritative pleocytosis below 150/3. All patients of this special group had a stiff neck, which in these cases is indicative for a beginning cerebral herniation but not for meningitis. The syndrome "meningism without meningitis" is considered therefore as a specific clinical risk sign in abscesses-bearing patients.

Bacterial flora consisted mostly of streptococci. The relativly high mortality of these patients corresponds to the general experience of high aggressivity of streptococci compared with Staph. aur.

As far as other risk factors are concerned, the figures indicate that patients with an otogenic focus or patients aged above 60 years have a poorer outlook than the average.

At the beginning of the disease clinical symptoms may be dominated by focal neurological signs (including epileptic seizures) or by severe signs of raised intracranial pressure. If the latter occurs, rapid development of the abscess, of accompanying cerebral edema, of accompanying meningitis or subdural empyema seems to be the reason according to our data. Such a clinical development should be taken as an indication of a dangerous clinical course.

The formal comparison of mortality rates with the various forms of treatment applied in our patients (Table 6) is misleading, because of the different clinical situations occurring within each group. Mortality after "conservative treatment" and after abscess drainage as monotherapy occur in patients with desperate clinical findings not allowing further procedures. It may be concluded however, that patients, for whom the combined therapy (local abscess drainage with antibiotic irrigation and secondary excision of capsule) can be planned and performed before one of the mentioned risk factors develops, have a very good prognosis.

The risk of post-operative sequelae include neurological deficits, psychogenic deficiency and epilepsy. Permanent focal neurologic deficits depend mostly on the localization of the abscess and can scarcely be influenced. A decrease in cerebral vitality according to our data is generally an effect of prolonged unconsciousness and may be prevented partially by early diagnosis and therapy. Epileptic seizures after abscesses should be considered as a general risk. However, the probability of this complication can be reduced by excision of the capsule of the abscess, even if it is sterile and not inflammatory after drainage therapy.

Summary

75 patients with cerebral or cerebellar abscess were observed. 23 patients died, i.e. a mortality rate 31%. Multiple or very large abscesses in combination with severe meningitis (> 10 000/3 cells in CSF), or in combination with subdural empyema are complicating risk factors indicating the highest probability for a fatal course. Generalized edema and secondary cerebral phlegmons are risk factors of similar value. High age, streptococcus population, otogenic etiology and meningitis below 10 000/3 seem to be factors with less risk, but they still cause a mortality of 40-50%. The rapid development of severely raised intracranial pressure (severe headache, somnolence or meningism without meningitis) seems to be a clinical sign for the development of these risk factors.

Perhaps earlier diagnosis and therapy may decrease the fatal effects of these risk factors. Those patients for whom a combined therapy (drainage of the abscess, secondary excision of capsule) can be planned and performed, seem to have a favourable prognosis. The incidence of post-operative epilepsy seems to be less if the capsule is excised than after abscess drainage alone.

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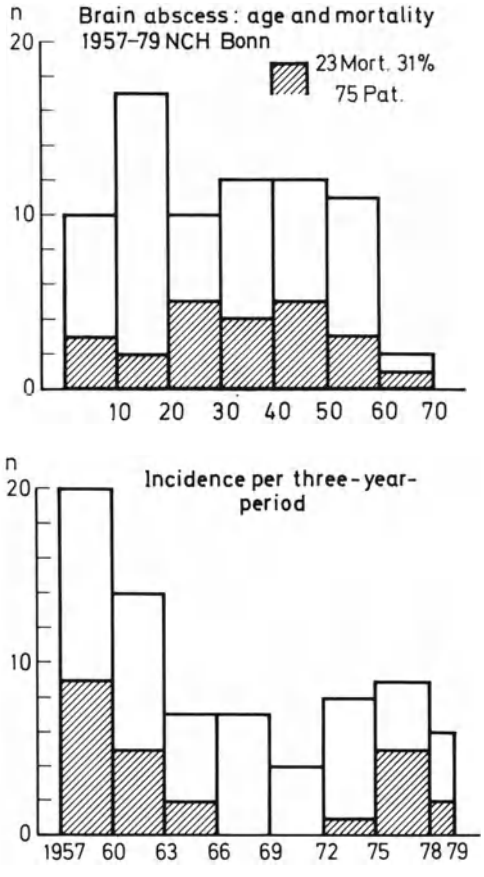

Fig. 1. Age distribution *(above)* of cerebral/cerebellar abscess shows the relatively good outcome of young patients, but the tendency for an unfavourable prognosis beyond the age of 60 years. Since 1957 no significant change in the survival rate

Brain Abscess in Childhood

D. P. LIM, R. LIERSCH, R. POTHMANN, and H. K. SEIBERT

Introduction

Since the introduction of CT, early recognition of brain abscess, its dimensions and localisation as well as its course, often without clinical parameter has become much easier to follow up, especially in pediatric neurosurgery.

Timing and choice of therapy have both been easier to decide on, and this reflects positively on the prognosis.

The incidence of brain abscess in children with congenital cardiovascular disease is high. In a collective study with routine exploration of the cerebrum prior to correction of cardiovascular malformations, the diagnosis of cerebral abscess was established in some cases.

Material and Approach

Between 1976 and 1980, we established the diagnosis of cerebral abscess in 12 children with CT. They were between 2 and 12 years old. Out of the 12, 8 had congenital malformations of the cardiovascular system (Table 1). The remainder had oto-rhino-laryngological infections spreading to form brain abscess. Sexual distribution: male : female was found to be 4 : 1. With the very young children (toddler) symptoms ranged from intrasigent hyperpyrexia through anorexia and vomiting. Signs of headache, nuchal rigidity and impairment of consciousness were found more with older children. Neurological deficits were typical for the localisation. Papilledema was frequently found at ophthalmological examination.

Table 1. The correlation of the therapeutic procedures and sex difference to the etiologies of the 12 patients with brain abscesses in this series

Etiologies	Surgical procedures			Non-surgical procedure	Sex	Total (n)
	Aspiration	Excision Primary	Excision Secondary			
Congenital heart diseases	6	1	1	1	M:7	8
Rhinogenic	2	0	0	0	M:1 F:2	2
Otogenic	2	0	1	0	M:1 F:1	2

Table 2. Patient data

No. of patient	Age (year)	Sex	Site of abscess	Etiology	Preoperative status	Surgical procedure	Follow-up status
1. AR	2	F	Parietal (deep)	Congenital heart disease	Fever, hemiparesis	Aspiration	intact[a]
2. BO	3	M	Frontal	Congenital heart disease	Fever, CSF purulent, lethargy, papill-edema	Nonsurgical	intact
3. MN	5	M	Temporal	Congenital heart disease	Hemiparesis, aphasia fever, headache	Aspiration	intact
4. IG	12	F	Temporal	Otogenic	Headache, papill-edema	Aspiration excision	intact[b]
5. WP	11	M	Parietal	Congenital heart disease	Headache	Aspiration excision	intact
6. KF	11	M	Frontobasal	Congenital heart disease	Fever, headache, papilledema	Excision	retarded
7. KP	11	M	Praecentral	Congenital heart disease	Headache, meningitis fever	Aspiration	intact
8. WF	12	M	Parietal	Rhinogenic	Hemiparesis, papill-edema	Aspiration	intact[b]
9. GC	9	M	Temporal	Congenital heart disease	Hemiparesis, fever, headache	Aspiration	intact
10. KD	3	M	Parietal	Congenital heart disease	Fever, enteritis	Aspiration	intact
11. RC	9	F	Frontal	Rhinogenic	Headache, fever	Aspiration	intact
12. SA	6	M	Temporal	Otogenic	Fever, meningitis	Aspiration	intact

[a] Died during cardiac surgery. [b] Residual paresis.

The approach of therapy was first burrhole-aspiration, and then there was follow-up with CT at intervals of 7 days under systemic-antibiotic coverage.

Ten children (80%) responded very favourably to the method of burr-hole-aspiration (Fig. 1). The rate of complication was rather low (Table 2). In the case of 2 children (Fig. 2) craniotomy had to be performed and the abscess removed since follow-up CT in the intervals already mentioned failed to show any improvement. We carried out a total removal of the abscess in the frontal lobe in one child in the first instance. One child was treated conservatively (Fig. 3). A purulent spinal tap was obtained and adequate antibiotic therapy was initiated, follow-up CT showed complete resolution of the abscess.

All children responded very well to therapy. In a parallel study in adults, we found a mortality rate of around 27%, so that the prognosis in pediatric cerebral abscess was unquestionably better.

Discussion

Operative therapy with burr hole-aspiration of the cerebral abscess under systemic antibiotics and serial CT follow-up tends to show better results (Table 2). The antibiotic coverage should be adequate, and the surgical procedure relatively minor. Should extension of the abscess take place, CT follow-ups make it possible to recognize this early enough. In cases where the causative organism is isolated, a trial of conservative therapy may be attempted, provided the regular CT check-ups are kept in mind.

In our series of patients cardiovascular malformations of congenital origin, were predominantly significant. We would recommend routine CT-examination for all cases of congenital malformation prior to cardiosurgery.

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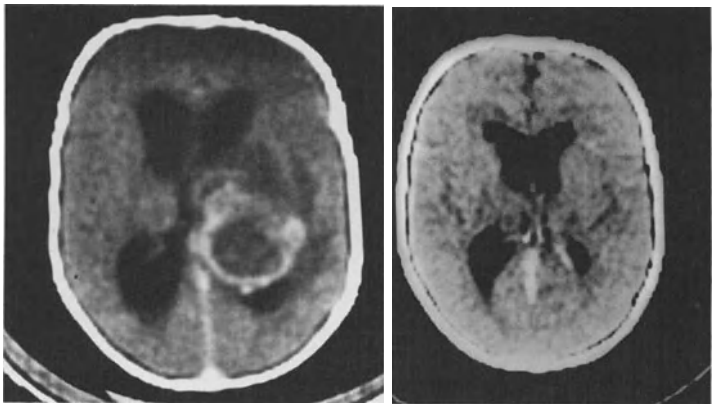

Fig. 1. Patient No. 1 from Table 2 CT-scan, brain abscess parietal. *Left:* preoperative; *right:* post-aspiration

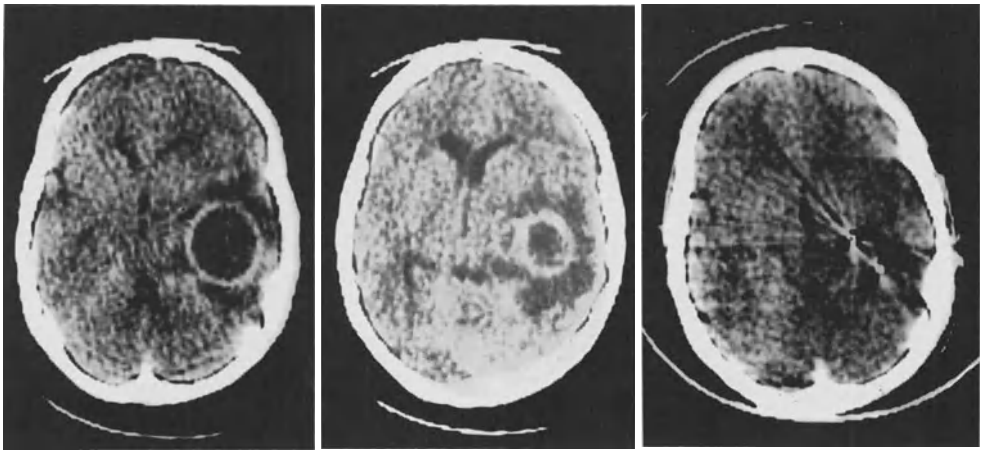

Fig. 2. Patient No. 4 from Table 2 CT-scan, brain abscess temporal. *Left:* preoperative; *middle:* post-aspiration; *right:* post-excision

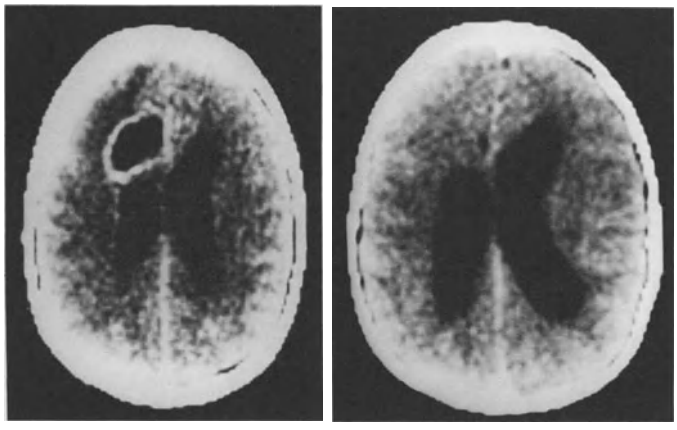

Fig. 3. Patient No. 2 from Table 2 CT-scan, brain abscess frontal. *Left:* initial scan; *right:* 7 months after antibiotic therapy

Brain Abscess in Children

H. SCHUSTER and W. KOOS

During the past 40 years, 130 case studies of children with various stages of brain abscess were observed at the Neurosurgical Clinic of Vienna. The purpose of this report is to point out the importance of early diagnosis and how brain abscesses in children differ from those in older age groups.

Clinical Material

The series consists of 130 children and adolescents up to 16 years of age, treated in our center during the 40-year period from 1940-1980. The incidence of brain abscess shows a pronounced peak around the ages of 1,7 and 15 years of age (Fig. 1). The predilection of the disease for these age groups may be explained by cardiopulmonary, otorhinogenic and partly traumatic sources.

A preponderance of males over females in a ratio of 3 : 2 was found among our patients.

The etiology in correlation to various age groups is presented in Table 1. The highest incidence of metastatic abscesses was found between birth and 5 years of age including children with congenital heart disease. During the following 5 years, abscesses due to ear and nose infections increased. In adolescence there were no significant variations in incidence.

The temporal and frontal lobes were affected most frequently (Table 2). The abscesses were divided equally between both hemispheres. In a high percentage, the site of the abscess was ipsilateral or adjacent to the infected ear or sinus. This fact suggests a contiguous type of spread.

Table 1. Etiology of brain abscess in children

Age	Post-traumatic	Oto-genic	Rhino-genic	Metas-tatic	Cardiac	Unknown	Total
0- 5	1	5	1	13	10	4	34
5-10	5	16	7	8	5	5	46
10-16	9	17	11	4	6	3	50
Total	15	38	19	25	21	12	130

Table 2. Localization of brain abscess in children

Frontal	32	(24,6%)
Temporal	39	(30,0%)
Parietal	18	(13,8%)
Occipital	6	(4,6%)
Infratentorial	12	(9,3%)
Multiple	23	(17,7%)

9,3% of the abscesses were located in a cerebellar hemisphere, usually attached to the posterior surface of the petrous bone. In 23 children we found multiple abscesses, 15 of them in different lobes of the same hemisphere, 8 in both hemispheres.

The duration of clinical symptoms, i.e. the time from the first clinical sign to the surgical therapy, ranged from a few days to several months. Especially otogenic abscesses often had a long preoperative period with non-specific symptoms (Fig. 2). On the other hand, the majority of metastatic abscesses run a fulminant course leading to high intracranial pressure in a few days. They are, as a rule, deep-seated and not infrequently paraventricular with a tendency to rupture into the ventricles.

Brain abscesses are divided into three different stages: acute, subacute and chronic. Those of the first type contain free pus, have no macroscopic boundary, and merge with the surrounding edema. The second type has liquid pus, partly surrounded by a thin capsule of irregular shape. The third group has a consistently thick capsule. The mortality rate in acute abscesses was 46,4%, in the subacute group 47,8% and in the chronic stage 12,6% giving an overall mortality of 35,6% (Table 3).

Four different methods of surgical therapy were used: aspiration through a burrhole, drainage through craniotomy, marsupialization and total extirpation (Table 4). The method of choice in a chronic abscess is, without a doubt, total extirpation. Unfortunately, in acute or subacute abscesses this method does not seem to be applicable because of the poor condition of the patient.

The overall mortality rate of all types of operations performed was 35,6%. The high percentage of deaths in the first two groups (aspiration and drainage) was due to the fact that nearly all cases treated with these methods were acute or subacute. Marsupialization was the only method used which had satisfactory results in the treatment of acute abscesses (mortality 7,7%).

Table 3. Stages of brain abscess in children

		(%)	Dead	(%)
Acute	28	(21,5)	13	(46,4%)
Subacute	23	(17,7)	11	(47,8)
Chronic	79	(60,8)	10	(12,6)
Total	130	(100,0)	34	(35,6)

Table 4. Surgical results of brain abscess in children

		(%)	Dead	(%)
Aspiration	12	(9.2)	7	(58.3)
Craniotomy and drainage	18	(13.8)	9	(50.0)
Marsupialization	13	(10.0)	1	(7.7)
Total extirpation	87	(67.0)	17	(19.5)
Total	130	(100)	34	(35.6)

Discussion

With the introduction of antibiotic therapy, the prognosis for brain abscess has definitely improved. Since the advent of this therapy, pyogenic abscess even in children has markedly diminished in frequency. The cause for this reduction, of course, is the improved treatment of primary foci such as otitis, sinusitis, bronchiectasis, congenital heart diseases and traumatic lesions. However, according to INGRAHAM and MATSON (2), it is important to remember that brain abscess secondary to these sources of infection does still occur occasionally. Also, with the widespread use of antibiotics, the clinical features of the lesion may be masked and go long unrecognized.

In many children the symptoms and signs caused by this disease may be extraordinarily few. Over a long period of time they may complain of headache and it is necessary, therefore, to keep abscess in mind in the differential diagnosis, even if fever, chills, leucocytosis and other systemic evidences of infection are lacking. These observations correspond to those of RAIMONDI and co-workers (3), who found only headache sometimes accompanied by vomiting in many of the 19 cases of children with congenital heart disease.

As a result of this fact many children are sent to the neurosurgeon in a moribund state. Surgical procedures at this state are much more problematic than those in children in a good general condition.

Computerized axial tomography (CAT-Scan) has proven to be an excellent method for earlier diagnosis. In this manner, treatment will be initiated as early as possible in order to limit the destructive infective process and the associated deterioration of the patients condition (4). Furthermore, diagnosis may be made more frequently before the development of the abscess. This is frequently referred to as the cerebritis stage of abscess evolution.

According to HEINEMANN et al. (1), intraparenchymal regions of cerebritis are believed to be more readily curable with antibiotics alone than well-formed abscesses. This may lead to a decrease of surgical interventions with its attendant risks.

Brain abscesses due to congenital heart disease are a specific affection of early childhood. In a large number of cases they are found to be multiple. The operative risks in this kind of abscess is relatively high and an early diagnosis, again, sometimes helps to avoid an unnecessary surgical procedure (5).

Conclusion

In our experience the methods of surgical intervention during childhood and adolescence are not different from those in older age groups. The risks in corresponding abscess stages are nearly the same.

However, in many cases of brain abscess in children, there seems to be a greater difficulty in early diagnosis in comparison to older age groups. This difficulty may be overcome by a more exact case history and better interdisciplinary communication between pediatrician, neuropediatrician and neurosurgeon.

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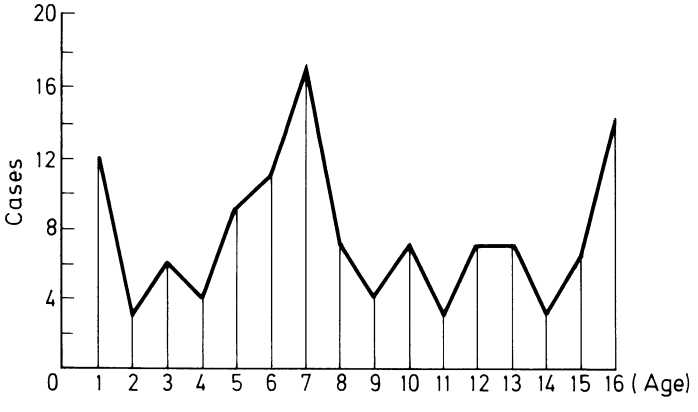

Fig. 1. Age distribution of brain abscess in children

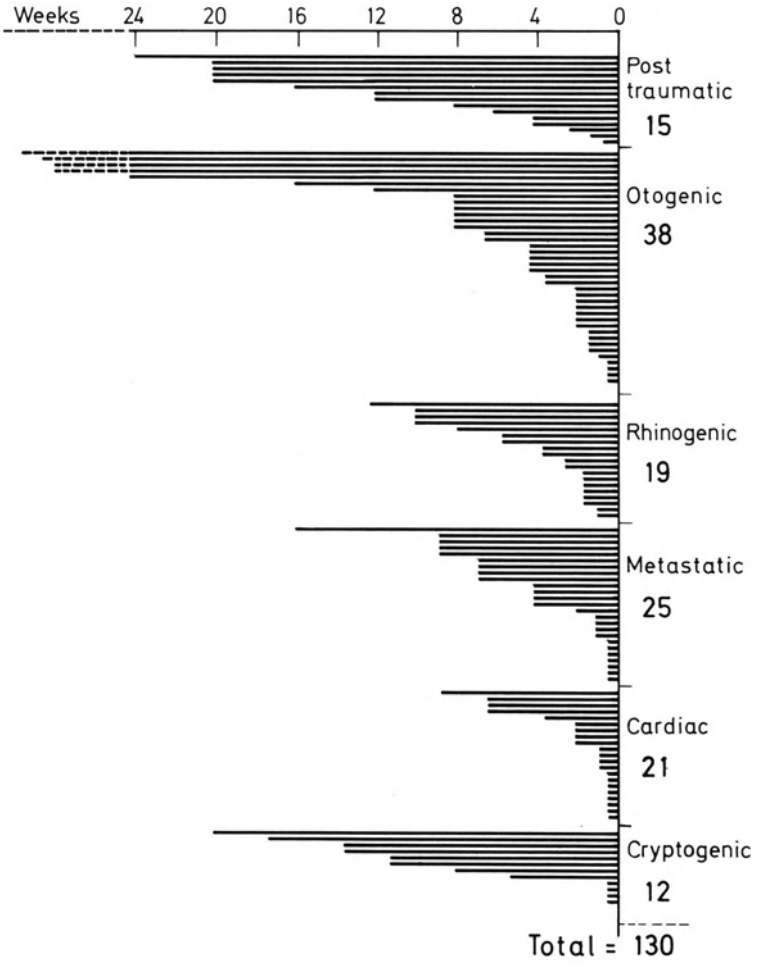

Fig. 2. Duration of symptoms prior to operation

Brain Abscess in Children with Congenital Heart Disease

M. BRANDT, H. ALTENBURG, and P. BÖHM

Introduction

Brain abscess is a serious complication of congenital heart disease. According to the literature, the incidence of hematogenous brain abscess in cyanotic congenital heart disease is about 4-6% (2, 4, 6). Different reasons are given for the relative frequency of brain abscesses as a complication of cyanotic heart disease. Because of the right-to-left shunt, venous blood is allowed to circulate in the arterial system without passing through the pulmonary circulation system to which a filtering effect on bacteria by phagocytosis is ascribed (12). In cardiac insufficiency, encephalomalacia and thrombosis may occur followed by focal infection (8). Also reduced microcirculation with polycythemia and raised hematocrit may favour the development of a hematogenous brain abscess.

Clinical Material

Among the 30 patients with brain abscess which have been operated in the neurosurgical university clinic of Münster during the last five years, there were five children with congenital heart disease. A surgical correction of the heart disease had not yet been undertaken in all five children.

Regarding the symptomatology, it must be mentioned that four of our five cases of brain abscess with heart disease had to be operated on as emergency cases, as a disturbance of consciousness had already occurred. In all cases papilledema was found. There were no cells or only 100-1000/3 cells in the CSF. Headaches and other signs of increased intracranial pressure were reported by all patients. Clinical signs of an infection appeared in the case history of a single patient. Only in one case were meningeal signs observed four weeks before the occurrence of the brain abscess. In one case the blood-sedimentation rate was 72/113, in the other cases it was not raised. Slight fever had occurred only for a short time in two cases. It should be mentioned that there was no endocarditis in all five cases. The arterial pO^2 was only between 40 and 50 torr in three of the five cases. The hematocrit was raised in three of the cases. Some cases had been treated with antibiotics before, especially if a certain increase of the number of cells in the CSF had existed. Table 1 shows the characteristics of a brain abscess in patients with congenital heart disease as they are described in literature and as they were also observed in our cases (3, 5, 7, 11).

In three cases of the era before computer tomography, the brain scintigram resulted in positive findings early. In order to clarify the diagnosis we carried out angiography in these three cases which resulted

Table 1. Characteristics of brain abscess in children with congenital heart disease. Results of 5 cases of the present series

Cyanosis	4
Right-to-left-shunt (Tetralogy of Fallot most common)	4
Polycythemia (Hb, hc, ery ↑)	3
pO_2 significantly low	3
Over 2 years of age	5
Increased intracranial pressure (headache, vomiting)	5
Papilledema	5
Focal neurological signs	3
No or only low fever	5
No endocarditis	5
Lumbar spinal fluid: leucocyte count not or only slightly increased, cultures negative	4
Streptococcus most common in abscess cultures	2

in characteristic findings. In these three cases we first carried out an osteoclastic trepanation and treated the abscess by puncture and instillation of an antibiotic. After the contents of the abscess were sterile, we performed the total removal of the abscess without complication in two cases. In the third case the patient fell into a state of restlessness one day before the total removal of the abscess, so that he fell out of bed. The immediate osteoplastic trepanation showed a large space-occupying intracerebral hemorrhage originating from the abscess capsule. Unfortunately the patient died of this hemorrhage. Another child died because of its cardiac defect two years after an uncomplicated abscess exstirpation. The other three children survived the operation of the brain abscess without serious neurological complications.

Here is a short description of the two cases in which the diagnosis of brain abscess was confirmed by computer tomography.

Case 1

A 7-year-old girl with tetralogy of FALLOT was admitted to the university children's clinic with a 3-week history of headaches and vomiting. The cardiac operation had been planned when the girl was 8 years old. On the day of admission, a paresis of the left arm developed and the child became somnolent. Because of a congenital scoliosis, no lumbar puncture but a suboccipital puncture was carried out, which showed 45/3 cells. About six hours later the child quickly became unconscious. At that time the child had bilateral dilated fixed pupils, CHEYNE-STOKES-breathing and nuchal rigidity. Following immediate dehydration therapy, the left pupil became narrow again. Computer tomography showed multiple right temporo-parietal brain abscesses (Fig. 1). At the immediate large osteoplastic trepanation about 50 ml of pus were aspirated. No real abscess membrane was existing yet. The abscess pus was sterile. The child has recovered well in spite of the initially hopeless situation. We would agree that the cardiac operation be performed before the final plastic correction of the skull defect.

Case II

For this 10-year-old girl with transposition of the great vessels, the correction of the cardiac defect was being planned when cerebral symptoms occurred. At first, signs of cerebral embolism were found. Computer tomography carried out at this time showed the picture of encephalomalacia (Fig. 2a). But hardly two months later the child presented an organic psychosyndrome with signs of increased intracranial pressure and papilledema of 3 dptr. Computer tomography now showed an extended brain abscess, which was situated exactly in the region of the cerebral infarct observed before (Fig. 2b). This means that cerebral infarction was already the initial stage of the brain abscess. Because of the cerebral symptoms, immediate osteoplastic trepanation was carried out. But because the abscess membrane was still thin and the ventricular system very near, only a puncture of the abscess which was situated in the left Sylvian fissure exactly in the area of the centre of Broca was performed. After the aspiration of 35 ml pus, irrigation with H_2O_2 and the instillation of an antibiotic, the dura was closed. The bone flap was not reinserted because of the brain swelling. The child recovered very well after this operation. The pus was sterile. Repeated aspirations did not show any pus. A computer tomogram 12 days after the puncture treatment showed the shrunken abscess capsule. The child went on to a good recovery. It is now without neurological defects especially without dysphasia. A computer tomogram two months later showed the shrunken abscess with abscess capsule (Fig. 2c). Together with the child's parents we decided to carry out the correction of the heart defect first and then afterwards to undertake the total removal of the brain abscess in the dominant hemisphere.

Conclusions

For brain abscesses in combination with congenital heart disease the usual criteria of brain abscess treatment should be valid, at first puncture with aspiration of pus and later total removal (9, 10). But in individual cases, for example if the abscess is located in the dominant hemisphere, it seems reasonable to postpone the total removal of the abscess following puncture, until the correction of the heart defect has been carried out. From the neurosurgical point of view correction of the heart defect before the age of two years is likely to reduce the incidence of brain abscess in congenital heart disease.

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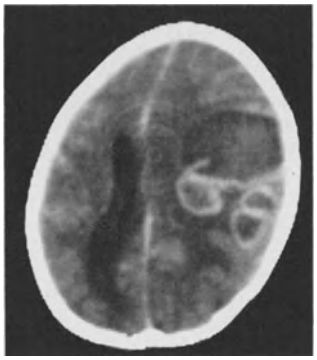

Fig. 1. CT of multiple right temporo-parietal brain abscesses in a 7-year-old girl with tetralogy of FALLOT. Treatment by large osteoplastic trepanation and removal of 50 ml pus

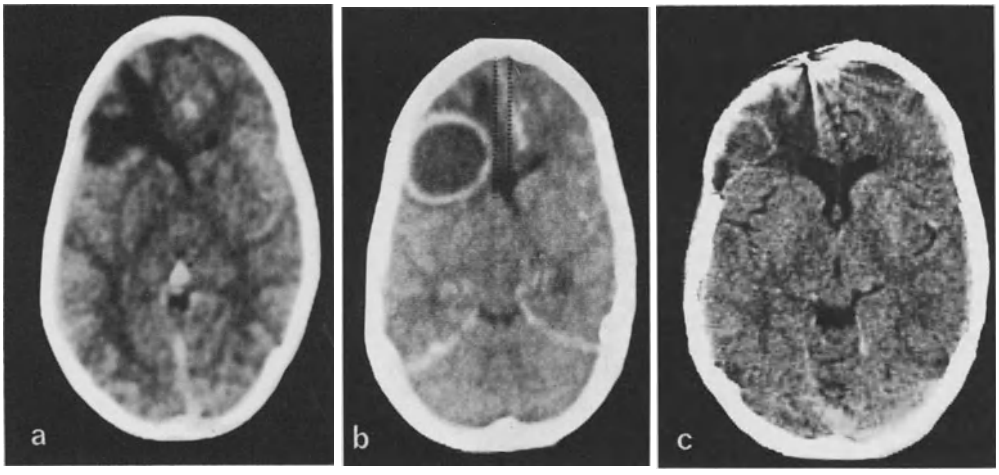

Fig. 2. a CT of a 10-year-old girl with transposition of the great vessels. The hypodense area in the left fronto-temporal region was interpreted to be due to encephalomalacia. b The CT-control, 2 months later shows a large brain abscess in the same area, which was treated by osteoplastic trepanation, puncture and aspiration of 35 ml pus. Repeated aspiration revealed no pus. c CT-control, 2 months after the puncture treatment, shows the shrunken abscess capsule. The child has no neurological defects. Total removal of the brain abscess is postponed until correction of the cardiac defect has been carried out

Experience with Delayed Chronic Brain Abscesses

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The problem of brain abscesses due to gunshot wounds has not become a negative reminder of the war in "To-days World", it is still a problem. Not only the wound infections and the acute brain abscess after missile injuries, but also the development of the delayed chronic brain abscess which may possibly recur, must be discussed.

In a period of 33 years in the "Veterans Hospital" in Bad Pyrmont, we have had the opportunity of observing and studying an unusual number of 15 delayed brain abscesses following missile and other injury, some with an abnormally long latent period up to 31 years.

Clinical Material and Methods

All observed patients were males, 5-54 years old, and all had delayed brain abscesses. The etiology was as follows:
- 9 cases after a shell splinter and 2 after gunshot injuries,
- 3 patients after an traffic accident.

The delayed abscesses developed after a latent period of 1,5-31 years (see Table 1).

In another group of patients, recurrences were observed after operative removal of the abscesses. In those 4 cases, 2-4 reoperations of late recurrent abscesses were necessary in a period of 1-28 years following the first operation (Table 2).

Clinical Course

There were some difficulties in the interpretation of the apparent clinical signs because, in most cases, signs of serious traumatic lesions of the brain persisted: Hemiparesis in 12 cases, hemianopsia in 2, blindness in 2 and mental deterioration in 6 cases. Epileptic seizures were observed in 12 cases.

Many of our patients were treated repeatedly in different departments of our hospital for several years. Therefore, a deterioration of the general condition and of the neurological signs generally led to the suspicion of a delayed abscess, since the slowly expanding lesion in many cases had the same localization as the original traumatic brain injury. Signs of a rapidly expanding lesion were present in only 6 cases.

1 We would like to acknowledge the generous permission of Med. Director Dr. G. VOGT (Bad Pyrmont) to use his clinical material in this study.

Table 1. Delayed brain abscesses

N	Case	Born on	Injury Year	Type	Localisation	Latency in years
01	R, R.	1917	1943	Shell splinter	Frontal right	31
02	B, K.	1914	1945	Shell splinter	Parietal right	27
03	R, C.	1944	1949	Car accident	Parieto-occ. left	14
04	S, W.	1919	1944	Gunshot injury	Frontal right	12
05	F, H.	1921	1944	Shell splinter	Frontal right	11
06	L, E.	1905	1942	Shell splinter	Frontal left	8
07	T, H.	1910	1944	Shell splinter	Parietal left	7
08	S, B.	1938	1945	Gunshot injury	Occipital left	4
09	U, H.	1948	1968	Car accident	Frontobasal	4
10	S, A.	1910	1944	Gunshot injury	Parietal left	3
11	B, H.	1909	1945	Shell splinter	Parieto-occ. left	1,5

Table 2. Delayed abscesses with multiple recurrences

n	Case	Born on	Injury Year	Type	Localisation	No. of re-currences	Latency in years	No. of operations
01	M, E.	1921	1944	Shell splinter	Occipital right	3	11-12-28	5
02	F, M.	1916	1942	Shell splinter	Frontal right	2	1-30	3
03	B, M.	1919	1944	Shell splinter	Parietal right	2	3- 4	3
04	K, H.W.	1927	1943	Car accident	Frontobasal	2	1- 2	5

Laboratory examinations yielded a leucocytosis of no more than 12000 leucocytes as well as an accelerated sedimentation rate in only 8 cases, in others the blood counts were normal. Only 3 patients had fever at the time of admission. In one patient there was serious worsening of the condition with a lethal outcome during a course of spa treatment. A retrospective review of our records revealed that most patients with delayed abscesses had periodic febrile states with laboratory evidence of chronic inflammatory processes in the past months or years. But because of other chronic disturbances such as cystopyelitis, osteomyelitis, fistulas and decubital ulcers, particularly in polytraumatic cases, the patients were treated with various antibiotics repeatedly for several years.

The correct diagnosis of a delayed abscess was made in 13 patients. In one very chronic case, a diagnosis of multiple sclerosis and brain atrophy was assumed in another similar case.

Local signs in patients with large bony defects of the skull leading to swelling of the skin and prolapse of the brain were important diagnostic signs.

X-ray examination revealed intracranial bone or metallic splinters in all cases. The air studies of the early post-war years belong nowadays to the history of medicine. In later cases accurate diagnosis was made by means of arteriography and scintigraphy. More recently, computer tomography was used for control examinations in our patients.

The localisation of the abscesses was as follows: frontal and frontoparietal in 7 cases, parietal and parieto-occipital in 8 cases (Tables 1, 2).

Surgical Treatment

Operative procedures were different depending on the general condition of the patient and also of the operation area. There were important scars of the skin and meningocerebral scars, bony defects and fistulas in many cases. In 3 cases of delayed abscesses, simple evacuation and drainage of the lesion was performed.

In 3 other cases, removal of the capsule was performed several weeks after evacuation of the abscess, and total removal of the abscess in 4 cases. In our last 2 cases an evacuation of the abscess with subsequent irrigation with antibiotics and "abscessography" before radical exstirpation proved to be a valuable procedure.

In 4 cases with several recurrences, all possible operative methods such as evacuation, splitting or drainage or exstirpation of the capsule or of the whole abscess were performed (Table 2).

We have not observed any new recurrences in cases controlled up to date by CT.

Bacteriological Results

In all chronic cases with recurrences a beta haemolytic staphylococcus was cultured in the pus. In one case Pseudomonas pyocyaneus and in another a not exactly determined diplococcus was discovered. In 4 patients with a very prolonged delay, the bacteriological examina-

tion remained negative. In 4 patients a bacteriologic result was not registered.

Results

In the whole series of delayed abscesses, the general condition and some neurological deficits were improved in 9 patients following operative treatment. The frequency of seizures had diminished.

In 4 chronic cases with recurrences only a slight improvement of the neurological deficits was registered. 2 patients died of meningitis and pyocephalus after an acute exacerbation of the delayed abscess.

Discussion

In our clinical material, relatively long periods of latency in the evolution of delayed abscesses were observed. Similarly solitary case reports are usually cited in the literature (9, 4, 2, 6). Analogous was the observation of our 4 cases of multiple recurrences with a delay of up to 28 years after removal of the first abscess, which is a little known rarity (5).

The cause of such a delay must, in our opinion, be a very low virulence of the microbes, probably concealed in a bone or metal splint in the abscess. Another factor may be the repeated treatment of our patients with antibiotics for various other causes and for many years. Therefore, bacteriological examination revealed no microbes in the pus of the abscess in our very delayed cases. The beta haemolytic staphylococcus surprisingly found in all our cases of recurrence may already be a sequel of hospitalism because of repeated operative procedures.

It has been shown (1, 3) that many antibiotics penetrate the abscess capsule in a therapeutic concentration. However, evacuation of the abscess was necessary in all cases. Simple evacuation of the abscess with systemic and local antibiotic treatment proved to be favorable in cases where the scalp was in poor condition with important scars and fistulas as well as in aged patients a markedly delayed evolution of large abscesses.

If the patients are in good general condition and whenever the scalp make it possible to do so, the best method remains a total exstirpation of the lesion. Systemic preoperative and postoperative antibiotic treatment and CT controls make it possible to heal such patients definitively today.

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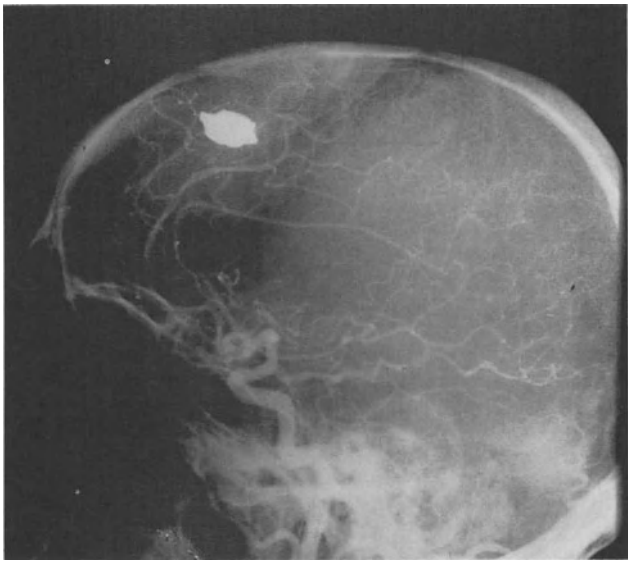

Fig. 1. Carotid angiogram, lateral view, showing a large shell splinter in the centre of the lesion. Delayed abscess 11 years after the injury

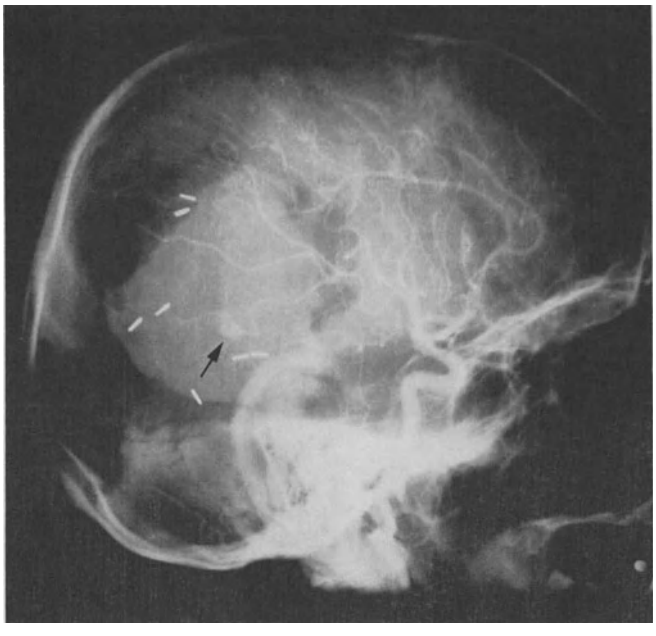

Fig. 2. Carotid angiogram in a case of abscess recurrence 28 years after the exstirpation of the first abscess. Note the extensive bony defect after the injury and previous operations. Bone splinter in the centre of the lesion

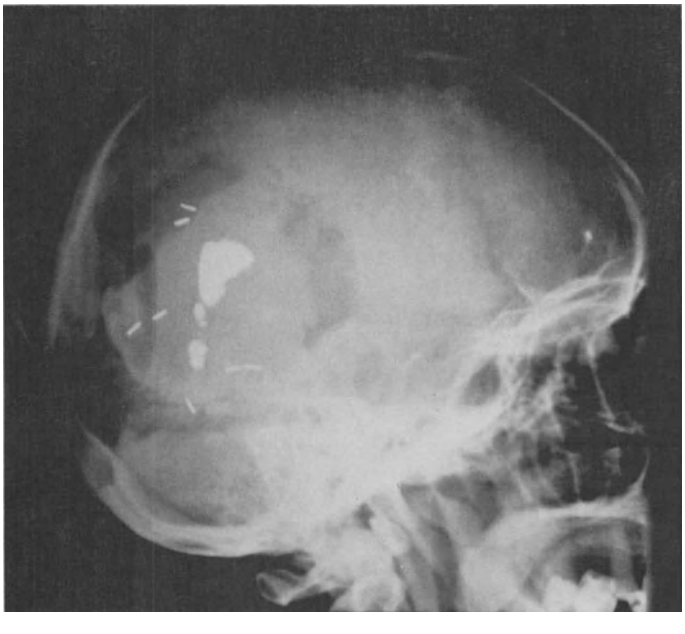

Fig. 3. Combined air and Pantopaque visualization of the abscess cavity by means of transcutaneous "abscessography" in the same case

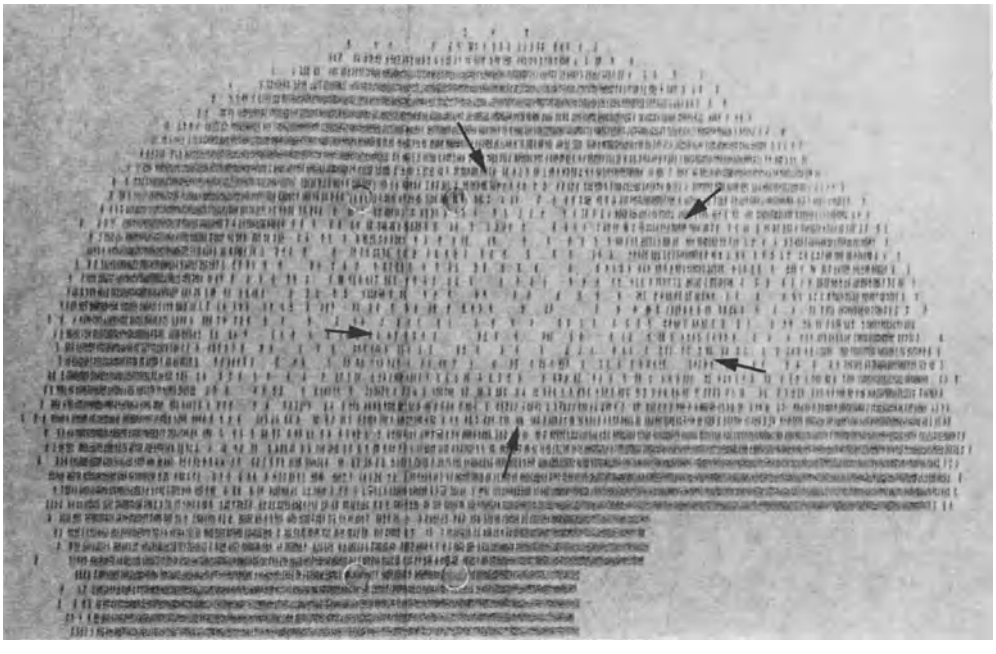

Fig. 4. Technetium 99 brain scan of a large delayed abscess, 31 years after injury

Intrasellar Abscesses

U. MUHTAROGLU, H. KLINGE, and J. LEMKE

Most cases of intrasellar abscesses described in the literature were either surgically treated under the assumption that they were pituitary adenomas (3-6, 11-12, 14, 16-22) or they were revealed at autopsy (9, 13, 17). Clinical symptoms of accompanying meningitis are obviously rare, while pronounced hormone dysfunctions such as hypopituitarism are more frequently observed, as we have seen in 2 of our own cases.

A 40-year-old male patient was treated in 1972 for frontal sinusitis. One year later an extensive neurological examination including pneumencephalography was carried out because of persistent headache. In the air study, the chiasmatic cisterns could not be filled, but this was not thought to be pathologic at that time. A year later signs of thyroid and adrenal insufficiency appeared and hormone substitution therapy was prescribed. After another 6 months, a bitemporal hemianopsia developed so quickly that an intrasellar tumour was suspected.

The sella was not definitely enlarged. At angiography the horizontal part of the anterior cerebral artery appeared to be slightly elevated. At surgery the optic nerves were found to be slightly elevated and compressed. The capsule between the optic nerves was strikingly durable (Fig. 1), thick pus flowed out which was bacteriologically steril. After complete removal of the abscess and membranes, the field of vision improved but not the hormone status. Histologically, the capsules showed not only profuse leukocyte infiltration, but also a gland-like epithelial complex similar to the transitional epithelium of the nasal sinuses (Fig. 2).

In our second case, it might have been more likely to suspect an abscess. The patient was a 41-year-old man who was examined because of diffuse headaches, lack of appetite, nausea and increasing loss of weight. Subfebrile temperatures were measured occasionally. The blood sedimentation rate and the transaminases were high and the liver and spleen slightly enlarged. The spinal fluid contained 2000/3 cells and when controlled some days later still showed 400/3 cells. Treatment was prescribed under the assumption of aseptic meningitis, until bitemporal hemianopsia suddenly appeared about 6 months later.

At that time the livid yellowish skin was also pronounced and the hormone status showed signs of hypopituitarism.

The sella was somewhat decalcified, but not much enlarged, and the anterior chiasmatic cisterns appeared slightly deformed in the computer tomogram. Surgery was finally undertaken because of the unequivocal bitemporal hemianopsia, where the possibility of a small craniopharyngioma was considered. In the chiasmatic area, the arachnoid membrane was somewhat swollen and between the optic nerves a very thin abscess

membrane was found which tore open during puncture and thick pus gushed out under the intensive pressure (Fig. 3). Histologically, the capsule membrane showed a chiefly lymphocytic infiltration (Fig. 4).

In this patient, too, the field of vision improved; not, however, the hypopituitarism, which still requires substitution therapy.

The pathogenesis of intrasellar abscesses is obviously variable (19) where infection from the sphenoid sinus are not rare (7). Abscesses have, however, also been found in chromophobe adenomas (2, 23) and in intrasellar craniopharyngiomas (14, 18, 6). The hormonal dysfunctions are usually more pronounced in abscesses than in chromophobe adenomas of the same size, while radiological symptoms of intrasellar space-occupying lesions are relatively rare. Computer tomography with modern machines will no doubt facilitate diagnosis.

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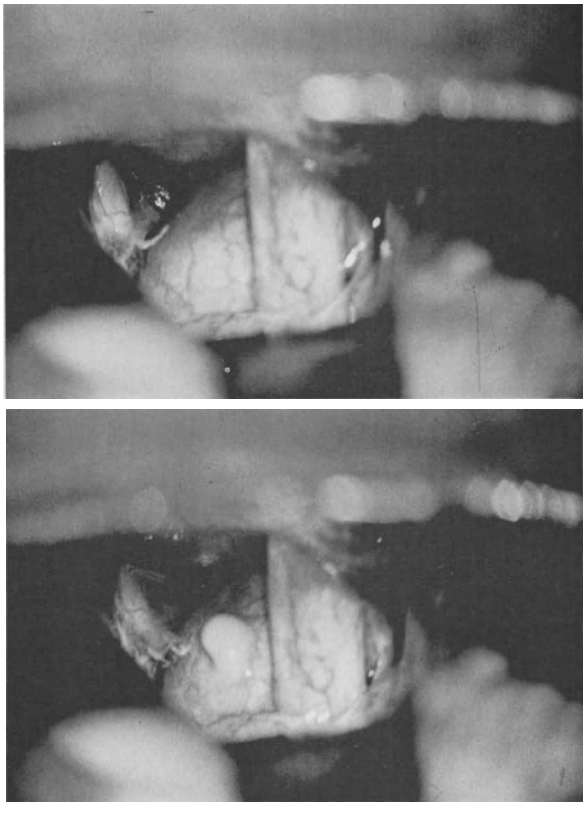


Fig. 1. Case I: abscess in the sellar region after puncture. Note drops of pus

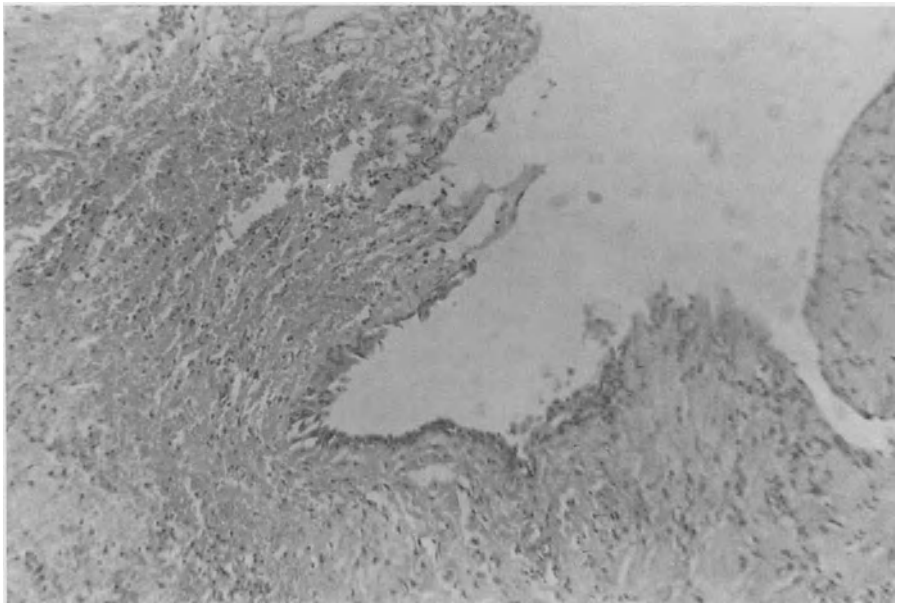
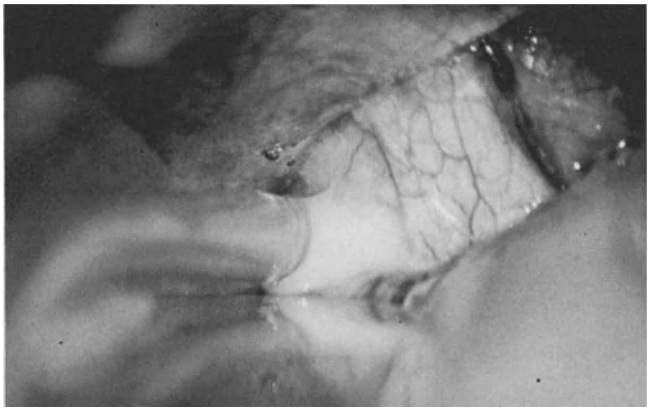


Fig. 2. Case I: epithelial layer within the abscess membrane

Fig. 3. Case II *(above):* abscess in the sellar region with thin fibrous capsule. *Below:* abscess cavity after partial evacuation of pus ▷

Fig. 4. Case II: microscopic aspect of the hypophyseal abscess with leucocyte infiltration



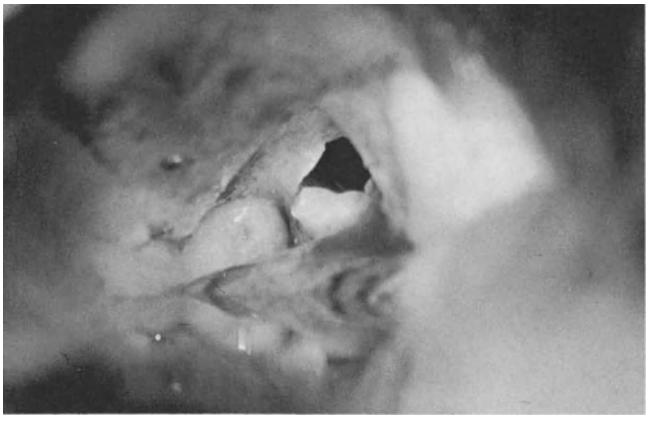
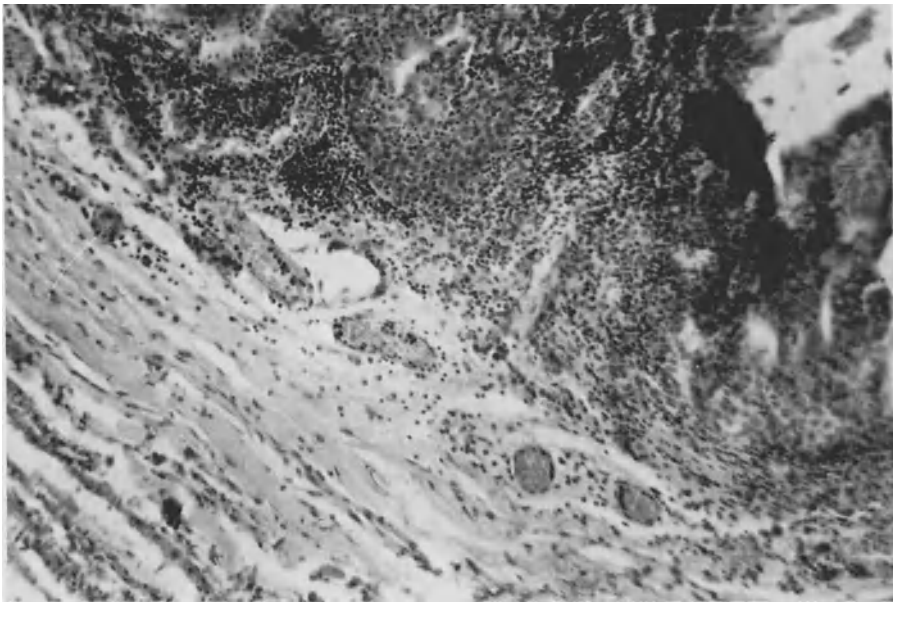


Fig. 3 *(right)*
Fig. 4 *(below)*



Brain Abscess as a Complication of Extension Therapy with Crutchfield Cramp

TH. ROMMEL and J. MENZEL

Introduction

Brain abscesses are caused by conduction or develop in a metastatic or traumatic way (2, 3, 4, 11, 12). CRUTCHFIELD extension (1), a well-known treatment of injuries of the cervical spine was the cause of a complication observed by us, which is not unknown in the literature as well (6, 7, 9). In two cases we observed a cause-and-effect relationship between the extension treatment and a brain abscess, whose traumatic genesis could not be doubted.

Case Reports

A 49-year-old female patient fell down and suffered a fracture of the odontoid process and the left arch of the first cervical vertebra. When she was admitted to the hospital, she had a hemiparesis on the right side. A CRUTCHFIELD cramp was applied and the extension treatment performed. During the next days, the neurological symptoms subsided. Already at that time, a continual secretion could be seen in the area where the left cramp bolt was fixed and a local treatment was performed. Six weeks after application of the CRUTCHFIELD cramp, the patient suddenly became aphasic. Angiography demonstrated a space-occupying lesion in the left temporal lobe. During the subsequent operation, we found an osteomyelitic lesion with signs of sequestration at the insertion of the cramp at the squama temporalis. Furthermore a cord-like epidural granulation extended to a circumscribed cortical scar and an encapsulated abscess of the size of a plum was located in the left angular region.

As early as 1970 MASUHR, MENZEL and PISCOL (8) reported on a 54-year-old patient, who had suffered a contusion of the brain as well as a fracture and luxation of the cervical spine at the C4/5 level, caused by a car accident five years before. Neurologically there was a hemiparesis of the right side. In a peripheral hospital, a CRUTCHFIELD cramp was applied. A psychosis resulting from the contusion and motor restlessness repeatedly caused a loosening of the CRUTCHFIELD cramp. Thus its position had to be corrected. Eight months later the patient's dismissal was possible. After a period of four years during which the patient was able to work, a continuous headache suddenly developed. Furthermore a deterioration in the level of consciousness and a left sided hemiparesis were observed. After the patient's admission to the hospital, angiography demonstrated a large space-occupying lesion in the right temporal lobe. Parieto-temporal craniotomy revealed an old scar in the middle of the skin flap, a remnant of the fixation with the CRUTCHFIELD cramp. The scar formation extended through a lesion in the skull to a defect in the dura and to the cortex, ending in an encapsulated abscess the size of an egg, which was located in the depth

of the temporal lobe (Fig. 1). The abscess was extirpated radically. In the post-operative phase, the hemiparesis of the left side decreased rapidly.

Discussion

In both cases a CRUTCHFIELD cramp modified according to HERION (5) was used. The pathogenetic mechanism leading to these abscesses became clear through operative findings. In the area of the drill hole we found a circumscribed epidural cicatrization identical in both bases. This extended through a defect in the dura to a cortical scar and to the membrane of the abscess. From this point of view, and since other causes could definitely be excluded in both cases by accurate oto-rhinological inspection, two possible causes of the brain abscess have to be discussed. On the one hand a perforation of the lamina cortex may already have occurred when the drill hole was made. This could have led to a direct bacterial infection. On the other hand, marked tightening of the cramp may also cause a perforation of the lamina interna through the cramp bolts (Fig. 2). The latter possibility was described by JAMIESON et al. (7) in a comparable case. In our cases, further factors were the local infection in the area of the cramp bolt and of course the patient's motor restlessness, which required repeated corrections of the cramp's position. In order to prevent these complications, the following precautions are essential. Securing the insertion of the drill and the cramp bolt generally prevents a perforation of the bone. This requires an adequate thickness of the skull, which is most probably found in the area of the dorsal squama temporalis and the tuber parietale. TÖNDURY (10) speaks of a retroauricular buttress of the skull. The ideal depth of the drill hole seems to be about 2 mm (Fig. 3). Finally the cramp should not be tightened too much and after fixation its side bars have to be locked. In that way a deeper penetration of the cramp bolt during extension can be prevented. The cramp's position may be corrected only under strictly aseptic conditions.

Summary

In this report two temporal abscesses due to extension therapy with CRUTCHFIELD cramps are presented. In the first case the brain abscess occurred six weeks after application of the CRUTCHFIELD cramp. In the second case, the brain abscess became evident four years after extension of a cervical spine fracture. In both cases total removal of the encapsulated abscess was possible. The mechanism of this injury as well as measures for the prevention of this deleterious complication are discussed.

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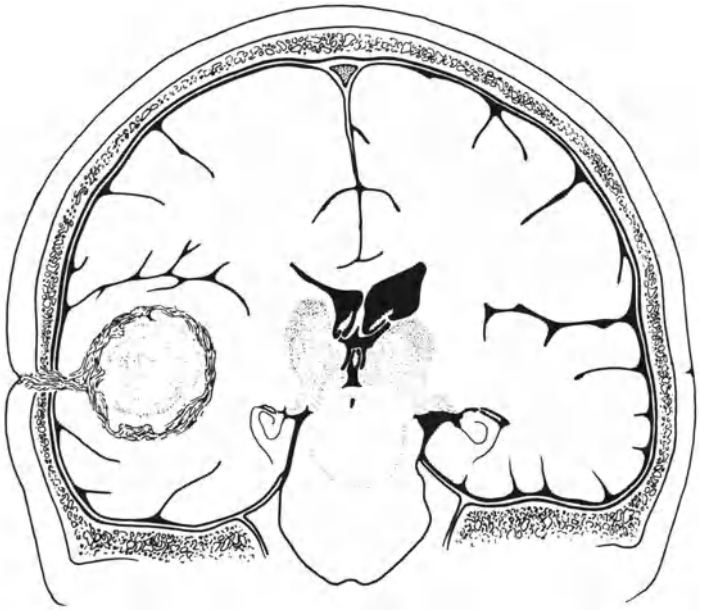

Fig. 1. Schematic presentation of the right-sided brain abscess with scars in the skin, the bone and the dura

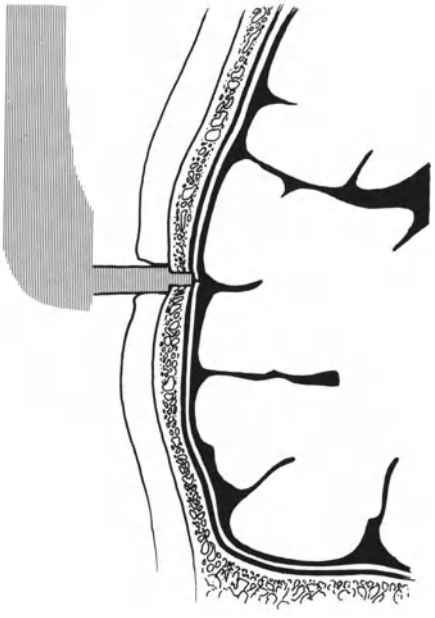

Fig. 2. Schematic presentation of the perforation of the lamina interna and the dura by the CRUTCHFIELD cramp bolt

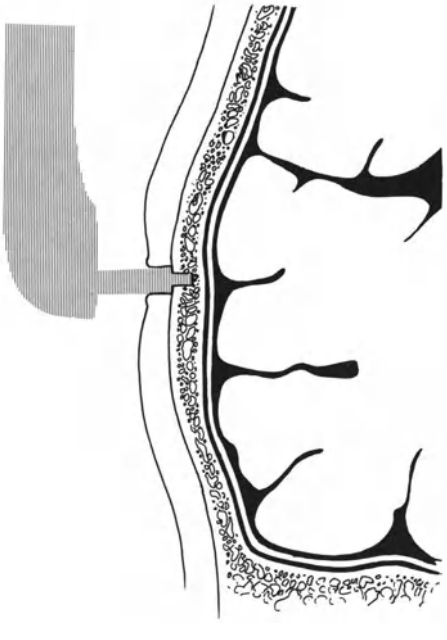

Fig. 3. Correct insertion of the CRUTCHFIELD cramp

Newer Antibiotics for Brain Abscess Treatment Investigated in Animal Experiments

M. KLINGER, TH. WALLENFANG, and B. BERGSTEN

The treatment of the brain abscess is the treatment of a dynamic process of inflammation. The antibiotics employed here exert their effect on an ever-changing blood-brain-barrier, whose penetrability is constantly changing. In the initial stages of the intracerebral inflammation, the penetrability of this barrier is great and one may expect high antibiotic concentrations in the vicinity of the phlegmonous process. As the capsule formation progresses, the amount of edema decreases, the penetrability of the blood-brain-barrier sinks and the concentration of the antibiotic near the abscess is also lower.

In order to investigate these assumptions about the behavior of antibiotics in the vicinity of the brain abscess, the effect of different antibiotics on brain abscesses were studied in animal experiments. The evaluation of the substances tested was either indirect or by a direct determination of the antibiotic concentrations in the respective tissue.

For the indirect evaluation of the antibiotic effect, it is necessary to simulate the clinical situation of the brain abscess in the animal experiment. The prerequisite for a comparison of the effectiveness of various antibiotic substances on an intracerebral infection is the certain development of an infection in every inoculated experimental animal. If the implanted infection leads to a massive inflammation which leads to the death of the experimental animal in every case, then the survival rate of the animals treated with antibiotics is an index for the effectiveness of the antibiotic given.

The implantation of the abscesses was carried out according to the method described by HASSLER and FORSGREN (1964). A mixture of agar and bouillon together with bacteria are implanted by stereotactic inoculation (Fig. 1). The total volume of 0.03 ml contain approximately 1 million to 1.5 million staphylococcus aureus A8. This inoculation led to a massive inflammation in every case which led to decerebration and death if treatment was not initiated. All 10 experimental animals of the untreated group died within 16 hours of inoculation. Since all these untreated animals succumbed to the infection, the prerequisite for the indirect evaluation of the antibiotic was given.

Previous examinations of the CSF-permeability had shown that of the seven substances examined, Co-trimoxazol, Ticarcillin and Chloramphenicol crossed the barrier from the blood to the CSF particularly well. Therefore these three antibiotics were employed in the treatment of the experimental animals with induced brain abscesses (Table 1). The treatment pattern began with an intravenous injection of the antibiotic within the first 8 hours after the inoculation, followed by injections every 12 hours over a period of 3 days.

Table 1. Antibiotic activity on infected brain tissue measured according to the survival rates of rabbits with induced brain abscesses (indirect determination of antibiotic activity)

Antibiotic	No. of experimental animals	Survival rate (%)
Untreated	10	0
Co-trimoxazol	11	54,5
Ticarcillin	8	87,5
Chloramphenicol	11	81,8

The first group of 11 experimental animals were given Cotrimoxazol in a dosage of 4,5 mg/kg body weight, since this dosage was most likely to result in antibiotic levels in the CSF which most closely approached the therapeutic concentrations in man. In the second group, 8 rabbits received Ticarcillin in a dosage of 500 mg/kg body weight via the intravenous route according to the above-mentioned pattern. Experimental animals in the third treatment group received Chloramphenicol in a dosage of 40 mg/kg in the same time intervals as in the other treatment groups.

The results of these tests are presented in Table 1. They show a survival rate of 87.5% for animals treated with Ticarcillin, a survival rate of 81,8% for animals treated with Chloramphenicol, while the animals, who were treated with Co-trimoxazol had a survival rate of only 54,5%. Thus the penetrability into brain tissue is very good for Ticarcillin and Chloramphenicol, while Co-trimoxazol concentrations lie somewhat lower.

Through the treatment with antibiotics, brain abscesses developed in the rabbits. Two days after inoculation, a mantle of leucocytes had formed around the central core of agar (Fig. 2). The macroscopic picture of the two-day-old inflammation (Fig. 3) indicates a large displacement of the midline structures, due to inflammation and edema. The edema can be visualized by injecting Evans blue just before the animal is sacrificed. Two days later, i.e. four days after inoculation, the infection is clearly delineated in the macroscopic picture (Fig. 4). This edema is now more perifocal and no longer involves the entire hemisphere. By the seventh day the edema has decreased even further and the first signs of capsule formation become visible (Fig. 5). The histological examination of the border of the abscess shows signs of fresh organisation with fibroblast proliferation. Due to increasing capsule formation, edema continues to decrease and edema formation is no longer present by the 28th day after inoculation.

The second section of these experiments deals with the direct determination of antibiotic concentrations in brain tissue. Using the previously described procedure, brain abscesses were induced in a series of cats, where abscess formation was possible without additional antibiotic treatment. Once abscesses had formed, Cefazedon was employed as the anitbiotic substance. In group I, a single intravenous injection of Cefazedon (50 mg/kg) to animals with a seven-day-old abscess. The control animals in group II were inoculated with an agar-bouillon mixture without bacteria and then treated with a single injection of Cefazedon (50 mg/kg). In group III the experimental animals with a seven-day-old abscess were treated with an intramuscular injection of 25 mg/kg Cefazedon every 12 hours over a period of 3 days. In group IIIb, the treatment was extended over 13 days. After

this time interval, the brain edema has clearly decreased, however water content measurements show an increased water content even on the 20th day. The antibiotic concentrations were determined on the 20th day.

In group IV dexamethasone is included in the treatment plan. Group IVA involves 7-days-old abscesses which are treated with Cefazedon and dexamethasone from the seventh to the tenth days. Half of the daily dose of 50 mg/kg Cefazedon and 0.5 mg/kg dexamethasone are given in intervals of 12 hours. In group IVB, the period of treatment was extended to 13 days, and the determination of the antibiotic concentrations was performed on the 20th day.

The results of these studies are summarized in Table 2. In the case of 7-day-old abscesses with marked edema, a concentration of 2,6 µg/g dry weight were measured approximately 3 hours after a single intravenous injection three hours before. This value is still within the minimal inhibitory concentration of 1-2 µg/ml for Staphylococcus aureus A8. Group II did not contain any infected tissue and therefore no effective Cefazedon concentrations were to be measured.

Following a regular 12-hour intramuscular injection of Cefazedon in group III, the antibiotic concentrations in brain tissue were 6.96 µg/ml after 3 days and 4,79 µg/ml after 13 days. After a long treatment period and in the presence of suprainfections, the antibiotic concentrations are higher than in the group with a single intravenous injection.

When dexamethasone was added to the treatment plan in group IV, edema decreased rapidly and this led to a distinct improvement in the neurological state of the experimental animals. Since there was a simultaneous improvement in the disturbance of the blood-brain-barrier as well, the penetrability of this barrier dropped, resulting in considerably lower antibiotic concentrations in the brain tissue and the CSF. The difference is evident when we compare group III with 6,96 µg/ml and 4,79 µg/ml with group IV, where the values were 1,5 µg/ml and 1,4 µg/ml. However, even the concentrations in group IV are still within the minimal inhibitory range for this organism.

In summary, these experiments have shown that induced abscesses in experimental animals are a useful model for the evaluation of antibiotics either by direct determination of antibiotic concentration in brain tissue, CSF and serum, or indirectly by way of survival rates. The latter method indicated that Ticarcillin and Chloramphenicol exert a very good effect on intracerebral infections.

Table 2. Direct determination of antibiotic concentration of Cefazedon in the serum, CSF and brain tissue of experimental animals

Abscess group	Duration of treatment	Concentration of antibiotic			
		Serum	CSF	Brain	Tissue
I	One dose	20	8.3	2.6	0
II	One dose	20-35	0	0	0
IIIA	3 days	13.13	8.05	6.9	1.6
IIIB	13 days	15.87	5.01	4.7	0.3
IVA	3 days	10.46	1.37	1.5	1.4
IVB	13 days			0.47	0.36

The second part of these experiments showed that the antibiotic Cefazedon accumulates only in inflamed and edematous brain tissue because the blood-brain-barrier is disturbed here. When dexamethasone is employed this disturbance normalized rapidly as was seen by the low antibiotic concentrations following dexamethasone treatment. For this reason it seems reasonable to suggest that dexamethasone should be employed in the treatment of brain abscess only as long as the edema is a severe threat to the patient. Later it should be stopped while the antibiotic continues to be given, making use of the penetrability of the disturbed blood-brain-barrier in the presence of inflammation.

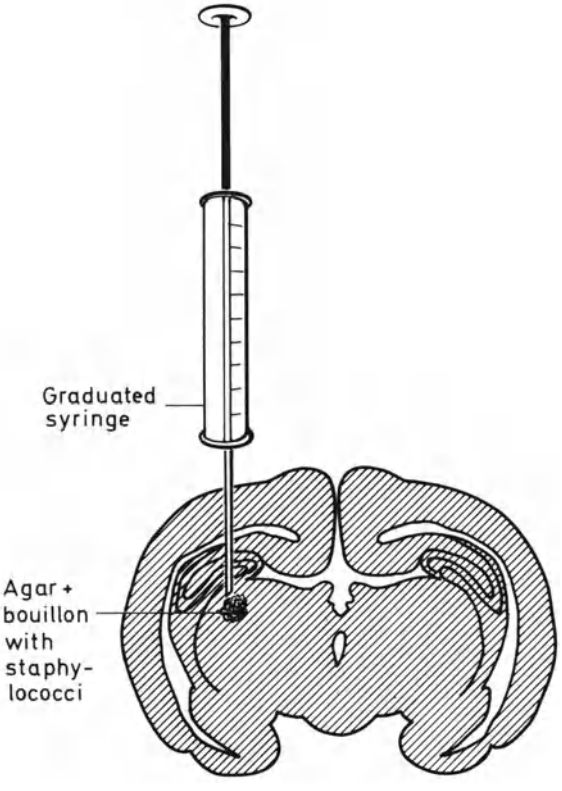

Fig. 1. Diagram of the stereotactic inoculation of agar and bouillon together with bacteria in order to induce brain abscesses in experimental animals

Fig. 2. Histological picture of a developing brain abscess, 2 days after inoculation. Note mantle of leucocytes around the inoculated agar mixture

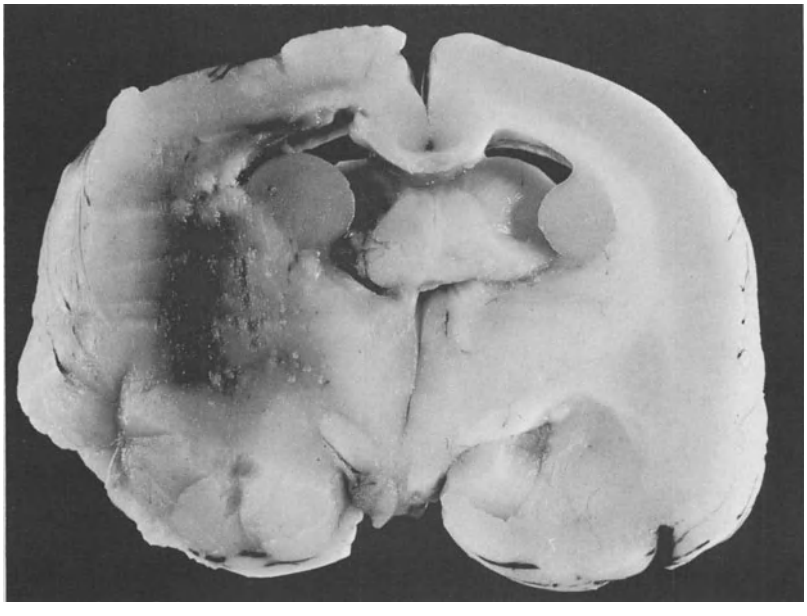

Fig. 3. Macroscopic picture of a developing brain abscess, 2 days after inoculation. Note the large dark zone indicating marked edema and swelling (edema is visualized through the injection of Evans Blue)

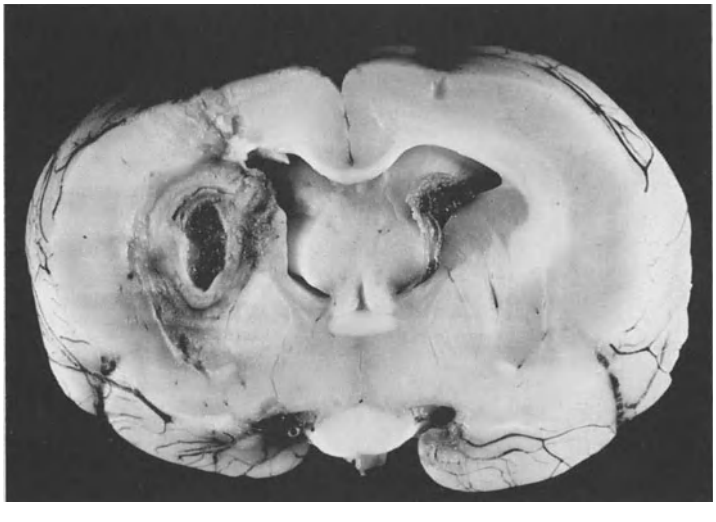

Fig. 4. Macroscopic view of a 4-day-old induced brain abscess with a central necrotic zone. Edema is only in the perifocal region

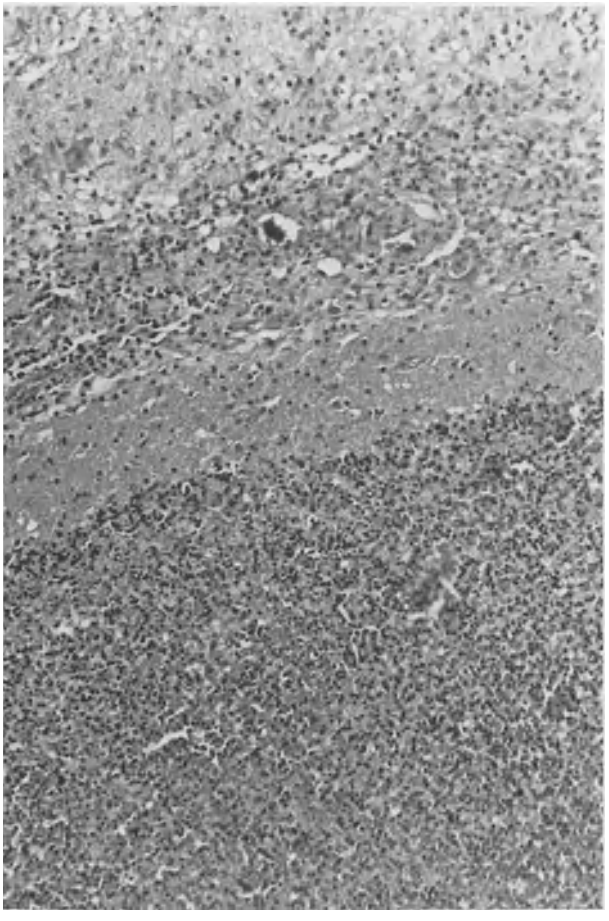

Fig. 5. Histological structure of a 7-day-old abscess. Note fibroblast proliferation as an indication of fresh organisation

Concentrations of Antibiotics in Cerebral Abscess Fluid and Cerebrospinal Fluid

O. BRÜCKNER, H. COLLMANN, M. ALEXANDER, and J. WAGNER

Purulent infections of bacterial origin are preferably treated by antibiotics which yield high concentrations, possibly even several times higher than the minimal inhibitory concentrations (MIC) of the relevant bacterial strains over a long period of time. Inactivation of these antibiotics by local factors such as binding to tissue proteins or degradation by enzymes for example should be as low as possible. Furthermore they must not cause severe side effects if applied in therapeutic dosages.

Antibiotic concentrations in the fluids of five operatively removed or drained brain abscesses were determined by the agar-well-diffusion-technique (21). Antibiotics were given preoperatively for several days in cases 1-3, but only once in cases 4 and 5 (Table 1). Time-matched sera were examined in the same way, if available. Levels of two antibiotics in the same material were determined by using bacterial test strains of different sensitivity patterns with complete resistance against one of the antibiotics used. Aminoglycosides were tested by the addition of β-lactamases in sufficient amounts (27).

Cefoxitin, an antimicrobial agent with a broad spectrum of activity against anaerobes (4, 28), often encountered in brain abscesses (7, 10-12, 23, 24), as well as the other applied β-lactam-antibiotics amoxycillin, cephamandole and cefotaxime, were found in sufficient amounts in the few available brain abscess fluids.

The aminoglycoside tobramycin was hardly detectable or not found at all.

Gentamicin is an aminoglycoside recommended in treatment of proven or suspected gram-negative bacterial meningitis caused by eneterobacter strains (1, 8, 9, 19, 26). Gentamicin levels in cerebrospinal fluid (CSF) and serum in 11 determinations of 8 patients suffering from meningitis and treated by a combination therapy including gentamicin in a dosage schedule of 80 mg i.m. three times daily are presented in Fig. 1. CSF concentrations exceeding 1,5 mcg/ml were achieved only in patients with renal impairment and high serum levels. MIC values of many enterobacter and pseudomonas strains are higher than 1-1,5 mcg/ml. Thus, sufficient levels of gentamicin in the CSF are achieved rarely. CSF and serum levels of gentamicin in 18 determinations of 8 neurosurgical patients with no inflammation of the meninges showed gentamicin levels in a therapeutic range only in one of these patients with an almost intact blood-CSF-barrier. None of these patients had renal impairment. These results correspond to those of other authors (2, 9, 13, 19).

Systemic application of tobramycin, 80 mg i.v. three times daily, did not result in sufficient levels in the CSF of this aminoglycoside antibiotic with better activity against pseudomonas strains than gentamicin

Table 1. Levels of antibiotics in brain abscess fluids

No. of abscesses	Antibiotic	Concentration in serum (µg/ml)	Concentration in abscess fluid (µg/ml	Time after last application (h, min)	Dosage
1	Cefoxitin	Ø	11.5	12.00	2 g i.v.
	tobramycin	Ø	<0.1	12.00	80 mg i.m.
2	Amoxycillin	1.8	4.2	4.00	1.5 g i.v.
	tobramycin	Ø	Ø	10.00	80 mg i.m.
3	Amoxycillin	12.7	9.6	6.30	1 g i.v.
	cephamandole	Ø	35.0	13.45	2 g i.v.
4	Cefoxitin	Not done	4.9	2.30	2 g i.v.[a]
5	Cefotaxime	63.5	6.1	0.30	2 g i.v.[a]

[a] Single dose.

and, probably with lower nephrotoxicity (Table 2). Levels higher than 1 mcg/ml were achieved only in 1 test out of 10 of 7 meningitis patients, but in none of the 14 determinations of 9 neurosurgical patients. No patient in this group suffered from renal impairment.

Direct application of aminoglycosides into the CSF compartment by the intraventricular route whenever possible or, less recommendable, by the intralumbar route, is a major request in aminoglycoside therapy of gram-negative bacterial meningitis and ventriculitis (5, 9, 14, 15, 17, 20).

Table 2. Tobramycin levels in serum and CSF of 9 neurosurgical and 7 meningitis patients

No. of patients	CSF cell count	CSF protein (mg/100 ml)	Tobramycin concentration serum (µg/ml)	Tobramycin concentration CSF (µg/ml)	Interval from last application (h/min)	Serum creatinine (mg/100 ml)
			I. Patients with meningitis			
1	1790/3	286	1.6	1.35	5 h 00'	0.8
2	20500/3	320	2.7	0.47	2 h 15'	1.3
	5060/3	63	2.1	<0.1	1 h 15'	1.1
3	8600/3	117	2.4	0.15	2 h 45'	0.9
	4800/3	122	1.8	0.18	2 h 30'	0.9
	864/3	n.d.	1.5	<0.1	2 h 30'	0.8
4	173/3	67	1.0	0.42	?	0.6
5	2000/3	377	1.9	0.72	4 h 00'	0.7
6	261/3	137	0.21	<0.1	1 h 25'	1.1
7	9048/3	87	<0.1	0.15	5 h 00'	0.8
			II. Neurosurgical patients			
8[a]	30/3	13	0.8	Ø	5 h 00'	0.6
9	88/3	164	Ø	Ø	6 h 30'	0.5
10	67/3	127	6.9	0.1	3 h 30'	0.6
	703/3	176	0.8	0.15	7 h 30'	0.6
11[a]	170/3	60	4.0	Ø	3 h 15'	0.4
[a]	40/3	37	1.8	Ø	2 h 30'	0.2
[a]	15/3	49	4.6	0.4	4 h 45'	0.6
[a]	n.d.	n.d.	1.6	0.28	4 h 00'	0.5
12	19/3	72	0.7	0.28	3 h 15'	1.0
	21/3	n.d.	4.9	0.15	3 h 00'	0.8
13	34/3	n.d.	4.0	0.14	5 h 25'	0.9
14	114/3	28	0.8	Ø	2 h 07'	0.7
15[a]	n.d.	n.d.	0.7	Ø	4 h 00'	0.9
16	24/3	34	0.15	Ø	0 h 10'	0.9

n.d. = not done; Ø = no tobramycin detectable.

[a] collected CSF from external ventricular drainage.

Serum and CSF concentrations of cefotaxime were determined only once in 2 patients with intact blood-CSF-barrier, in one patient suffering from viral meningitis in a later stage and in 9 tests of a patient with E.-coli-meningitis and ventriculitis after shunt infection (Table 3). Concerning the extremely low MIC-values of cefotaxime against nearly all enterobacterial strains, levels in a therapeutic range from 2,5-16 mcg/ml were achieved in all tests of the latter

Table 3. Cefotaxime levels in serum and CSF of 3 patients with almost intact blood-CSF-barrier and 1 patient with shunt infection due to E. coli

No. of patient (diagnosis)	CSF cell count	CSF protein (mg/100 ml)	CSF origin	Cefotaxime serum (µg/ml	CSF (µg/ml)	Time after last application	Serum creatinine (mg/100 ml)
1. E.N. (cerebral stroke)	16/3	77	Lumbar	88.0	1.7	1 h 30'	3.4
2. A.G. (lues latens)	2/3	34	Lumbar	35.0	Ø	2 h 00'	0.8
3. B.G. (viral meningitis)	91/3	34	Lumbar	24.0	Ø	2 h 30'	0.7
4. I.F.	2220/3	220	e.v.d.	40.0	2.5	?	0.5
(E. coli infection of ventriculo-auricular shunt)	1970/3	n.d.	e.v.d.	2.8	2.8	7 h 00'	0.4
	1231/3	214	e.v.d.	Ø	6.4	8 h 10'	0.5
	423/3	232	e.v.d.	2.1	15.6	8 h 00'	0.4
	423/3	232	e.v.d.	61.0	6.0	1 h 00'	0.4
	3072/3	201	e.v.d.	3.6	2.9	?	0.6
Cefotaxime 3 x 2 g i.v./die	26/3	115	e.v.d.	44.0	16.0	?	0.9
MIC test for concerned	114/3	183	Lumbar	7.8	4.9	5 h 15'	0.9
E. coli: 0.06 µg/ml	53/3	69	e.v.d.	9.1	4.5	5 h 00'	0.8

e.v.d. = external ventricular drainage.

patient. CSF was taken from an external ventricular drainage in most cases but also from lumbar puncture. E. coli-meningitis of this patient, emerging during therapy with tobramycin and cephamandole, was cured by treatment with only 2 g cefotaxime three times daily intravenously. As stated by other authors, this cephalosporin compound seems to be recommendable for treatment of meningitis due to enterobacteria (3, 22, 25).

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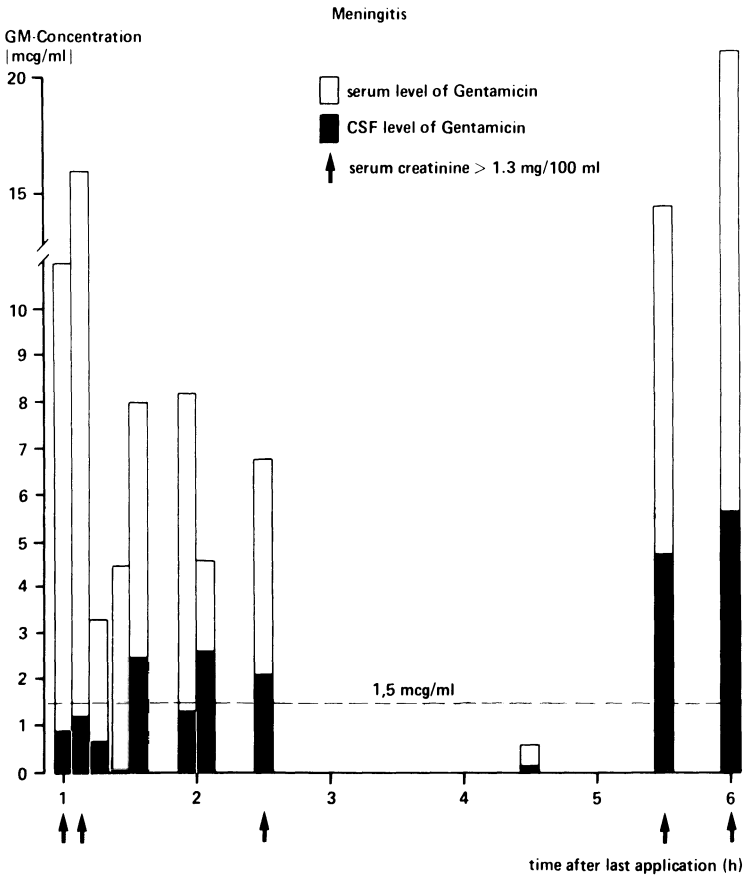

Fig. 1. Time-correlated concentrations of gentamicin in serum and CSF of meningitis patients. Arrows indicate patients with signs of renal impairment (serum creatinine > 1,3 mg/100 ml)

Investigations of Antibiotic Levels in the Cerebrospinal Fluid

H. FRIEDRICH and G. HAENSEL-FRIEDRICH

During the last five years we have investigated systematically the penetration of several antibiotics into the cerebrospinal fluid (CSF) by determining serum and CSF levels simultaneously in patients with and without meningitis. The CSF-samples were taken from external ventricular drainage systems which had been performed for various indications.

The penetration of the combination *Trimethoprim-Sulfamethoxazol* into the CSF has been reported elsewhere (6, 9). This substance gives high CSF concentrations irrespective of the degree of meningeal inflammation. The maximum CSF concentration of Sulfamethoxazole (SMZ) was 46,5% of the maximum serum concentration, while the Trimethoprim (TMP) concentration in the CSF reached 68,9% of the maximum serum levels. Thus therapeutically effective concentrations can be achieved even when the blood-CSF-barrier is intact. Consequently TMP-SMZ should be of great value in the postacute state of meningitis, since the blood CSF-barrier becomes less penetrable at this time and the CSF penetration of the antibiotic administered during the acute state decreases. In the literature *Chloramphenicol* is said to have a good capacity to penetrate the intact blood CSF barrier (10, 11, 17). Our investigations showed that CSF levels of Chloramphenicol determined with High-Pressure-Liquid-Chromatography as developed by ROSIN et al. reach a considerably lower rate than expected (16) (Fig. 1). Out of the beta-lactam-antibiotics, we tested *Mezlocillin* and four Cephalosporine-derivatives.

Mezlocillin was used for perioperative short-time chemoprophylaxis as well as for the therapy of meningitis (7).

Serum concentrations reached 160-730 µg/ml and were considerably above the minimal inhibitory concentration (MIC) of Mezlocillin susceptible pathogens in patients with meningitis.

In patients without meningitis, maximum CSF levels of Mezlocillin ranged from 0,2-0,9 µg/ml, which was therapeutically inadequate (Fig. 2). During acute meningitis Mezlocillin concentrations between 10,4 and 32,5 µg/ml were found in the CSF (Fig. 2). The postacute state of meningitis leads to a marked decrease of the CSF levels which drop to therapeutically ineffective values.

From the Cephalosporin-derivatives four different substances were tested, all of which showed very poor penetration into the CSF of patients with normal meninges irrespective of their different pharmakokinetics (3, 4). During meningitis *Cefuroxime* concentrations in the CSF reached 3-7,5 µg/ml (Fig. 3). Since the MIC particularly of gram-negative pathogens mostly exceeds these concentrations, a monotherapy of meningitis with one of the cephalopsorin-derivatives is to be rejected (8, 12).

Table 1. Serum and CSF concentrations determined simultaneously

"Antibiotic"	No. of patients	Plasma-CSF-concentrations
I. Combination		
- Trimethoprim	7	70
- Sulfamethoxazol		
II. Chloramphenicol	4	32
III. β-Lactam antibiotics		
a) Acylureido-penicillin		
- Mezlocillin	5	76
b) Cephalosporins		
- Cephalothin	2	10
- Cefazolin	4	25
- Cephacetril	6	133
- Cefuroxime	5	72
IV. Aminoglycosides		
- Gentamicin	3	36
- Sisomicin	6	75

With normal meninges the Aminoglycosid-antibiotics *Gentamicin* and *Sisomicin* also showed maximum CSF concentrations of only 0,4 µg/ml despite adequate serum levels. With inflamed meninges Gentamicin concentrations increased up to 2 µg/ml (2, 15). Since these levels are therapeutically insufficient even in cases of meningitis, an additional intraventricular administration is necessary (14). Intrathecal application by repeated lumbar punctures is ineffective (1, 13).

Table 2 demonstrates the penetration of antibiotics into the CSF of our neurosurgical patients after systemic administration.

Table 2. Penetration of antibiotics into the CSF of patients with and without meningitis in relation to maximal serum concentrations (poor: below 2%, fair: more than 10%, good: more than 20%)

"Antibiotic"	CSF-penetration normal meninges	Meningitis
I. Combination		
- Sulfamethoxazol	Good	Good
- Sulfamethoxazol	Good	Good
II. β-Lactam antibiotics		
a) Acylureido-penicillin		
- Mezlocillin	Poor	Fair
b) Cephalosporins		
- Cephalothin	Poor	Poor-fair
- Cefazolin	Poor	Poor-fair
- Cephacetril	Poor	Poor-fair
- Cefuroxime	Poor	Poor-fair
IV. Aminoglycosides		
- Gentamicin	None	Poor-fair
- Sisomicin	None	Poor-fair

Conclusions

For the therapy of meningitis of the central nervous system the following proceedure is recommended:

1. identification of the pathogen involved (often multi-resistant organism)
2. determination of the MIC
3. whenever possible additional intraventricular administration of the antibiotic in order to achieve therapeutically effective concentrations at the site of infection.

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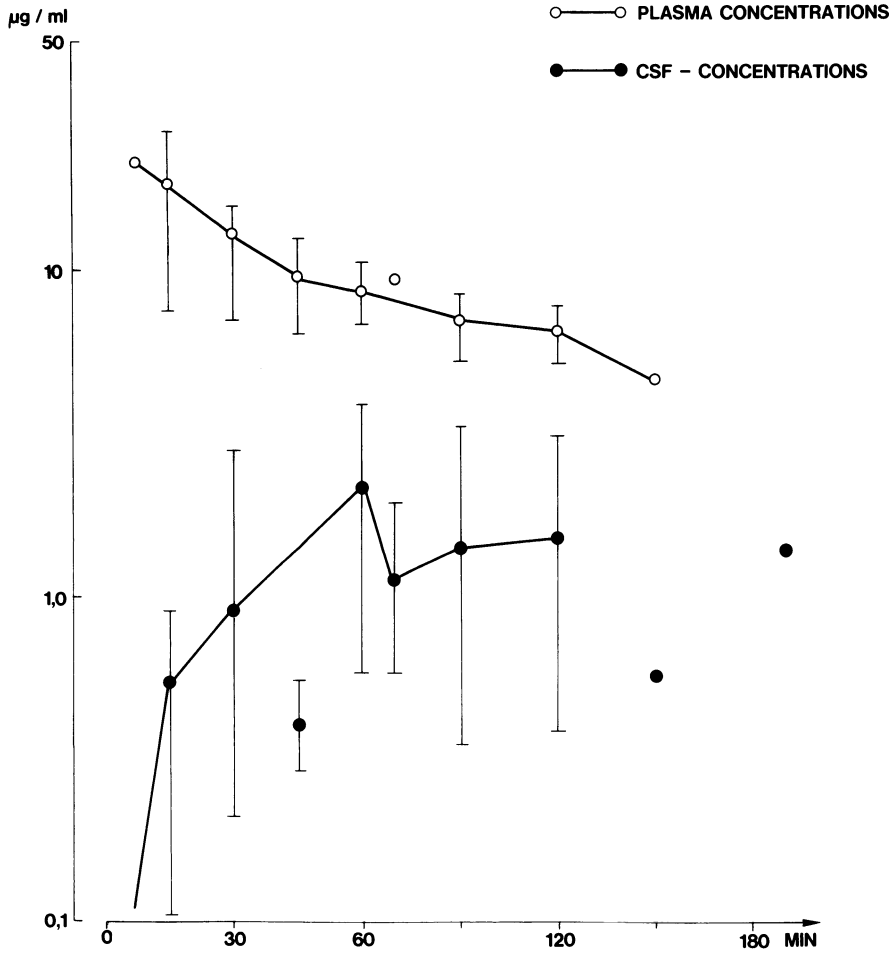

Fig. 1. Chloramphenicol concentrations in patients without meningitis (1 g i.v. normal meninges)

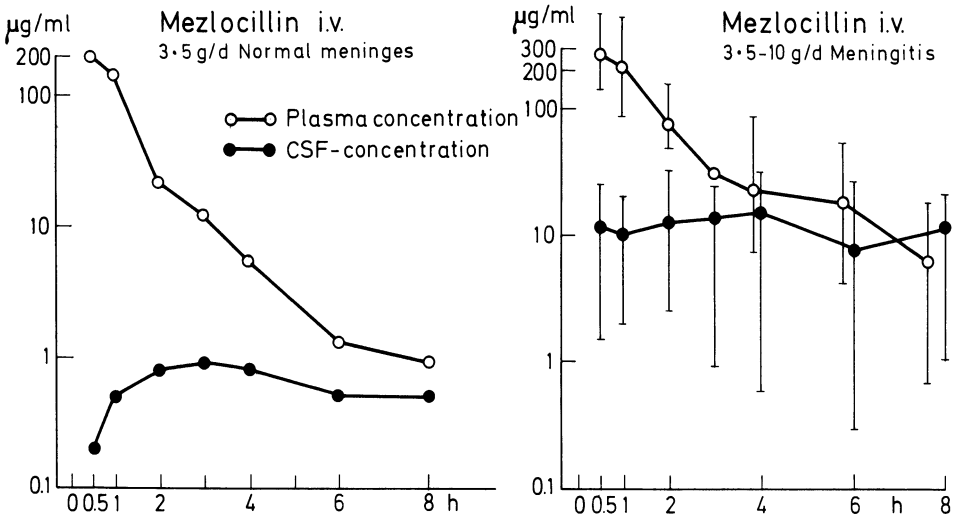

Fig. 2. Mezlocillin concentrations in patients with and without meningitis

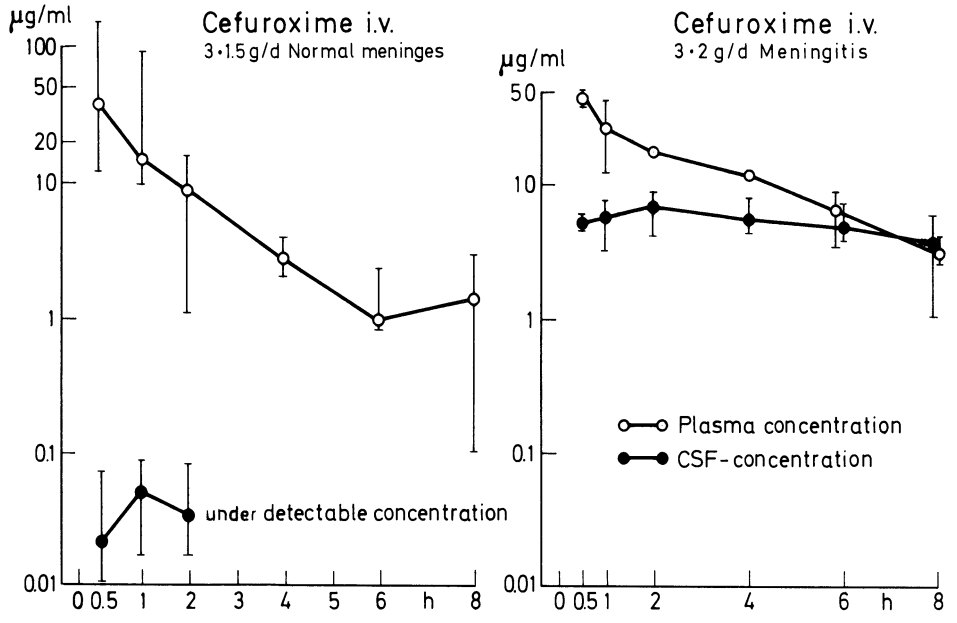

Fig. 3. Cefuroxime concentrations in patients with and without meningitis

The Effect of Glucocorticoids in the Combined Treatment of Experimental Brain Abscess in Cats

I. BOHL, TH. WALLENFANG, H. BOTHE, and K. SCHÜRMANN

Glucocorticoids in the treatment of brain edema are well accepted nowadays, while the usefulness of corticosteroids in the management of inflammatory brain edema, caused by an abscess, is still doubtful, in spite of encouraging clinical experience (5, 6). An experimental study is needed to analyse the varying factors, which determine the prognosis of this disease under therapy with and without glucocorticoids.

Materials and Methods

0.03 ml of a mixture of agar and bouillon (ratio 1 to 2) containing nearly 1 million pathogenic bacteria (Staphylococcus aureus) were inoculated stereotactically into the right hemisphere of 64 male cats with a body weight of 3.5 to 4.5 kg under ketamine anesthesia (Ketanest 20 mg/kg body weight). The left hemispheres served as controls, as did the right hemispheres of 6 animals that had received only a sterile mixture without bacteria. Evans Blue (2% solution, 1 ml/kg body weight) was injected intravenously to demonstrate the brain edema macroscopically. The development of the abscesses was documented by computerized tomography.

Therapy with antibiotics alone (cefazedone[1] 50 mg/kg body weight) and the combined therapy with dexamethasone[2] (0.5 mg/kg body weight) was started on the 7th day. Measurements of intraventricular pressure and determinations of water content and electrolyte concentrations in the close vicinity of the abscess as well as in remote regions were performed on the 7th, 10th and 20th day. The brains of animals which had died due to elevated intracranial pressure were fixed in formaldehyde solution and embedded in paraffin.

10 animals were sacrificed by transcardiac perfusion with a solution of 3.9% glutaraledhyde and were used for lightmicroscopic and ultrastructural studies.

Results

Those animals that had received only agar and bouillon demonstrated nearly normal behavior at the neurologic examination. But the other cats showed symptoms of raised intracranial pressure from the 4th day on. The diameter of the abscess - situated in the white matter of the right hemisphere - was greatest on the 7th day. It was surrounded by a marked edema in the white matter of the whole right hemisphere

1 Refosporin (E. Merck, Darmstadt).
2 Decradon (MSD Sharp & Dohme, Munich).

(Fig. 1). Computerized tomography, too, revealed the space-occupying lesion to be largest on this day with a shifting of the ventricular system to the left. Ten min after the injection of contrast medium there was an increased diffuse enhancement in the brain areas altered by the inflammatory changes. On the 7th day, the water content in remote areas of the white matter was nearly as high (80.4 ± 0.59 g/100 g w wt) as in the neighbourhood of the abscess (82.33 ± 0.39 g/100 g w wt) (Fig. 2). The mean value of water content in the control group was only 71.3 ± 2.6 g/100 g w wt).

In untreated animals, the water content in the vicinity of the abscess remained high during encapsulation from the 7th (82.33 ± 0.39 g/100 g w wt) to the 20th day (80.0 ± 2.48 g/100 g w wt) and only slowly decreased in remote white matter areas (down to 73.13 ± 1.78 g/100 g w wt). After 3 days of therapy with antibiotics alone the surrounding brain edema was slightly reduced (on the 10th day). Measurements of water content revealed a reduction of 3.5% in the neighbourhood of the abscess (79.35 ± 3.22 g/100 g w wt) and less than 1% further away (74.94 ± 4.63 g/100 g w wt). After 13 days of therapy with antibiotics, the brain edema in remote areas was unchanged, but showed a further slight diminution near the abscess (75.78 g/100 g w wt).

Under the combined therapy with antibiotics and dexamethasone, however, the reduction of the brain edema which occurred in all areas was statistically significant. The slope of this decrease of water content was steepest during the first 3 days of therapy. Not far from the abscess, a reduction of 11% was found (from 82.3-73.2 g/100 g w wt). Further reduction of brain edema was minimal in the area close to the abscess, while in remote areas the water content dropped to 67.98 ± 2 g/100 g w wt).

Corresponding to the decrease in brain edema under the combined therapy with dexamethasone, the intracranial pressure too decreased more rapidly (statistically significant) than after therapy with antibiotics alone.

Repeated computerized tomography showed an obvious reduction of the diameter of the abscess after combined therapy from the 7th day on, characterized by a rapidly appearing and vanishing ring enhancement after the injection of contrast medium which corresponded to the developing encapsulation (10). The striking difference in the amount of brain edema in cats after *combined therapy* compared with *untreated* animals could also be seen macroscopically in frontal sections of the brain by means of Evans Blue injections (Fig. 1).

The most striking histopathologic findings in the brains of untreated cats (on the 10th day after inoculation) were intensive inflammatory mesenchymal reactions. The center of the abscess contained remnants of the inoculated material with microcolonies, necrotic tissue and a lot of detritus. The inner surface consisted of a broad zone with granulocytes and macrophages adjacent to a loose ring of granular tissue, rich in blood vessels and in inflammatory infiltrations, especially perivascular. The surrounding white matter showed marked perifocal edema with accumulation of fluid in the enlarged extracellular spaces, with many macrophages, with beginning glial proliferation and with an accumulation of inflammatory cells in the wide perivascular spaces of VIRCHOW-ROBIN. These alterations were evident in remote areas, too.

Without therapy the intensity of these inflammatory reactions was still prominent on the 20th day (Fig. 3). As a consequence of the

proliferation of histiocytes and fibroblasts, the capsule seemed denser, cells and vessels were arranged closer together. The glial reaction in the surrounding white matter was more obvious, but the edema had decreased in regions further away from the abscess. In the neighbourhood of the inoculated material (agar and bouillon) in the center of the abscess, a strong foreign body reaction with multinucleated giant cells could be observed.

After therapy with antibiotics and dexamethasone from the 7th day on, however, these inflammatory mesenchymal reactions were obviously less marked. Around a zone of macrophages and foam cells in the middle of the abscess, a loosely-arranged envelope of proliferated blood vessels with only scanty granulocytic infiltrations and with little histiocytic and fibroblastic proliferation was seen. A foreign body reaction was not observed. The surrounding white matter was still slightly edematous and showed a glial reaction. But remote areas seemed to be nearly normal on the 20th day.

Ultrastructural studies of untreated animals in the acute phase had revealed small gaps between the endothelial cells in the neighbourhood of the abscess, sometimes a widening of intercellular clefts and the formation of big vesicles or invaginations in the cytoplasm of the endothelial cells (Fig. 4). These defects in the endothelial cell layer could be attributed to the morphologic substrate of the disturbed blood-brain-barrier.

13 days after starting the combined therapy we did not find comparable alterations of the blood vessel wall. Endothelial cells with obviously degenerative changes were very rare. The most striking finding, however, was an occasional fenestration of the endothelial cells. Normally these fenestrations are found only in areas where the blood brain barrier is not present, e.g. in the plexus chorioideus. In untreated cats the histiocytes and macrophages formed a firm cell layer and very often indentations could be seen, but after combined therapy these cells only formed a loose network and had short clumsy cytoplasmic processes.

Discussion

This animal model of an intracerebral abscess demonstrates that the combined therapy with antibiotics and glucocorticoids leads to an obvious improvement of the clinical course compared with untreated animals and compared with antibiotic therapy alone (8, 9). Clinical, biochemical and morphological investigations showed that this improvement was due to a significant reduction of perifocal inflammatory brain edema (2, 3, 7). This diminution must be attributed to the effect of glucocorticoids. On the other hand, it could be stated that dexamethasone had an inhibitory effect on inflammatory mesenchymal reactions and led to a slightly delayed capsule formation. Obviously the antibacterial effect of antibiotics is not disturbed by the antiphlogistic efficacy of glucocorticoids. In those areas where virulent microorganisms are still in action, i.e. on the inner surface of the abscess, the disturbance of the blood-brain-barrier remains until the toxic effect of the bacteria has disappeared completely. In the surrounding white matter of the abscess, the tissue concentrations of antibiotics probably decrease as a result of the less intensive and slowly spreading brain edema after therapy with dexamethasone. But obviously this does not have a disadvantageous influence on the final result.

The application of dexamethasone alone without antibiotics in cases of intracerebral abscesses has fatal consequences on the subsequent

clinical course, as both clinical experience and experimental results have shown. Rabbits with stereotactically produced brain abscesses were treated exclusively with dexamethasone and developed widespread tissue necrosis with little inflammatory reactions but with an immense damage of the blood-brain-barrier. Thrombotic obliteration of blood vessels, fibrinoid necrosis of vessel walls and massive accumulation of edematous fluid, rich in proteins, were the most important histopathologic findings.

In addition to small gaps and widened clefts in the endothelial cell layer, possibly the formation of so-called fenestrations in the endothelial cells in areas where normally they are not normally found indicates a disturbance of the blood-brain-barrier (1, 4).

If any conclusions for neurosurgical practice may be drawn from these not yet completed experiments, the recommended therapy of an acute brain abscess is the combination of antibiotherapy and glucocorticoids. The exstirpation of the abscess should be performed in the chronic phase after slow reduction of the corticosteroids. The operation is best delayed until the primarily inhibited capsule formation around the abscess has progressed.

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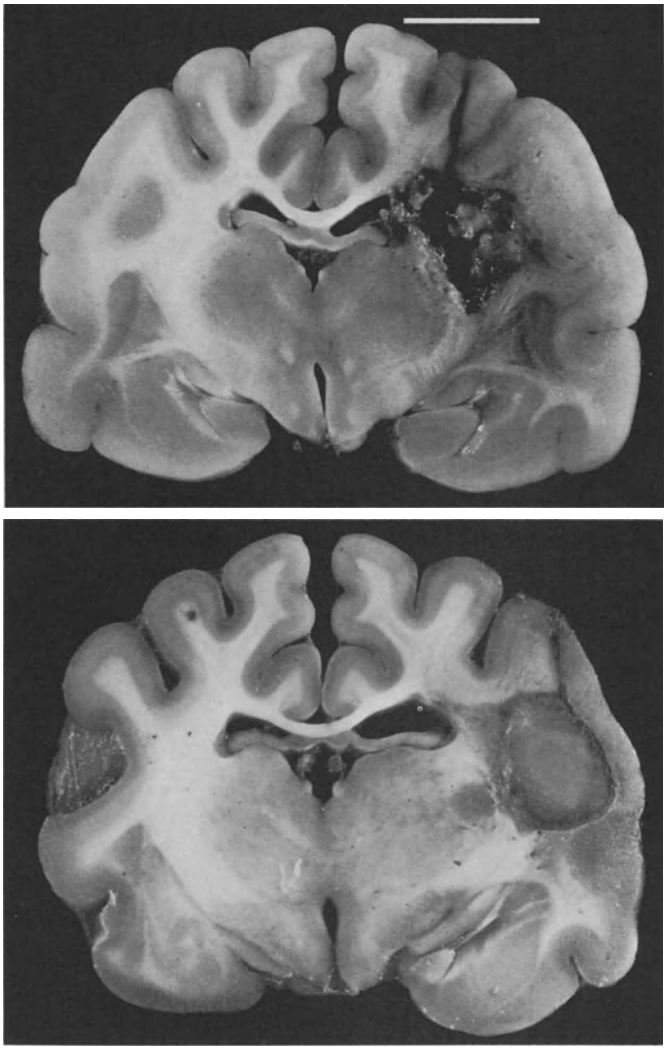


Fig. 1. *Above:* acute brain abscess on the 7th day with severe perifocal edema, demonstrated by the darker staining of the white matter (Evans Blue) and by the shift of the midline to the left.
Below: chronic brain abscess on the 20th day after combined therapy with marked reduction of brain edema and complete encapsulation; scale bar 1 cm

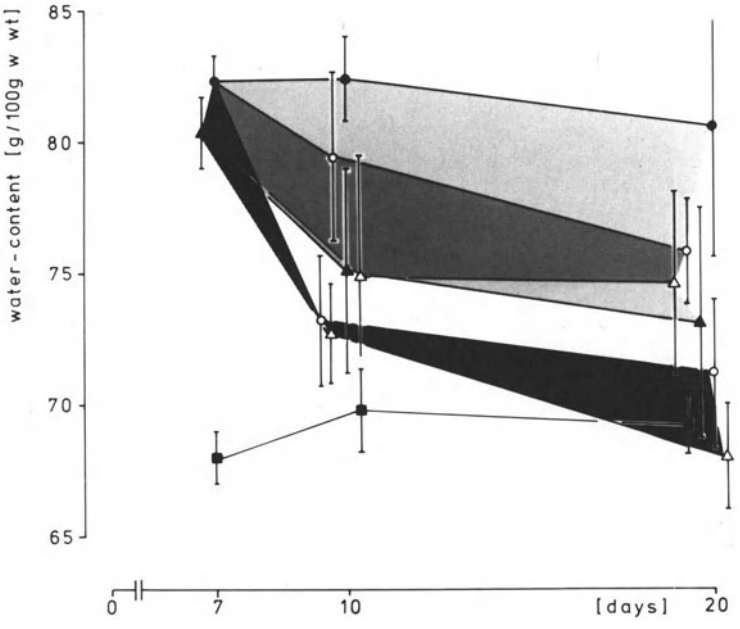


Fig. 2. Changes of water content in the various areas of white matter under treatment with antibiotics in combination with steroids *(black area)*, under antibiotic-therapy alone *(dark grey area)* and without any therapy *(light grey area)*. The upper boundaries of each area represent measurements adjacent to the abscess; the lower boundaries show values of remote regions. Single line at the bottom represents controls

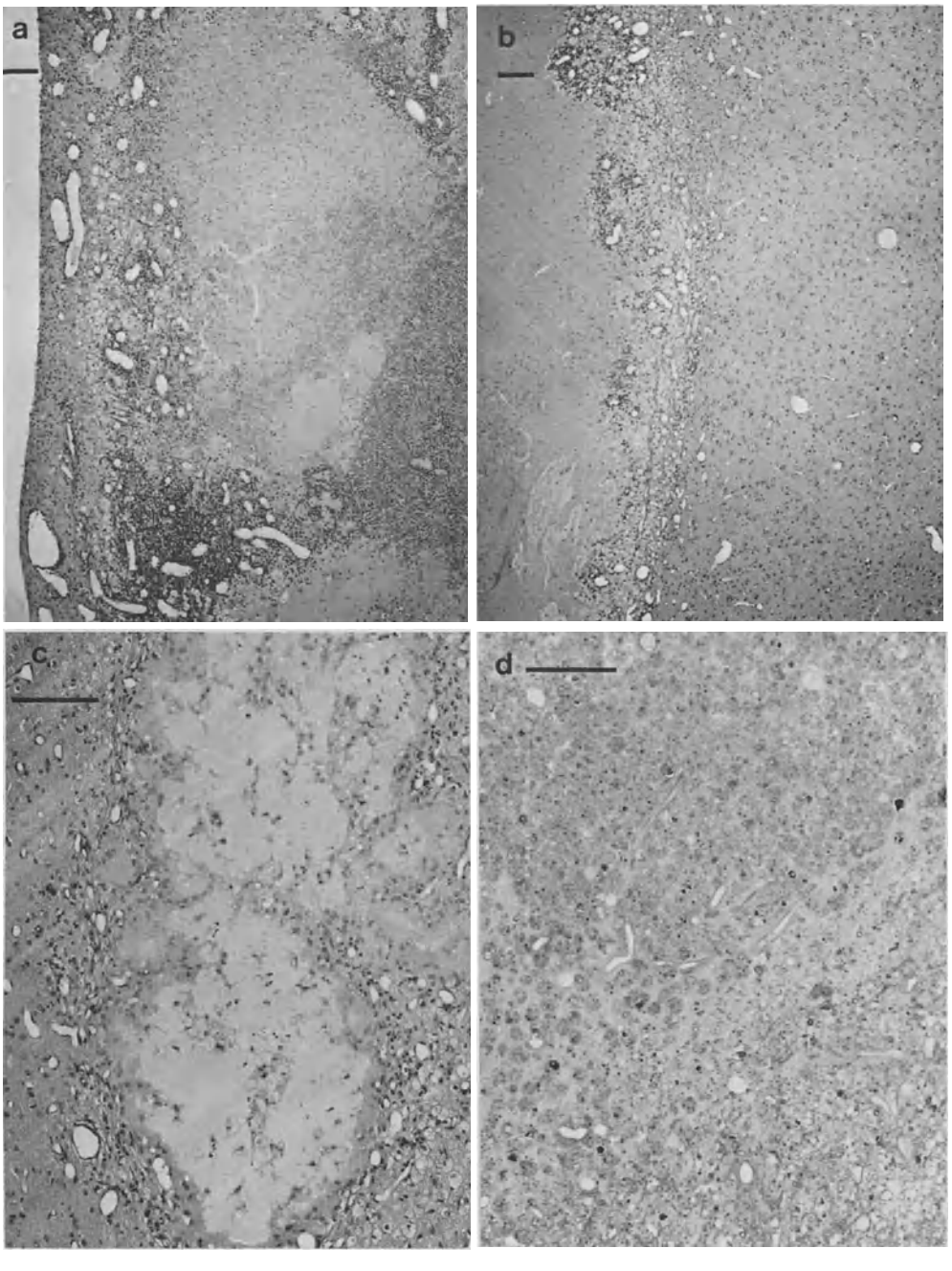
Fig. 3 a-d. Chronic brain abscess on the 20th day. Pictures on the left side (a, c) from untreated animals, on the right (b, d) from cats after combined therapy with antibiotics and dexamethasone, (a, b, c embedding in paraffin, HE. d embedded in expoxy resin, p-phenylen-diamin); scale bar 0.1 mm

a Pariventricular abscess with marked encapsulation and with severe inflammatory reactions

b Border of subcortical abscess with only slight inflammatory and mesenchymal reactions

c Intensive histiocytic proliferation around remnants of the inoculated material with foreign body reaction

d Margin of the abscess with macrophages and foam cells in the center and with nearly absent inflammatory reactions in the surrounding edematous white matter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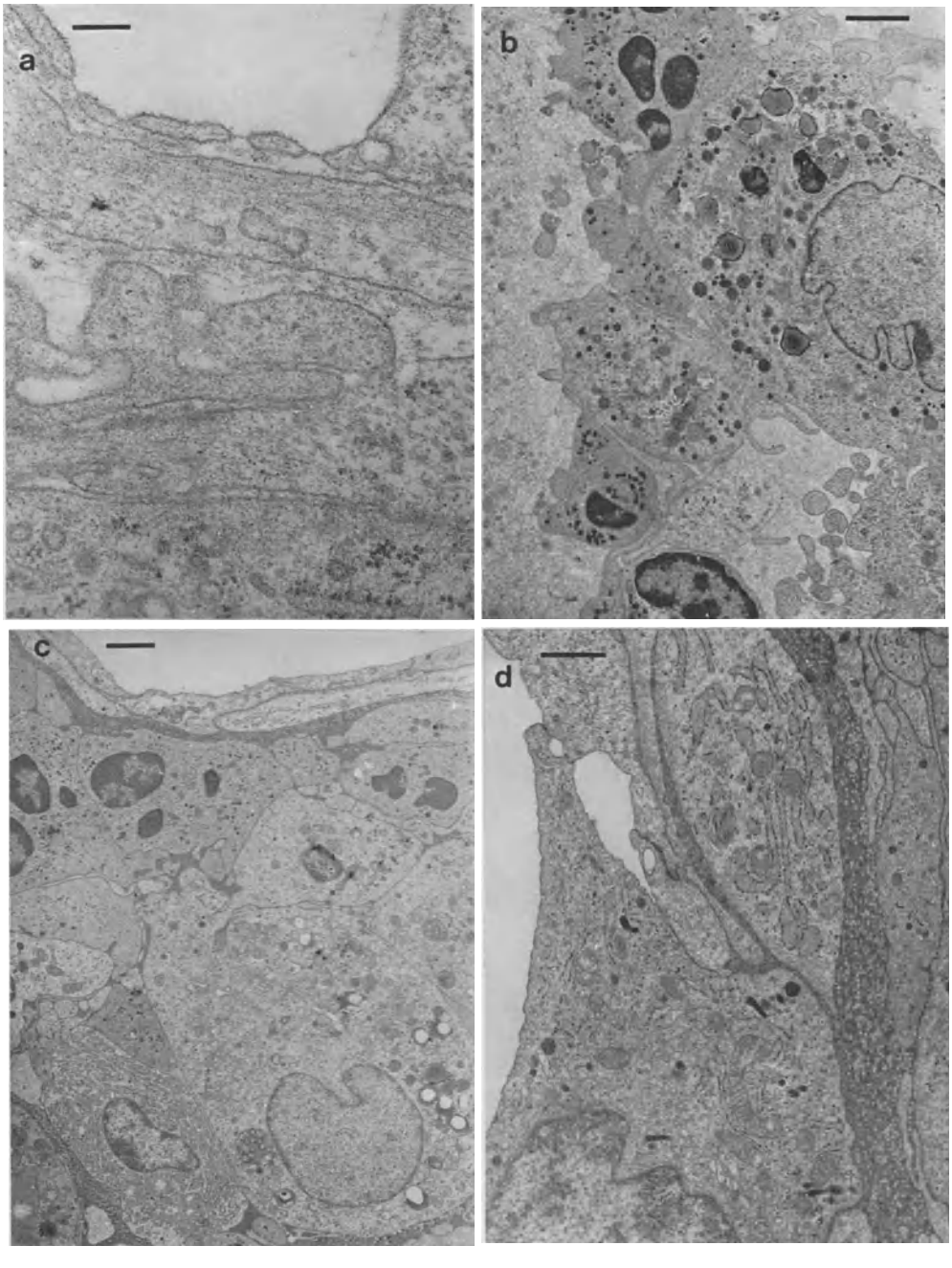
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Fig. 4 a-d. Chronic brain abscess on the 20th day: Ultrastructure. Upper pictures (a, b) from animals after therapy with antibiotics and dexamethasone, pictures below from cats without any treatment (embedded in epoxy resin)

a Small vessel wall with several fenestrations in the endothelial cell layer; scale bar 0.2 µ

b Some microphages and macrophages at the inner surface of the abscess with only a few, short and clumsy cytoplasmic processes; scale bar 2 µ

c Accumulation of inflammatory cells in the enlarged perivascular space; scale bar 2 µ

d Local dilatations of an intercellular cleft between two endothelial cells; scale bar 1 µ

Computer Tomographic Findings in Subdural Empyemas

E. HEISS and W. HUK

Since the introduction of CT into Neuroradiology there have been early (PAXTON and AMBROSE, 1974; NEW et al., 1974) and numerous reports on the computer tomographic picture of brain abscesses. Only a few authors reported on subdural empyemas.

During the last 4 years we were able to observe 15 cases of subdural empyemas and the computer tomographic findings of these patients will be described here.

It should be mentioned that 53% of the empyemas had their origin in paranasal sinus infections. Only in seven cases was bacteriological proof possible. One patient died from pneumonia due to Klebsiella.

The computer tomographic images of the empyemas were almost identical. Below the cranial vault there was a crescentic area of decreased density (Fig. 1a) of lenticular shape. In one case we found an additional, convex, low density area in the interhemispheric fissure (Fig. 1c). Occasionally septation within the empyema was noted.

Frequently a thin, irregular line of increased density enhanced by contrast medium was observed as a borderline to the adjoining surface of the brain. Unilateral empyema led to a displacement of the midline structures to the opposite side, as well as to a compression of the ventricular system and frequently to a deformation of the anterior horns altering its angle.

The native scan of about 2/3 of our observations especially in younger patients, showed an irregular area of decreased density within the brain substance adjacent to the empyema. The space occupation exceeded that of the empyema. We have interpreted this change to be a local encephalitis with perifocal inflammatory brain edema (Fig. 2).

After the administration of contrast medium, ring-shaped structures appeared in a number of cases (Fig. 3), as seen in abscesses. In one patient an abscess was demonstrated at surgery, in another case we found histologically verified encephalitis without signs of an encapsulation.

Only two groups of South African authors reported on a greater number of subdural empyemas investigated with computer tomography. In 1979 STEPHANOV, JOUBERT and WELCHMAN of Durban reported on 31 cases, seven extending not only over the convexity but also to the interhemispheric fissure. In 1980 DANZIGER, PRICE and SCHECHTER of Johannesburg presented their observations on 23 empyemas.

These authors, too, described the empyemas as a crescent-shaped, elliptical area of decreased density, the margins limited by a hyper-

dense, irregularly formed line with enhancement by contrast medium. In contrast to our observations, STEPHANOV et al. saw changes in the adjoining brain tissue only occasionally. They called this a "patchy enhancement". Probably this corresponds to the focal encephalitis of our cases.

In contrast to our findings, DANZIGER et al. even emphasized that edematous changings are seldom and negligible. In 17 of 23 cases they were unable to find any edema, and in the remaining cases the edema was slight.

To point out the difficulties of differential diagnosis in respect to chronic subdural haematomas we want to demonstrate the development of subdural empyema after the evacuation of a chronic subdural haematoma of the opposite side (Fig. 4). The empyemas (Fig. 4b) showed a more homogenous and more uniform area of decreased density than the haematomas (Fig. 4a). An edematous swelling of the adjacent cerebral tissue exceeding the degree of the space occupation which one would expect from the volume of the empyema alone also indicated the existence of an inflammatory disease. The exact knowledge of the clinical symptoms is almost indispensible in order to confirm the diagnosis by CT.

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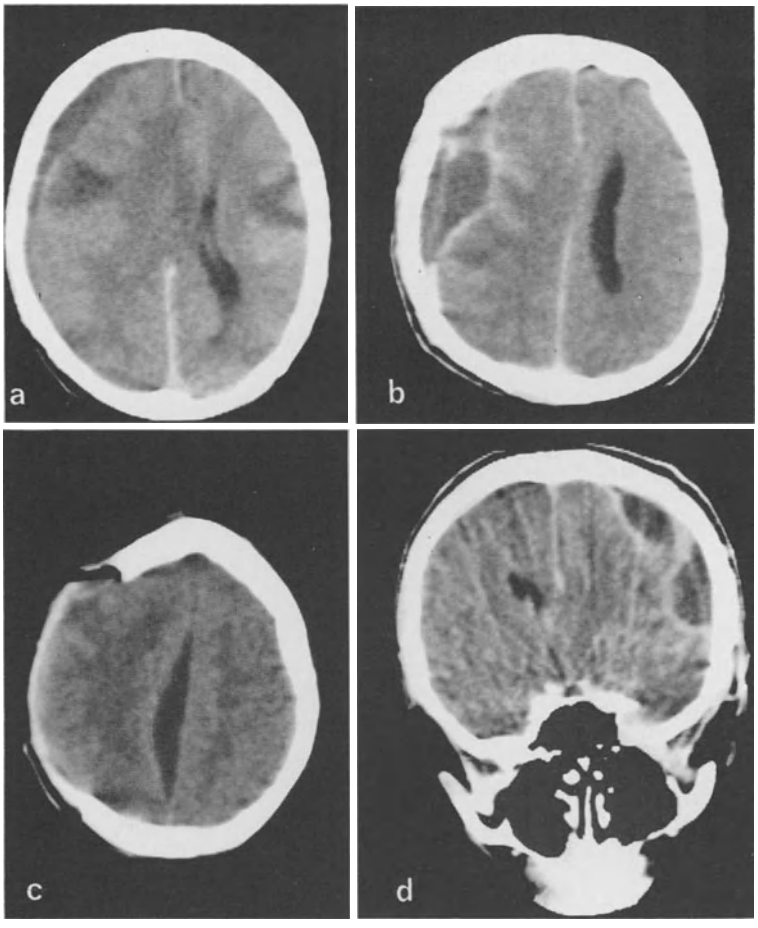

Fig. 1 a-d. Different forms of subdural empyemas with a thin, irregular borderline of increased density to the adjoining brain region. Septation is seen in Fig. 1d

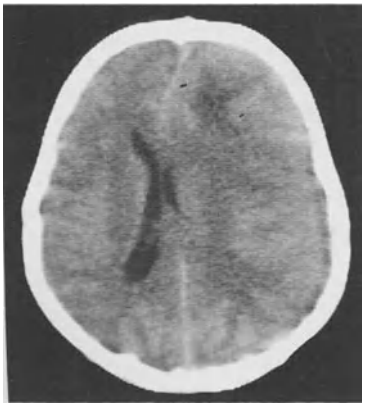

Fig. 2. Area of decreased density within the brain adjacent to the empyema. The space occupation exceeds that of the empyema because of focal encephalitis

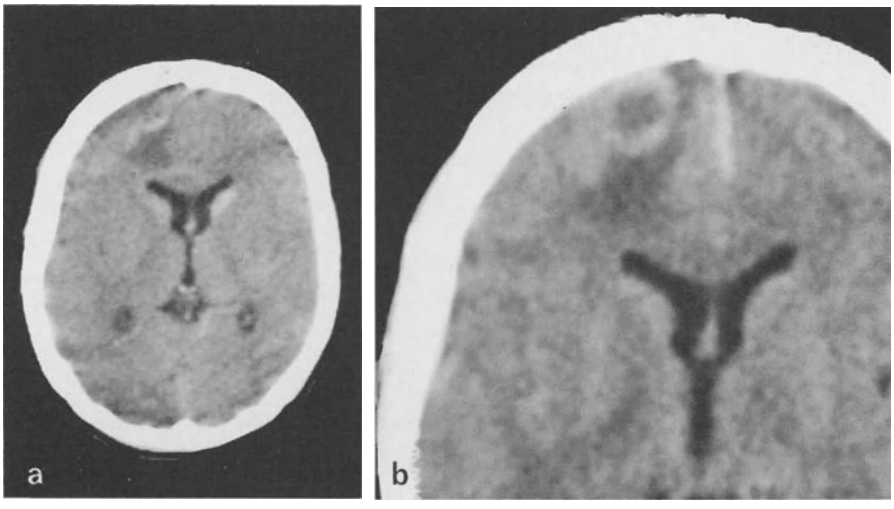

Fig. 3 a, b. Ring-shaped structure of a focal encephalitis adjacent to a subdural empyema. b is an enlargement of the left frontal region which shows the edema surrounding focal encephalitis more clearly

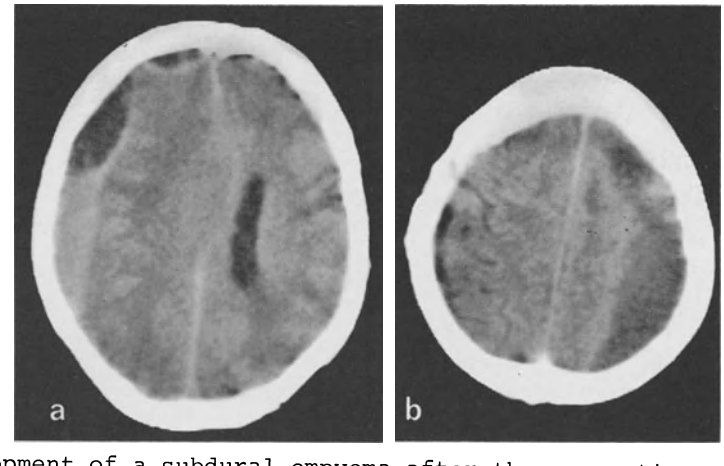

Fig. 4 a, b. Development of a subdural empyema after the evacuation of a contralateral chronic subdural haematoma. a Chronic subdural hematoma located in the fronto-temporal region left. b Large subdural empyema over the right hemisphere

Bacteriological and Morphological Investigations on Patients with Brain Abscess and Subdural Empyema

H.-E. CLAR, H.-E. NAU, V. REINHARDT, and E. ROSENTHAL

Brain abscess and subdural empyema still present major problems despite diagnostic and therapeutic advances. In order to compare morphological and bacteriological findings, we examined 21 cases treated since 1976. In 11 of these cases an autopsy was carried out.

Material and Method

All patients underwent CT investigation preoperatively. After the diagnostic procedures, puncture and drainage of the abscess capsule was carried out in all but two cases. Specimens were examined microscopically as well as by culture (both aerobic and anaerobic). In addition, antibiotic resistance was also tested.

In 17 cases the abscess capsule was removed after a period of drainage and local antibiotic treatment. Microscopic examination of the abscess capsule was performed routinely. In cases of death CT-scans of the brain sections were carried out.

Results

The results may be classified on the basis of our bacteriological findings.

Streptococci

Streptococci were isolated in 10 of the 21 cases: 3 cases from subdural empyema, 5 cases from isolated abscess and 2 cases from multiple cerebral abscesses. Though in most instances cultures and antibiotic sensitivity tests revealed a higher sensitivity for penicillin, relapses and progressive spread of abscesses were observed in three cases.

Case 1: L. C., 15 years, ♂

Diagnosis: Multiple subdural empyemas, anaerobic streptococci of the right hemisphere. 3 weeks before admission headache, high temperature, signs of meningitis. In CT hypodense area with ring structure in the right temporal region. CT-control: multiple abscesses.

Operation: 3 subdural empyemas which were closely adherent to the cerebral cortex were removed.
Culture: The abscess material contained anaerobic Streptococci.
Therapy: according to sensitivity test, treatment is performed with

penicillin and Co-trimoxazol (Bactrim). Three weeks after the first operation, new subdural empyemas in the frontal region demanded a second operative excision. Although the various culture results showed penicillin-sensitive anaerobic streptococci and despite maximum antibiotic therapy, new subdural empyemas sprang up at different locations in the right hemisphere. It was not possible to stop the spread of new abscesses by any operative or medical therapy. Infection led to death nearly 3 months after diagnosis. Brain sections revealed multiple subdural abscess capsules with signs of acute and chronic inflammation (Fig. 1).

Enterobacteriae: Enterobacteriae were found in 3 of our patients and in two of them together with other organisms, i.e. streptococci. In one fatal case salmonella bacteria were the only infective agents. Brain sections demonstrated a broad capsule with a chronic infective reaction.

Case 2: H. C., 8 years, ♀

Diagnosis: Subdural empyemas (Salmonella panama), myelomeningocele, hydrocephalus.
History: earlier case history was not known. 3 years after birth ventriculo-cardiac shunt because of hydrocephalus. Four weeks before admission, recurrent bladder infections. Clinical signs of sepsis. Operation because of valve insufficiency after admission, no signs of valve infection. 3 days later symptoms of intracranial pressure increase. CT indicated large ventricles, therefore implantation of a new ventriculo-cardiac drainage. For 2 days some clinical improvement. On the 3rd day unconsciousness, high temperature, CT-control showed the development of a giant subdural empyema (Fig. 2a). Operative drainage.
Culture showed salmonella panama. Exitus after two days under the signs of toxic shock. Brain section revealed an extensive subdural abscess capsule with marked proliferation (Fig. 2b).

Fungi: Fungi (Aspergillus fumigatus) were found in intracranial abscess material in only one of our cases.

Case 3: M. R., 13 years, ♂

Diagnosis: Brain abscess (Aspergillus fumigatus), panmyelopathy.
History: 3 weeks before admission anaemia, multiple petechial bleeding. Haemoglobin 5.8 g/%, erythrocytes 1,9 mill., leucocytes 2000, thrombocytes 15,000.
In the subsequent days, gradual loss of consciousness.
CT: hypodense area with irregular ring-like structure in the right frontal hemisphere.
Operation: Puncture and drainage of this region. Microscopy: examination showed aspergillus in aspirated pus. Therapy: Amphotericin B was administered. The patient died 3 days later in a cerebral coma.

Section revealed a sepsis of aspergillus with hyphae in the 4th ventricle, kidney, and prostata (Fig. 3b). In the brain section only a slight cellular reaction was observed, without development of an abscess capsule (Fig. 3a).

Sterile abscess. In 5 of our cases, bacteriologically sterile samples were found. In these cases, therapy could not depend on antibiotic sensitivity, but had to cover a broad spectrum.

Case 4: V. E., 64 years, ♂

Diagnosis: Abscess (sterile) right frontal, ventricular infection.
History: Headache for half a year, loss of memory, inability to walk.
CT: ring structure and hypodense area in the right frontal hemisphere.
After admission, puncture and drainage of the abscess.
Culture: Bacteriological examination of various abscess specimens proved to be sterile. Therapy with broad spectrum antibiotics. After 4 weeks, gradual loss of consciousness. CT: Diffuse signs of inflammation of the lateral and 3rd ventricles. Exitus in cerebral coma 2 months after admission. Brain section showed broad capsule of the frontal lobe with chronic granulation (Fig. 4).

Discussion

The study deals with the bacteriological and morphological findings of 21 cases of subdural empyema and brain abscess. Even now the mortality rate is high (3, 5).

In most instances it is possible to isolate the micro-organisms from the pus. De LOUVOIS encountered no sterile samples in his series of 63 specimens (1, 2). In our series 5 cases were sterile. This could be partly due to an inexact anaerobic procedure followed during the aspiration and inoculation. In three cases antibiotic therapy prior to puncture could have led to sterile samples. Sterile samples produce a therapeutic problem, because no direct antibiotic therapy can be administered based on the sensitivity test. Occasionally it may be possible to culture microbes from the venous blood in cases of septicaemia. If it proves to be impossible to isolate microbes either from pus or from venous blood, a combined antibiotic therapy is then necessary. Histological findings of sections of the capsula or the brain after death will not result in bacteriological diagnosis.

The most common infection in cerebral empyema and abscess originates from streptococci of various species. In our series this amounts to about 50% of all cases. These figures correlate well with those of other authors (De LOUVOIS et al., SIMON et al.). The microbes are isolated best by means of an anaerobic technique and inoculated shortly after aspiration of the material.

Even though streptococci are sensitive to penicillin, it is not possible to handle the infection. This may be the consequence of septicaemia originating from an unknown focus.

A very important factor seems to be the high fibrinolytic activity of the streptococci, which are dominant in multiple abscesses and recurrent infection even during maximal penicillin therapy (4).

Intracranial infections with enterobacteria were not frequent in our series. Difficulties in therapy depend on other factors such as the endotoxins, which may produce a toxic reaction in the cardiovascular system. Infection originates from dysentery of the urovascular system and is followed by septicaemia. A systemic therapy with Co-Trimoxazol or high doses of chloramphenicol are the antibiotics of choice here. Morphological studies of chronic abscess capsules reveal no differences to capsules of other microbes.

Many diagnostic and therapeutic problems arise in cases involving fungal infections. These pseudo-abscesses develop only in patients, who show a pathological cellular defence mechanism. In our case, a panmyelopathy was observed 3 weeks earlier. This may have led to a

septicaemia with Aspergillus fumigatus, which at the same time developed into cerebral and organ metastatic mycosis. The fungi could be detected in the pus from the cerebral abscess.

Though the antimycotic therapy was started with amphotericin B, the patient died in cerebral coma. Morphological examination of the abscess indicated only a slight cellular reaction, without granulation or encapsulation. The missing cellular proliferation was due to the primary disturbed cellular defence reaction of unknown origin in the patient.

Conclusion

Our study stresses the fact that subdural empyemas and brain abscesses still present therapeutic problems.

These problems are associated with:

1. Isolation of the microbes
2. Antibiotic sensitivity tests
3. High antibiotic therapy.

We therefore propose that the following procedure be adopted:

1. Inoculation of the specimen before any antibiotic therapy
   a) Aerobically
   b) Anaerobically
2. Culture of the venous blood
3. Morphological and histological examination of the pus and extirpated capsule
4. Antibiotic therapy with maximal dosage as indicated by the sensitivity test
5. In cases with negative culture, the therapy should be based on combined broad spectrum antibiotics.

Summary

This study relates to the findings from 21 cases of subdural empyema and brain abscess treated since 1976. The influence of different infective agents is described and discussed. The problems arising from infections with streptococci, enterobacteriae, fungi and sterile abscesses are mentioned. Proposals are made for attaining the best microbiological results for use in subsequent antibiotic treatment.

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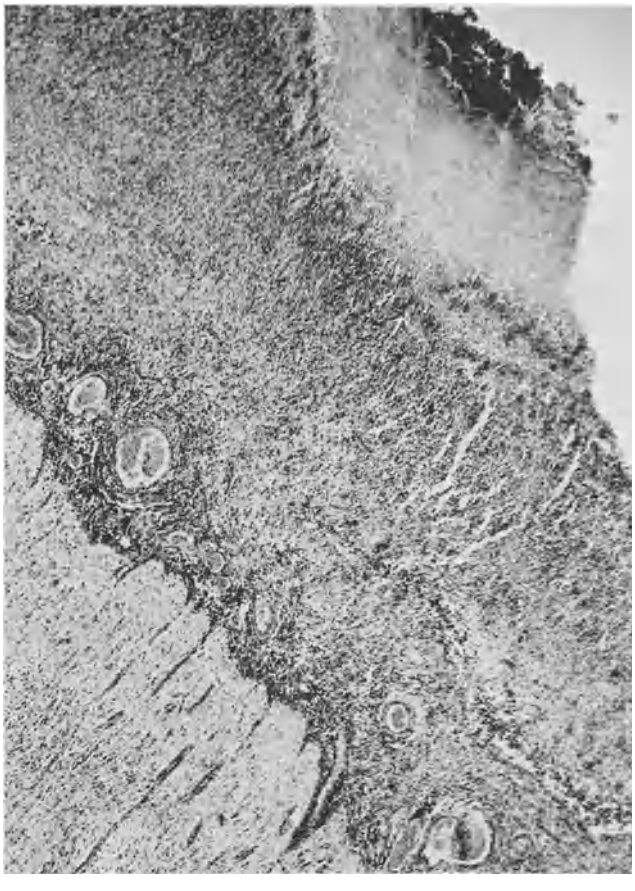

Fig. 1. Capsule of a subdural empyema (streptococci) of a 15-year-old boy shows fibrinoid wall, extensive cellular reaction and adhesive growth with cerebral cortex

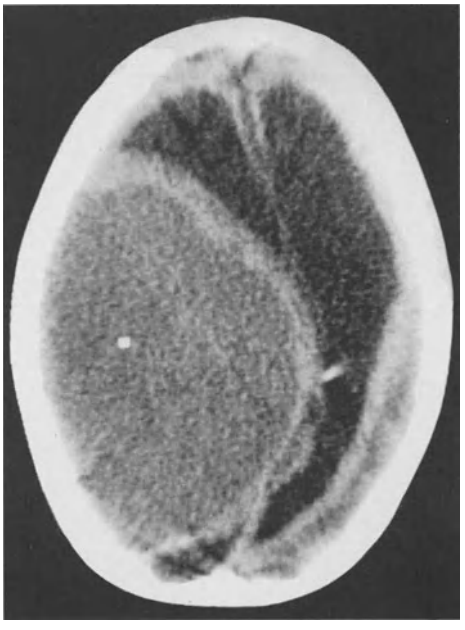

Fig. 2
a CT of a subdural empyema after ventricular drainage (enterobacteriaceae) of a 8-year-old girl

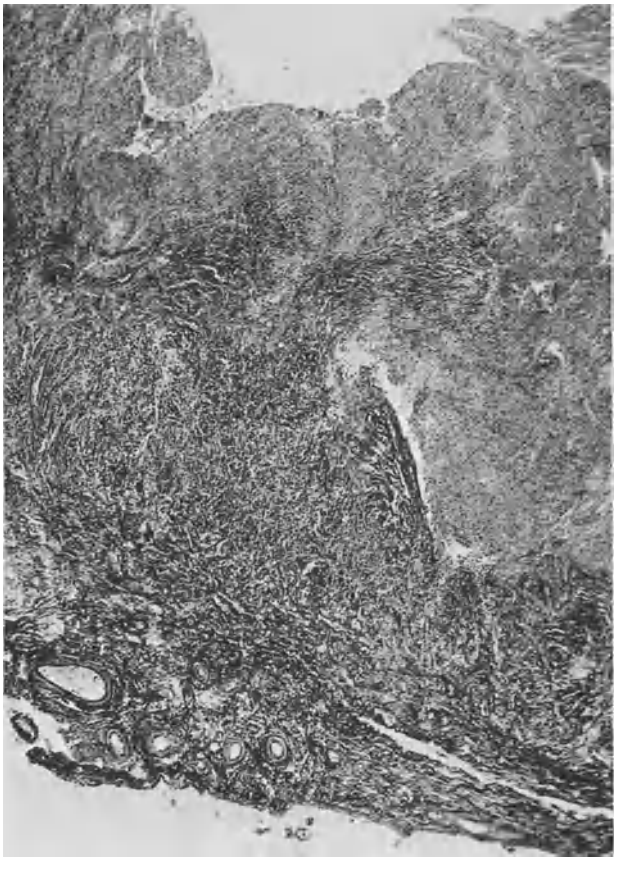

Fig. 2
b Capsule of the empyema with extensive cellular reaction and fibrinoid wall

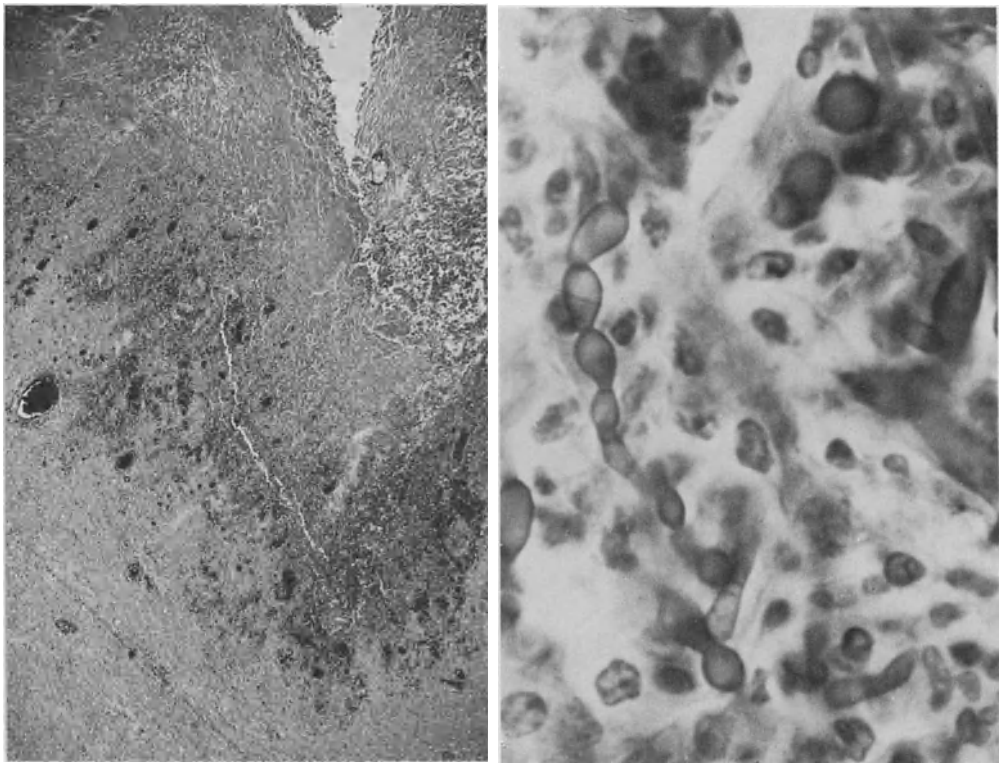

Fig. 3. *Left:* Pseudo-capsule of abscess due to Aspergillus in a 13-year-old boy. Haemorrhages and poor cellular reation indicate the wall of the abscess. *Right:* Microscopical finding in the pus of the abscess shows hyphae of Aspergillus fumigatus

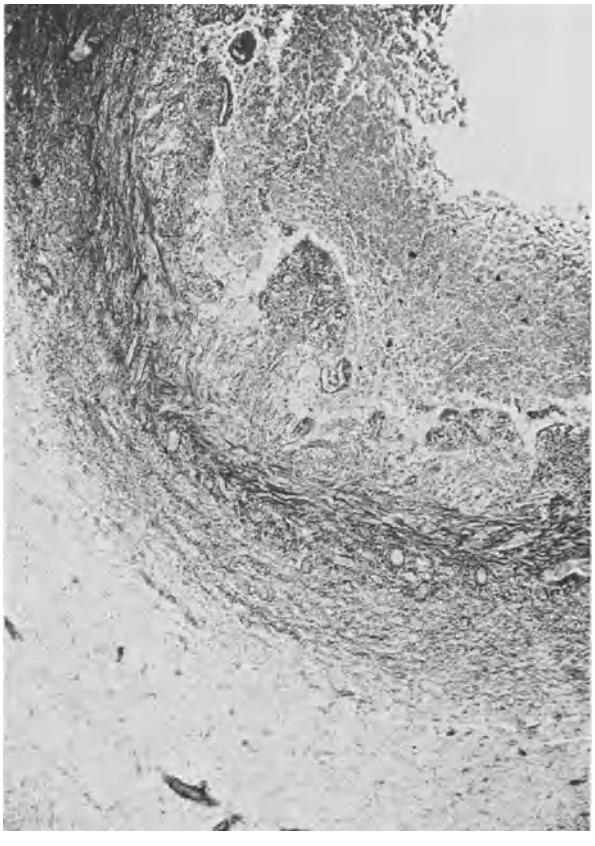

Fig. 4. Abscess capsule (sterile) of a 64-year-old man with chronic granulation and perivascular collagen fibres

CT Findings in Patients with Meningitis and Encephalitis

TH. GRUMME, R. LIST, E. KAZNER, and F. HANEFELD

The clinical diagnosis of meningitis and encephalitis is still based primarily on the history, neurologic and psychiatric examination and on bacteriologic and virologic studies of the CSF. What has the introduction of computed tomography contributed to the diagnosis of meningitis and encephalitis? Available reports on the subject (1-7) are both less numerous and less clinically relevant than publications on CT diagnosis of brain tumors, hemorrhage, brain injury and even brain abscess.

Our own studies cover the period from May 1, 1975 to Dec. 31, 1979 and were made using the EMI Mark I and the EMI CT 1010. Plain scans were supplemented by contrast studies in selected cases. The collective included 152 patients (including 58 children) who had previously suffered from one of the two diseases. We did not make a strict distinction between meningitis and encephalitis when compiling the data, since available records did not permit such a distinction in a number of cases.

In correlating CT findings with the severity of the clinical condition, the latter was classified in the following manner.

1. Patients with acute meningitis or encephalitis.
   Slight: nuchal rigidity, fever and increased number of cells in CSF
   Moderate: somnolence and slight neurologic deficits
   Severe: unconsciousness and severe neurologic deficits; all signs of serious illness.

2. Patients with a history of meningitis or encephalitis.
   Slight: minimal brain dysfunction
   Moderate: psychiatric abnormalities, slight neurologic deficits and mild seizure disorders
   Severe: major mental and neurologic deficits, severe seizure disorders.

Acute Meningitis and Encephalitis

Table 1 demonstrates that the number of evidently pathologic findings in the CT scan correlate directly with severity of the clinical condition from approximately 10-50%. There was no correlation between the severity of the CT findings and the number of cells in the CSF. The number of cases was too small to allow a significant correlation between the microorganism causing the disease and associated CT findings. In general, it would appear that pathological CT findings are more common in children than in adults, as one may see in Table 1 (number in brackets). Table 2 illustrates the correlation between the pathological CT findings and the clinical condition. We most frequently

Table 1. Correlation between CT findings and the clinical condition in patients with acute meningitis or encephalitis. Numbers in brackets refer to children

Clinical condition	n	Pathologic	Questionably pathologic	Normal	Additional pathology
Slight	47 (18)	4 (4)	2	40 (13)	1 (1)
Moderate	76 (27)	27 (18)	15 (6)	30 (3)	4
Severe	29 (13)	16 (8)	2 (2)	10 (2)	1 (1)
	152 (58)	47 (30)	19 (8)	80 (18)	6 (2)

Table 2. Correlation between pathologic CT findings and the clinical condition in patients with meningitis and encephalitis. Numbers in brackets refer to children

Clinical condition	n	Density decrease	Diffuse edema	Dilatation of CSF spaces	Hygroma
Slight	4 (4)	2 (2)	-	2 (2)	-
Moderate	27 (18)	10 (5)	5 (3)	9 (7)	3 (3)
Severe	18 (10)[a]	8 (2)	3 (2)	5 (4)[a]	2 (2)[a]
	49 (32)[a]	20 (9)	8 (5)	16 (13)[a]	5 (5)[a]

[a] Mentioned time.

encountered a circumscribed zone of reduced density. Contrast enhancement during the acute phase of the disease produces a streaky or patchy area of increased density in the periphery of the affected tissue and - on occasion - in the affected tissue itself (Fig. 1 and 2). However, the circumscribed zone of reduced density may extend to large areas of one or both hemispheres. Evaluation of CT studies may present difficulties in cases of septic embolism, since it is sometimes impossible to distinguish between brain infarction and changes due to infection. In addition, CT findings in this condition may present a continuous transition to fully developed brain abscess. Fig. 2 illustrates a representative case in which the pathologic CT findings improved with medical therapy. However, the neurosurgeon is well advised to perform frequent CT studies, since an abscess may occasionally develop, as occurred in one case in our series. Dilatation of the CSF spaces was most often observed in children. Studies with contrast enhancement of the ependyma were not performed in these cases. We found an increase in brain volume without changes in tissue density in 8 patients, 5 of them children. Evaluation of these cases presents special problems, since secondary changes in the ventricles and cisterns may result in CT studies which appear essentially normal. Follow-up examination allows definitive differentiation between normal and pathologic findings. 19 cases are listed as questionably pathologic, since no follow-up studies were performed. Hygromas were observed exclusively in children.

Patients with a History of Meningitis or Encephalitis

Table 3 summarizes the CT findings in 204 patients who had suffered from either meningitis or encephalitis. It is evident that the severity of clinical findings correlates directly with incidence of pathologic CT results. CT studies were normal in 50% of patients with slight neurologic and psychologic deficits, in 30% of cases with moderate deficits and in only 16% of the patients with the most severe sequelae. The fact that this group demonstrated a much higher incidence of pathologic findings, as compared with the patients suffering from acute infections, may be explained by a selection factor, since former patients who have recovered fully rarely appear for follow-up studies.

Table 4 summarizes the pathologic CT findings, which were most often encountered in children. The total of individual findings is greater than the number of patients as a result of multiple pathologic findings in individual patients. The commonest findings were dilatation of the CSF spaces and tissue defects (Figs. 3 and 4). Hygromas in association with hydrocephalus were found only in children. Intracranial calcification was associated with toxoplasmosis in all but one case. Other correlations between CT findings and microorganisms were not evident in this series.

Table 3. Correlation between CT findings and the clinical condition in patients with a history of meningitis or encephalitis. Numbers in brackets refer to children

Clinical condition	n	Pathologic	Questionably pathologic	Normal	Additional pathology
Slight	65 (28)	17 (14)	8 (2)	33 (14)	7 (1)
Moderate	97 (53)	55 (40)	8 (4)	30 (7)	4 (2)
Severe	42 (26)	33 (24)	1	7 (2)	1
	204 (107)	105 (79)	17 (6)	70 (23)	12 (3)

Table 4. Correlation between pathologic CT findings and the clinical condition in patients with a history of meningitis or encephalitis. Number in brackets refer to children. Multiple entries for individual patients

Clinical condition	n	Tissue defect	Dilatation of CSF spaces	Tissue defect and hydrocephalus	Hygroma and hydrocephalus	Calcification
Slight	17 (14)	5 (2)	8 (8)	-	1 (1)	3 (3)
Moderate	55 (40)	16 (9)	28 (23)	7 (6)	3 (3)	10 (9)
Severe	33 (24)	19 (12)	11 (8)	3 (2)	3 (3)	2 (2)
	105 (79)	40 (23)	47 (39)	10 (8)	7 (7)	15 (14)

We have reached the following conclusions:

1. Computed tomography holds a secondary position behind CSF studies in the diagnosis of acute meningitis and encephalitis. Normal CT findings do not exclude the possibility of intracranial infection. Failure to perform lumbar puncture can have fatal consequences.

2. Computed tomography is capable of demonstrating the sequelae of meningitis and encephalitis. The incidence of these findings may be correlated directly with the severity of residual deficit.

3. Pathological CT findings are more common in children than in adults.

4. Follow-up studies suggest that prognostic evaluation is virtually impossible in adults. Infants with pronounced diffuse edema or extensive low-density zones generally have an unfavourable prognosis.

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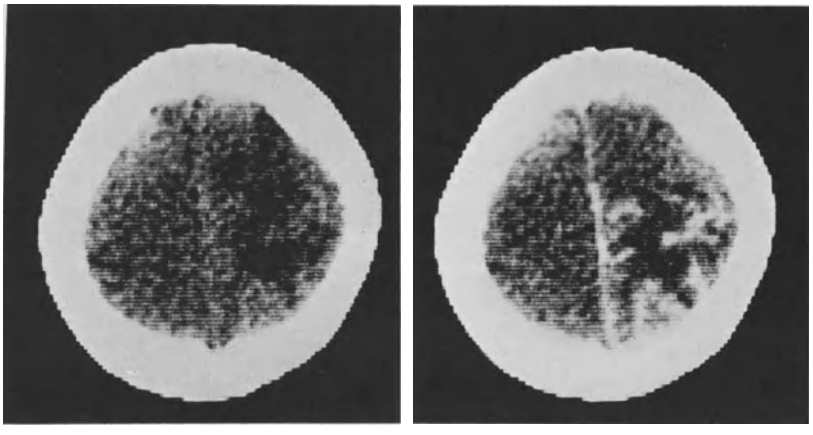
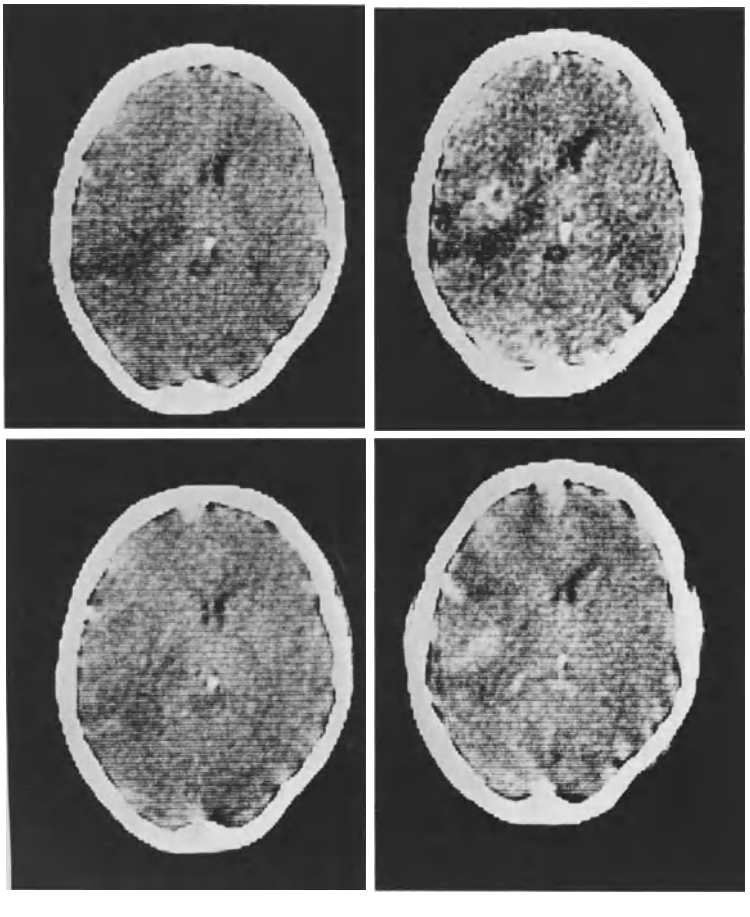


Fig. 1. Encephalitis in the right parietal region without contrast enhancement *(left)* and with contrast enhancement *(right)*



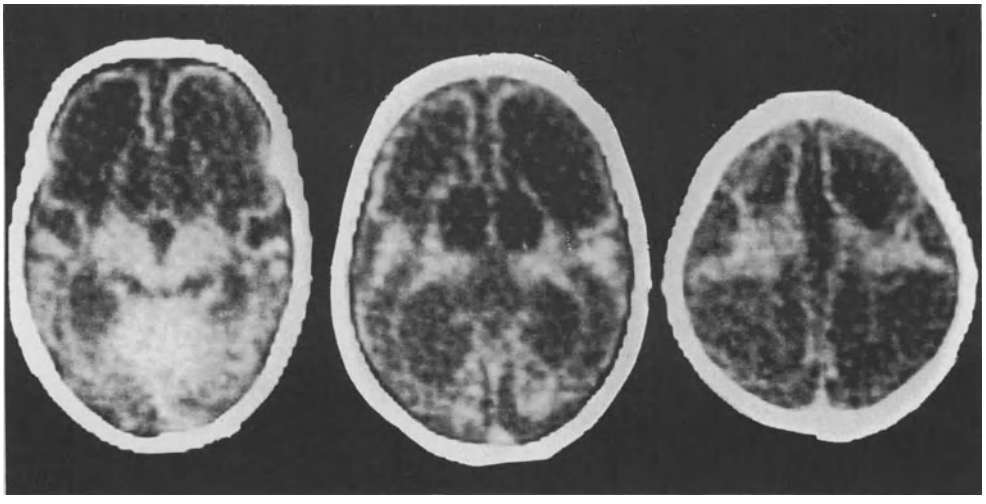


Fig. 3. Severe tissue defects ("status spongiosus") 3 months after streptococcus B-meningo-encephalitis in a 5-months-old infant

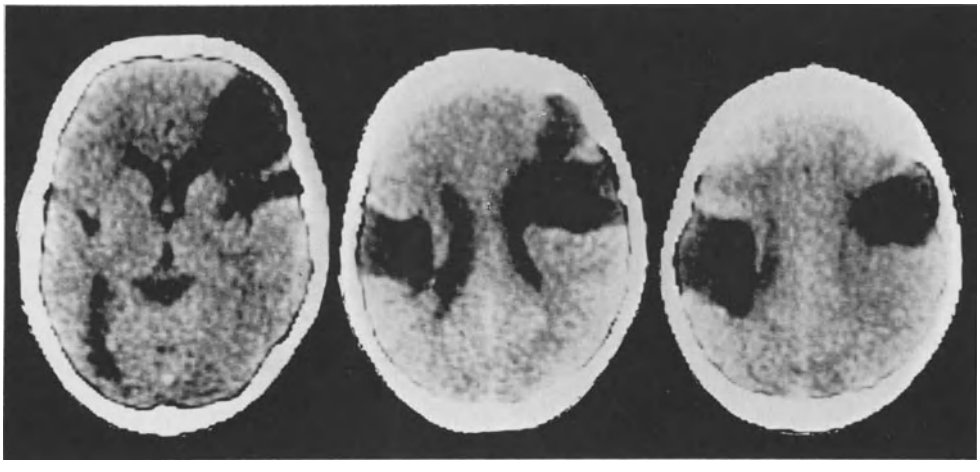


Fig. 4. Multiple tissue defects 7 years after streptococcus meningo-encephalitis in infancy

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Fig. 2. Septic embolism of the left temporal region. Upper series (March 5, 1976): contrast enhancement in the low-density region; lower series (March 30, 1976): follow-up study 25 days later

Special Aspects of the Clinical Course of Tuberculous and Purulent Meningitis[1]

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In the diagnosis of inflammatory diseases of the brain and the meninges, computed tomography (CT) was used mainly to assess brain abscesses. In meningitis it is useful for setting the indication of neurosurgical procedures in the course of a hydrocephalus, due to inflammatory changes in the ventricular system or the basal cisterns. Such pathologic-anatomic findings had been described in tuberculous and purulent meningitis as well as in lymphocytic meningitis (4, 8, 11, 13). Preliminary results of CT investigations in meningitis have shown that there is a certain number of pathologic findings demonstrable in CT (14). The investigations, since continued, were performed in order to obtain information about the incidence and the type of pathologic CT-findings, their development under medication, the assessment of complications and to determine the necessity for surgical procedures.

Case Material and Methods

In order to answer these questions, patients suffering from purulent, tuberculous and lymphocytic meningitis were investigated by means of CT (Siretom 1, Matrix 128 x 128)[1] in acute stages of the disease as well as later in the clinical course. Up to now 23 patients suffering from purulent meningitis, 15 patients with lymphocytic and 6 patients suffering from tuberculous meningitis were investigated. The diagnosis was confirmed by clinical, CSF and bacteriologic investigations. In 25 patients follow-up recordings were done. In order to get information about signs of bone destructions in cases of penetrating meningitis, a CT of the base of the skull was also performed after it had been demonstrated that this method sometimes furnished more relevant findings than conventional tomography (2).

Results

1. Tuberculous Meningitis

Of the 6 patients suffering from tuberculous meningitis, all had pathologic CT-findings. Besides ventricular dilatation, ventricular compression and ischemic lesions (in 3 cases), we also saw signs of a granulomatous form of meningitis. A more detailed analysis of most of the cases presented here had been given previously (15). Of special interest is the development of the pathologic findings as demonstrated by CT. In a 22-year-old woman with a very acute beginning of the disease, there was a narrowing of the ventricular system in the CT at first, later followed by a dilation, in spite of improvement in the

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CSF and the clinical symptoms. Finally the size of the ventricles became normal.

In case of a more chronic Tbc meningitis there was, as expected, a dilatation of the ventricles which normalized under appropriate therapy.

In the case of a 58-year-old woman, the CT was normal in the beginning, in spite of marked inflammatory signs in the CSF. While the clinical symptoms improved, the patient suffered an ischemic infarct two weeks later, leading to global aphasia and hemiparesis. Besides the vascular lesion, a marked dilatation of the ventricles could now be observed in the CT. An angiography performed 4 weeks later, there was still a narrowing of the carotid artery in the area of the siphon. The CSF was normal at that time.

Ischemic lesions in both hemispheres were found in a 49-year-old woman, in whom a tuberculoma of the posterior fossa has been removed 7 weeks before, although a histologic diagnosis could not be made and an appropriate therapy initiated (Fig. 1). When the patient was transferred to our hospital she was deeply somnolent, had signs of increased intracranial pressure, of meningitis and paresis of the right limbs. Besides dilatation of the ventricles an ischemic lesion in the left hemisphere was seen in the CT. One week later a further ischemic infarct in the right hemisphere became detectable and angiography revealed the typical narrowing of the internal carotid artery.

2. Lymphocytic Meningitis

Of the 15 patients suffering from lymphocytic meningitis, a clear pathologic CT-finding could only be demonstrated in a case with a chronic inflammation, located at the base of the brain as was proved by autopsy. The CT showed ventricular dilatation.

3. Purulent Meningitis

Of the 23 patients, suffering from purulent meningitis, a clear pathologic CT-finding was observed in 15, but not all patients were investigated in the acute stage of the disease and contrast medium was not always given. In 8 cases a dilation of the ventricular system, sometimes very marked was observable, in one case with accumulation of pus in the posterior horns and abscesses in the cerebellum. In 7 patients a clear narrowing of the ventricular system was demonstrated, partly with decreased density in the hemispheres, a collection of fluid above the hemispheres and in one case a subdural empyema in the interhemispheric fissure as confirmed by autopsy.

In a case with an massive dilatation of the ventricles which continued to progress (Fig. 2), in spite of improvement of the inflammatory signs in the CSF, but no improvement in the clinical state, we decided to perform a drainage of the ventricular system. But there was no reduction of the size of the ventricles, nor was there an improvement of the clinical symptomatology. The same procedure carried out in another patient who had signs of brain stem damage already, also proved to be unsuccessful. Autopsy revealed a severe leptomeningitis localised mainly at the base of the brain, an empyema of the ventricular system and signs of increased intracerebral pressure.

In a 19-year-olf female patient suffering from purulent meningitis caused by penetration of an infection of the frontal sinus in CT, a marked enhancement of contrast medium was demonstrable at the base of the brain and the interhemispheric fissure (Fig. 3). At autopsy various thromboses in the sagittal, sigmoid and transverse sinuses were found as well as signs of increased intracranial pressure and leptomeningitis over the hemispheres.

Investigations of the bony structures of the base of the skull by means of CT in many cases demonstrated destructive changes or the absence of air in the mastoid process, not detected so well by conventional X-ray technique. In the patient, depicted in Fig. 4 the finding led to mastoidectomy and a favorable outcome of the meningitis.

Discussion

These observations made in the different forms of meningitis demonstrate that pathologic CT-findings occur rather frequently in these diseases. As far as tuberculous meningitis is concerned, the findings are in agreement with the communication in the literature (1, 3, 4, 6, 7, 9, 10, 12, 16, 17, 18). Remarkable in our material is the incidence of ischemic lesions and their appearance at a time, when changes in the CSF and clinical symptomatology had already improved. Previously, we had already been able to demonstrate that these alterations, found at the internal carotid artery, outlast the normalisation of the CSF (15). Furthermore ventricular enlargement and improvement of the inflammatory signs in the CSF do not necessarily correlate, as shown by PRICE and DANZIGER (12) as well. Finally, a narrowing of the ventricles can also be observed in this disease. This is of importance insertion of the so-called Ommaya reservoir for intrathecal drug application is intended.

Marked dilatations of the ventricles were also seen in the acute stages of purulent meningitis, especially in cases with a severe clinical symptomatology, as described by ZIMMERMANN et al. (20) and WEISBERG (19). Obviously, circulatory disturbances of the CSF are also an early symptom of purulent meningitis. As a rule this is found when the disease is localized at the base of the brain. The narrowing of the ventricular system is seen especially in cases where meningitis is localized on the surface of the brain. The autopsy findings are in agreement with this assumption.

Therapeutic trials with drainages of the ventricles in cases with progressive dilatation in two patients, did not bring relief. There was neither a reduction of the size of the ventricles nor an improvement in the clinical symptomatology. In one case the failure might be due to an already existing damage to the brain stem. In the other case one might discuss that the ventricular dilatation was not the result of a circulatory disturbance of CSF but rather due to damage to the brain itself caused by the inflammatory lesion. The question of the use of drainages in the acute stage of meningitis is still open. In cases of tuberculous meningitis there was never an indication for such a procedure.

Conclusion

The high incidence of pathologic CT-findings in tuberculous and purulent meningitis justifies the use of CT in the early stages already

as well as later in the clinical course of these diseases. Through the use of this procedure, complications and the response to drug therapy can be assessed and possible indications for neurosurgical interventions can be timed, although the practical effect of these measures cannot be judged definitively at the present time. The use of CT at the base of the skull facilitates the diagnosis of inflammatory processes e.g. mastoiditis or frontal sinusitis.

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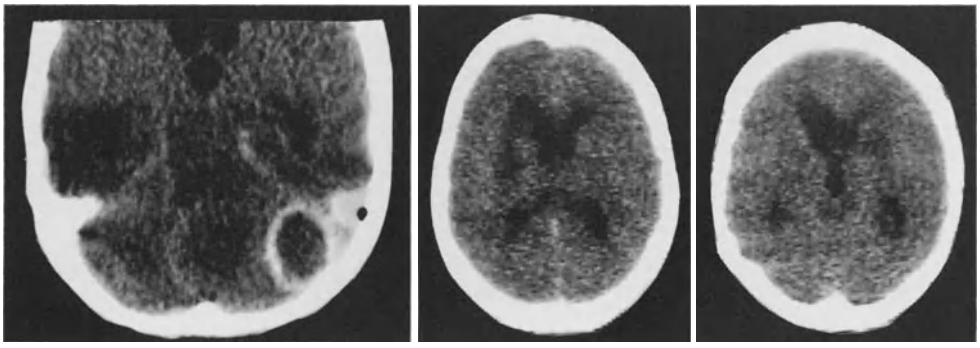

Fig. 1. Tuberculous meningitis and tuberculoma in a 49-year-old woman. *Left:* 29.5.1978: tuberculoma in the right posterior fossa. Enhancing rim and low density center. Dilatation of lateral and third ventricles. *Middle:* 22.7.1978: Ischemic lesion in the region of the left basal ganglia with compression of the left anterior horn. *Right:* 1.8.1978: Ischemic lesion in the region of the right basal ganglia with compression of the right anterior horn. "Fogging" effect in the region of the previous ischemic lesion in the left hemisphere (see also Nervenarzt 50, 794-799 (1979))

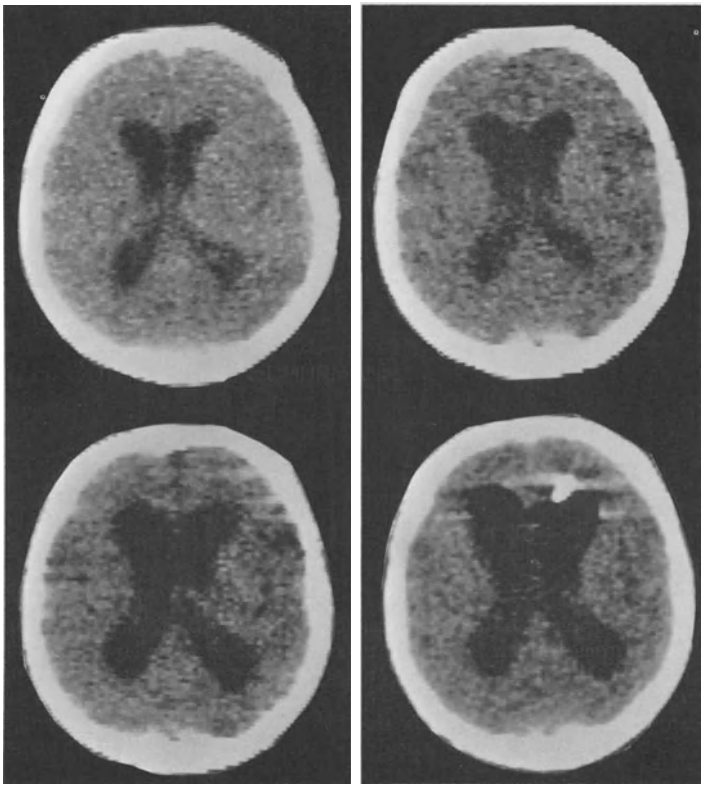

Fig. 2. Purulent meningitis in a 39-year-old man with progressive dilatation of the ventricular system. No reduction in the size of the ventricles after the insertion of a shunting tube (*left:* 9.11.1979; *right:* 20.11.1979)

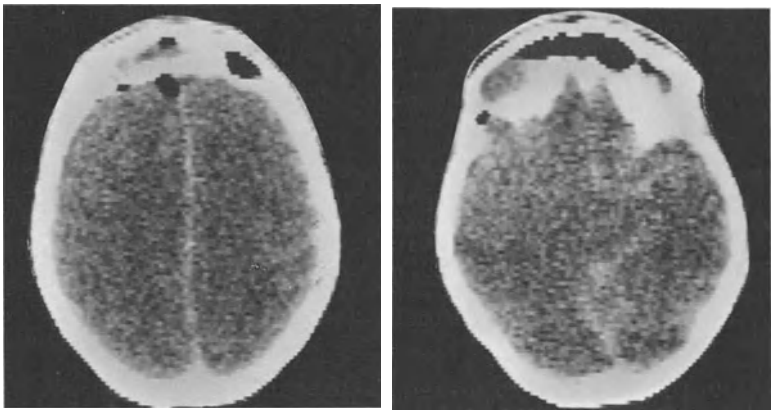

Fig. 3. Purulent meningitis due to frontal sinusitis in a 19-year-old woman. Fluid level in the left frontal sinus. Intracranial air bubbles. Abnormal contrast enhancement of the interhemispheric fissure and basal cisterns

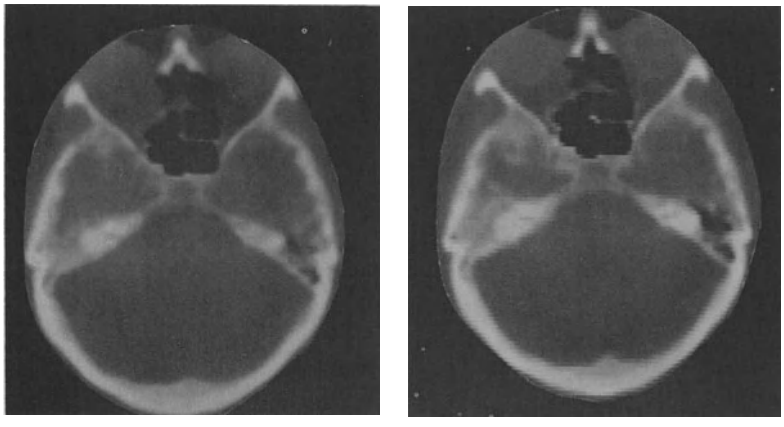

Fig. 4. Base of the skull of a 42-year-old man with purulent meningitis and mastoiditis on the left. Note the different pneumatisation of the mastoids

Intrathecal Injection of Gammaglobulin in the Treatment of Severe Forms of Meningitis

H. E. DIEMATH and J. STROHECKER

Abstract

In the course of the past five years 23 patients were treated with intrathecal gammaglobulins for severe posttraumatic or postoperative meningitis. Ten patients had posttraumatic, and ten had a postoperative infection, while three more suffered from cerebral abscesses. In all patients, the infection had occurred in spite of prophylactic treatment with antibiotics. We were able to effect a speedy reduction of the cell count in the cerebrospinal fluid accompanied by an improvement in the patients' general condition, followed by a complete cure only after intrathecal injections of between 250 and 500 mg per day of enzymatically decomposed gammaglobulin (Gammavenin TM).

Introduction

In spite of treatment with highly sophisticated antibiotics, there is still a considerable risk attached to all cases of severe posttraumatic or postoperative infection. According to LLEWELLYN et al. (6) for instance, the rate of wound infection in the United States lies around 2-5% without and 1% with antibiotics in all cases of general surgery. At the New Orleans neurosurgical department, the rate of infection is 1-2%, which more or less corresponds to our figures, severe cases of neurotrauma included.

Although it is now general practice to treat patients prophylactically with antibiotics, mostly during the perioperative phase, infections of this nature still occur. Among other factors this may be ascribed to a few cases of genuine antibody deficiency, but more probably to postoperative relative hypoimmunity or to protracted transient hypoglobulinaemia. Immunoglobulins were used in the treatment of bacterial infection as early as 1963 (4, 5) but they are still rather often regarded as a final resort in the treatment of infection. That immunoglobulins are often of therapeutic value in the treatment of bacterial infection and in the neutralisation of circulating bacteriotoxins was established by BARANDUM et al. (2) in 1976, and again by AX et al. (1) in 1978. Moreover, ZWISLER (8) was able to prove in 1978 that mutations of Staphylococcus aureus resistant to ampicillin could be arrested by administering gammaglobulin. Preparations of gammaglobulin have a neutralizing, antibacterial, antiviral, and antitoxic effect.

If treatment is accompanied by intrathecal injections of an antibiotic and of gammaglobulin, severe cases of meningitis will respond much better to treatment; this combination is now well established in the range of therapies. The concentration of the antibiotic is immediately bactericidal and remains so for a long time, and in combination with the gammaglobulin, the level of antibodies in the cerebrospinal fluid is kept high.

Whether or not an antibiotic will easily pass into the cerebrospinal fluid is of secondary importance if it can be administered intrathecally. We use Refobacin L (TM) for this purpose as a rule. The immunoglobulin we use is Gammavenin (TM), which is an enzyme-treated immunoglobulin with part of the Fc fragment missing. It consists mainly of the $F(ab')_2$-fragment of human gammaglobulin. $F(ab')_2$ is capable of cross-linking antigens and of activating the complemental system the alternative way (3).

Patients and Dosage

In the course of the past five years 23 patients were treated intrathecally with a combination of an antibiotic and Gammavenin for severe posttraumatic or postoperative meningitis. After the trauma or, respectively, after surgery, all these patients were prophylactically treated with antibiotics. Table 1 shows the group of patients discussed here, together with the antibiotic treatment they received. Ten patients had posttraumatic infections, 10 had postoperative infections, and another 3 suffered from cerebral abscess. The pathogens are listed in Table 2. In 8 patients, no pathogens could be demonstrated and the cultures remained sterile. After thorough culture and resistance tests, the patients were changed to the appropriate antibiotics and, in addition, given Gammavenin administered intrathecally by lumbar puncture. Whenever the resistance tests had shown Gentamycin to be indicated, we added an intrathecal dose of 5 mg of Refobacin. In all cases of sterile so-called meningitis, we administered fourth-generation cephalosporins together with Gentamycin and Gammavenin.

Infants and toddlers were given 250 mg of Gammavenin intrathecally, while adults received 250-500 mg each day, or, alternatively, at intervals of 2 or 3 days.

Results

The efficacy of this treatment was assessed on the basis of clinical findings, laboratory tests of the usual chemical parameters, and examinations of the bacteria in the blood serum and the cerebrospinal fluid.

We did not monitor the globulin fraction in the cerebrospinal fluid any longer because it has been shown to be irrelevant (7).

All patients responded to treatment within 2 to 4 days; their temperature sank, the cell count in the cerebrospinal fluid went down, and the clinical picture improved.

Figure 1 shows how the cell count in the cerebrospinal fluid dropped during intrathecal medication. In some cases, the number of cells rose again intermittently, especially if the patients were treated at 2 or 3-day intervals.

This penomenon may possibly be related to the biological half-life of $F(ab')_2$, which is 18-24 hours. On the average, the antibiotics were given for 10 days before the treatment with Gammavenin was started, because the antibiotic treatment showed no appreciable effect.

Intrathecal treatment was continued for 5-10 days on the average. All patients, with the sole exception of one who died due to an intercurrent infection some six months later, were discharged cured.

Table 1. Intrathecal treatment with gammablobulin (n = 23)

Age (years)		Diagnosis	Culture	Antibiotic
22	♂	Bolt gun injury	Clostrid. perfring.	Chloramphenicol
1	♂	Hydrocephalus	Proteus vulg.	Chloramphenicol
14	♂	Meningeoma	Hay bacilli	Chloramphenicol
41	♂	Cerebral abscess	Sterile	Chloramphenicol
8	♂	Craniopharyngioma	Staph. aureus	Chloramphenicol
6	♂	Subdural hygroma	Klebsiella	Gentamycin, Cefalotin
16	♂	Severe open cerebrocranial trauma	Airborne bacteria	Chloramphenicol
55	♂	Aneurysma	Sterile	Chloramphenicol
21	♂	Open head injury	Sterile	Chloramphenicol
33	♂	Maxillary sinus operation	Sterile	Chloramphenicol
69	♂	Open head injury	Klebsiella	Chloramphenicol
10	♂	Open head injury	B. pyocyaneum	Chloramphenicol
17	♂	Head injury	Sterile	Chloramphenicol
34	♂	Cerebral abscess	Staph. aureus	Gentamycin
26	♂	Open head injury	Pneumococci	Chloramphenicol
62	♂	Cerebellar metastasis	Sterile	Chloramphenicol
22	♀	Cerebral abscess	Staph. aureus, Proteus, Pseudomonas	Chloramphenicol, Gentamycin, Cefalotin
35	♂	Head injury	Klebsiella, airborne bacteria	Cefalotin, Gentamycin
36	♂	Open head injury	Sterile	Ampi-Oxacillin
7 months	♂	Subdural hygroma	Sterile	Penicillin
54	♂	Meningioma	Staph. aureus	Ampi-Oxacillin
12	♀	Glioblastoma	Staph. aureus	Cephalosporin
35	♂	Chronic subdural hygroma	Staph. aureus	Cephalosporin

During the intrathecal treatment with gammaglobulin we observed no anaphylactic phenomena.

However, it seems probable that even this therapy will not prevent residual damage after meningitis. In spite of the fact, that the cerebrospinal fluid of the one patient, who died, was found to be completely healthy, his meninges had become fused and thickened extensively at the base.

Table 2. Intrathecal injection of gammaglobulin in the treatment of severe meningitis

Staphylococcus aureus	Posttraumatic infection	0
	Postoperative	4
	Cerebral abscess	2
Proteus	Posttraumatic infection	0
	Postoperative	1
	Cerebral abscess	2
Clostrid. perfringens	Posttraumatic infection	1
	Postoperative	0
	Cerebral abscess	0
Klebsiella	Posttraumatic infection	2
	Postoperative	1
	Cerebral abscess	1
Airborne bacteria	Posttraumatic infection	1
	Postoperative	0
	Cerebral abscess	0
Pseudomonas	Posttraumatic infection	1
	Postoperative	0
	Cerebral abscess	1
Hay bacilli	Posttraumatic infection	0
	Postoperative	1
	Cerebral abscess	0

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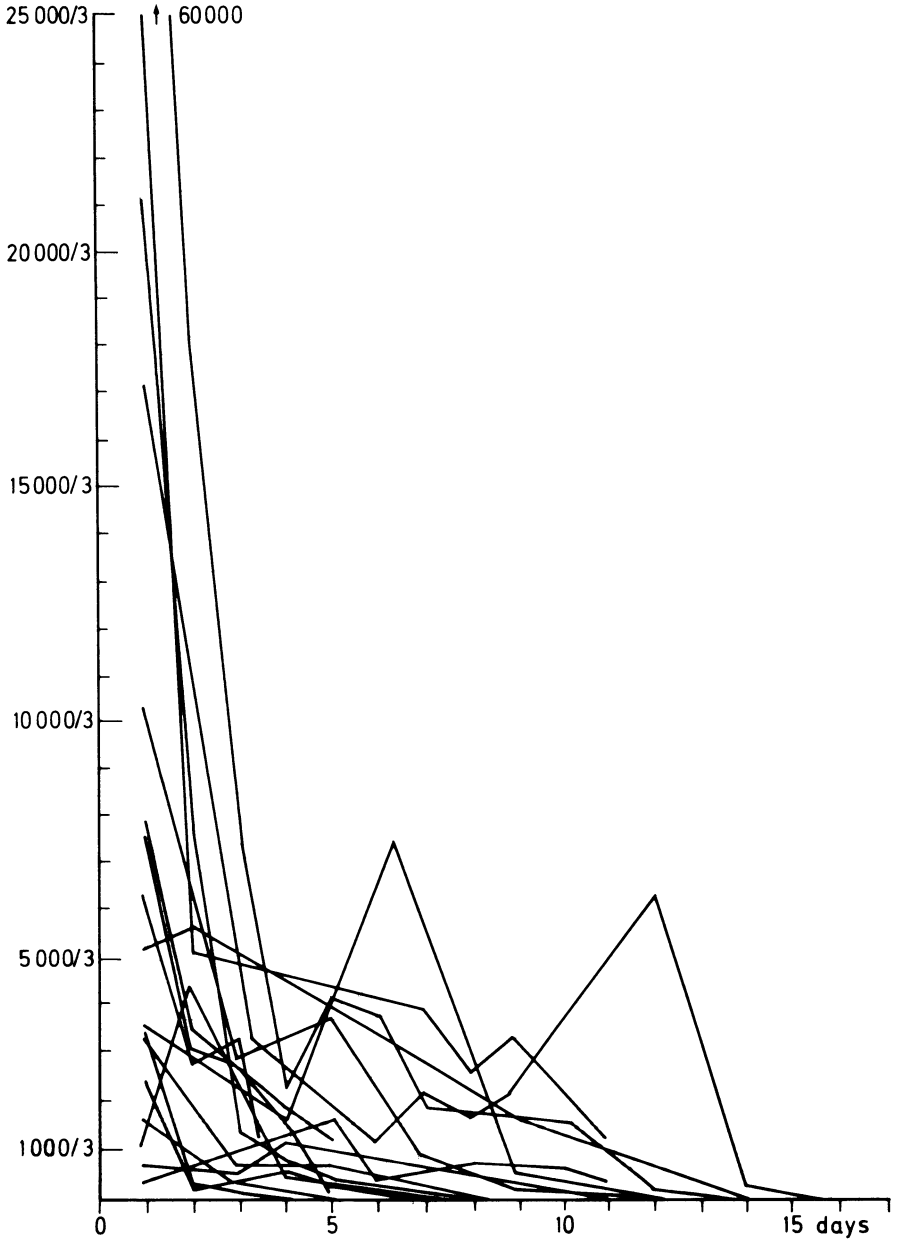

Fig. 1. Intrathecal injection of gammaglobulin in the treatment of severe meningitis

Meningitis and Hydrocephalus

R. W. OBERBAUER and H. GRUBBAUER

Introduction

Association of meningitis and hydrocephalus almost necessarily results in a neurosurgical intervention. Primary meningitis and/or ventriculitis may cause hydrocephalus requiring drainage of cerebrospinal fluid (CSF). Infections of hydrocephalus already treated by CSF drainage are considered a severe complication and, generally, require surgical revision. In the literature the occurrence of shunt infections varies from 6 to almost 40% and averages 15-20% (3, 5, 7, 12, 17, 22).

The acute form is distinguished from chronic or so-called "occult" infections (5). The favourable management is still subject to discussion. Opinions vary from conservative therapy with intraventricular and/or systemic antibiotics (10, 21), immediate replacement of removed shunts (6, 9, 17, 26) to shunt removal, temporary external ventricular drainage (EVD) and reimplantation of a new shunt system after complete eradication of the infection (3, 12). Secondary complications such as shunt nephritis (2, 11, 19, 24, 25) and others (4) play an important role for reflections about optimal treatment.

It is understandable that surgeons tend to avoid removal of functioning shunts, having further possible complications in mind.

In our patients, reinfections of simply exchanged shunt systems and long-lasting courses with conservative antibiotic therapy resulted in endless hospitalisations. These unsatisfactory results eased the decision to establish a uniform treatment plan with the goal of achieving the most reliable and fastest eradication of the infection.

Method

The diagnosis of shunt infection was primarily established by CSF-cultures, obtained from the shunt-reservoir (4, 16, 18, 23). Since some of the patients had received antibiotic therapy prior to admission, CSF cultures were not always positive. Clinical history and chemical CSF findings were still considered adequate, if other causes for infection were excluded. After diagnosis of shunt infection, the complete shunt system was removed and temporarily replaced by EVD. As soon as CSF findings and the clinical course had normalized, systemic and intraventricular antibiotic therapy was interrupted. Three further specimens of CSF and blood were examined at intervals of 24 hours. If no signs of infection existed during the latter period, the CSF drainage was again internalized at the same or at another operative site.

Results

From 1975-1979, 125 hydrocephalic patients had 225 shunt operations and revisions, respectively. Twenty-four suffered shunt infections, i.e. 10,6% per surgical procedure. This series includes a subgroup of 11 premature patients with multiple problems in addition to hydrocephalus. They deserve to be emphasized, since 6 of 11 became infected (more than 50%).

Ventriculo-atrial and ventriculo-peritoneal shunts were inserted in about equal numbers, no evident differences could be noted (1). The intervals between operation and onset of infection are listed in Table 1. The two later groups meet the criteria of chronic infections without immediate connection to the operative procedure. The most likely route of infection has been indicated by HOLT (7): "organisms are implanted at the time of surgery and lie dormant for a period of weeks or months". The two other theories concerning ventriculo-atrial shunts (transient bacteraemia and formation of thrombi at the distal catheter) appear less relevant, since infections do occur with the same frequency in ventriculo-peritoneal shunts.

The bacterial etiology of infections is presented in Table 2. The high incidence of Staphylococcus epidermidis is well known from numerous previous communications (3, 5, 8, 17, 21, 22, 23).

Table 1. Interval between operation and onset of infection (shunt infection)

Less than 2 months	16
2 months to 1 year	5
Over 1 year	3
Total	24

Table 2. Type of organism (CSF) (shunt infection)

Staphylococcus epidermis	10
Staphylococcus aureus	3
Streptococcus	2
Escherichia coli	3
Aerobacter	3
Mixed organisms	3
Undetected	6

In 19 patients EVD was employed after removal of the infected shunt. The drainage was left in place from 4 to 39 days, with an average 14,8 days. Clinical signs of infection disappeared within 1 to 16 days (4 days on the average). None of this group suffered reinfection after insertion of a new permanent shunt, 15 for more than one year, 4 patients 3-12 months.

The remaining 5 patients were treated in other hospitals. Two had undergone immediate replacement of the infected shunt, in 3 patients systemic antibiotics were given. Each group had 1 death due to septicaemia, 3 are considered cured for 24, 11 and 8 months after prolonged hospitalisation (3-6 months).

Discussion

The considerable number of publications is the best evidence for the fact that shunt infections still account for the most severe problem in the treatment of hydrocephalus.

SCHIMKE et al. (1961) reported on 4 out of 11 patients who were cured by systemic antibiotic therapy alone (21). McLAURIN and DODSON (1971) reviewed 20 patients with shunt infection, 50% being cured by intensive intraventricular and systemic antibiotic therapy without surgical shunt replacement (10).

In our series, in 2 of 3 patients in whom the shunt system remained in place, clinical cure was eventually accomplished by systemic administration of antibiotics.

However, it must be objected that bacteraemia persisted for a period of months (3, 4 1/2 and 6) with intermittent fever attacks, and implied long-term antibiotic therapy with hardly bearable prolonged hospitalization. In addition, a higher mortality rate is reported in the majority of communications.

NICHOLAS et al. (1970) reports satisfactory results in cases of shunt infections caused by S. epidermidis by replacing the shunt immediately at the time of its removal (13).

However, since mixed colonisation with more virulent organisms does occur and cannot be excluded with certainty, the higher risk of reinfection remains imminent. Both systemic and ventricular antibiotic therapy, as well as immediate shunt replacement, evoke the possibility of prolonged septicaemia and secondary complications; therefore, they should be considered too hazardous.

Conclusion

The primary goal in the treatment of shunt infections must be the complete eradication of bacteraemia. Our series supports the view of the majority of authors who advocate the removal of the entire shunt system. By means of EVD, intracranial pressure can be kept stable and intraventricular administration of antibiotics aids in shortening the duration of septicaemia. This method should be considered preferable since it turned out to be the safest way to get rid of shunt infections.

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Subarachnoid Hemorrhage: Timing Problems

Signal-SAH or Spontaneous SAH? Semantic and Conceptional Introduction to "Timing of Subarachnoid Hemorrhage"

J. GERLACH

The subject pertains to emergency neurosurgery. In neurosurgery, as well as in the whole medical field, successful research, theoretical discussion and practice require clearcut conceptions, exactly defined denotations and unmistakable designations. Concerning the more simple linguistic problems, I suggest abbreviating the clumsy term "subarachnoid hemorrhage" as SAH. The English abbreviation should be preferred to the German "SAB" adapted to the word "Timing" for better international understanding. Such abbreviations are generally used in the case of long terms such as CNS for Central Nervous System or CSF for Cerebrospinal Fluid. Moreover, they have been introduced in special fields e.g. problems of intracranial pressure (ICP). Their use may be recommended where these long terms are reiterated, so long as misinterpretation is not caused, and the abbreviations are explained. If preferred, all forms of intracranial hemorrhage (ICH) might be distinguished by abbreviations (Table 1) and might be listed in a Glossary.

More essential are the meaning, intention and extension of the denotations expressed by the words. First, attention should be called to the changing meaning of the German word "Blutung": it should only mean the extravasation of the blood from a vessel = "hemorrhage", though it is often used to denote "Clot" = "hematoma". Concerning the present subject, the difference is obvious because SAH is not necessarily followed by SAHa, as is the case with ventricular hemorrhage (VH), whereas in cases of epidural, subdural and intracerebral hemorrhage, a hematoma always results.

SAH is characterized by the fact that the blood leaving the vessel is always mixed with CSF. It does not remain in the vicinity of the vascular lesion, but is spread all over the intracranial and intraspinal subarachnoid space thus affecting extensive regions of the CNS' inner and outer surfaces. In the case of SAHa, this may arise at a considerable distance from the site of bleeding (e.g., blocking basal cisternas). By definition the intracranial vessels are necessarily involved in all sorts of ICH. The same is the case with the CSF-system in any instance

Table 1. List of abbreviations of intracranial hemorrhage and hematoma

Hemorrhage	Hematoma	Localization
ICH	ICHa	Intracranial
EDH	→ EDHa	Epidural
SDH	→ SDHa	Subdural
SAH	SAHa	Subarachnoidal
IVH	IVHa	Intraventricular
IBH	→ IBHa	Intracerebral

of SAH, having retroactive effects upon the vessels. "Vasospasm", therefore, does not only play an important pathophysiological but also clinical role, as shown by the titles of the papers which follow.

"Spontaneous" as well as "Signal"-SAH means SAH of unknown origin. "Spontaneous" does not give any positive information, and hides the fact that there must be a cause for any SAH which should be clarified and eliminated (e.g., isolating an aneurysm from circulation). The term "Signal-SAH" has *imperative* character and challenges exact diagnosis for proper treatment: removing the extravasated blood, searching and removing the cause. "Signal" also indicates the danger of recurrence of SAH. Now we come again to the main subject: *Timing of SAH.*

According to WEBSTER's Dictionary (1), Timing means:
1. Selection for maximum effect of the precise momentum for beginning or doing something, in medical use (Am. Med. Ass.): the proper timing of the operation in reference to the course of the disease.
2. Observation and recording of the elapsed time of an act, action or process, often by stopwatch.

Discarding this latter and substituting "process of the disease" for "process", we can now apply both denotations of timing to our subject. In order to do so, we must combine two lines of timing which run simultaneously: the first line being the observation and recording of the exact chronological order of the disease (diagnosis at any moment) and the second line being the timing required for determining when to wait and when to operate, taking into consideration the risks involved in either operating or waiting at any given time (Fig. 1). This procedure may be likened to the coordination between a boxer's blow and the opportunities offered for attack. Both SAH and Signal-SAH are preliminary terms which should be replaced by the final diagnosis as soon as possible, e.g. SAH from an aneurysm of the A. communicans anterior.

Timing is valid for any medical action. In the case of SAH it should be greatly emphasized because of the short duration of the critical periods and the great risk involved in both proceeding and/or waiting.

Conclusion

Linguistic and conceptional questions in respect to the subject are herein discussed. It is suggested to replace the term "spontaneous" by the prefix "signal" together with "subarachnoid hemorrhage", which may be abbreviated as SAH. This preliminary diagnosis should be replaced by the final as soon as possible. The concepts hemorrhage, hematoma and timing are defined.

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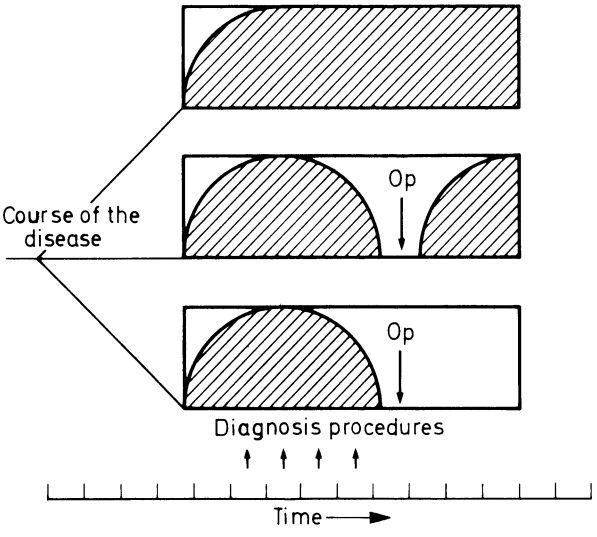

Fig. 1. The three main types of course and timing in SAH

Ultrastructural Studies of Cerebral Berry Aneurysms Obtained Operatively

R. MEYERMANN and M. G. YASARGIL

Since the first description of cerebral berry aneurysms (RUFUS von EPHESUS, 1549), this pathologically changed tissue of the cerebral vessel-wall has been studied mainly by histological methods. The findings can be summarized as follows:

Saccular aneurysms of the cerebral arteries occur as a result of a mural defect in the widest sense. These lesions can be caused by congenital abnormalities, inflammation of the vessel-wall, arterio-sclerosis and injury. This means that currently there are two basic views. The first is that they are the result of maldevelopment of the cerebral arteries - the so-called congenital theory. The second is that they are caused by acquired degenerative changes in the arterial wall - the degeneration theory (STEHBENS, 1972). Compared with the great number of histological studies, examinations of cerebral berry aneurysms by electron microscopy are very rare. The first description of the ultrastructure of cerebral arteries (NYSTROEM, 1963) supported the so-called congenital theory, whereas the following studies (LANG and KIDD, 1965; HASSLER, 1965; STEHBENS, 1975; EBHARDT et al., 1977) support the degeneration theroy. However, systematic studies are not available.

Following the development of diagnostic procedures (MONIZ, 1934), morphological studies about cerebral aneurysms are reduced in number. Additionally, the improvement of diagnostic and surgical techniques has diminished the opportunity to study cerebral aneurysms in autoptic material. Thus, nowadays the only way for studying cerebral aneurysms systematically is the examination of material gained operatively. On the other hand, this procedure has the handicap that the transition between normal and pathologic tissue is not available. However, ultrastructural studies (EBHARDT et al.,1977) showed the same changes in the transition area as in the fundus of the aneurysm.

Material and Methods

The surgical technique for isolating the aneurysm from the systemic arterial circulation has been described previously (YASARGIL and FOX, 1975). Following this procedure, the fundus of the aneurysm was dissected and fixed immediately in cacodylate-buffered (pH 7.4) 2.5% isotonic glutaraldehyde solution for 4 h. The specimens were postfixed in 1% osmium tetroxide for 1 h. Thereafter the material was embedded in Araldite following dehydration in an ascending alcohol sequence. The inner cell-layers of the aneurysm were aligned by flat embedding. Sections of 1 µm thickness were stained with toluidine blue. Ultrathin layers examined by electron microscopy were counterstained with lead citrate and uranyl acetate. In this way 141 cerebral arterial aneurysms were examined by electron microscopy (Table 1); 66 were located at the anterior communicating artery, 30 were removed from the proximal or

Table 1

Localization of cerebral aneurysms obtained at surgery	
Anterior communicating artery	66
Middle cerebral artery	30
Internal carotid artery	11
Anterior chorioidal artery	10
Posterior communicating artery	8
Ophthalmic artery	6
Anterior cerebral artery and pericallosal artery	6
Basilar artery	4
Total	141

distal bifurcation of the middle cerebral artery. Only one third of all aneurysms examined were located at the other arteries of the Circle of WILLIS, or the vertebro-basilar system.

Results

The outer cell-layers of the aneurysmatic vessel-wall are consistuted of the arachnoid and the tunica adventitia. Both are characterized by fibroblasts and bundles of ccllagen fibrilles. They could not be differentiated. Inside this connective tissue, blood vessels are often coated by necrotic endothelial cells. Only in cases of anterior communicating artery aneurysms and middle cerebral artery aneurysms are the outer layers of the aneurysm sometimes additionally constituted of brain tissue (Fig. 1). A network of glial fibres can be observed, separated from the connective tissue by one or two basement membranes.

There is no exact border between the tunica adventitia and the tunica media. The so-called modified myocytes have infiltrated the connective tissue. These cells are called modified because they are verse to normal contractile myocytes in number and shape, as well as in electron density and cytoplasm content (Fig. 2). The number of organelles is increased inside the cytoplasm. The myofilaments are displaced to the cytoplasm membrane. The rough endoplasmic reticulum is enlarged. In several specimens the surrounding basement membrane of the myocytes is splitted. Probably, following cell death the membrane is reconstructed again and again by new cells. This interpretation is corroborated by separated basement membranes without cellular content. The intercellular space contains not only so-called ground substances of the arterial wall, but also collagen fibrilles. However, these are not arranged in bundles described inside the connective tissue.

Only about half of the specimens examined had an internal elastic lamina. In case of a nearly intact lamina, the tunica media is well preserved. The preservation of the internal elastic lamina does not depend on the presence of an endothelial cell layer. Figure 3a demonstrates the tunica intima of an anterior communicating artery aneurysm. The splitted internal elastic lamina is covered only by an incomplete endothelial cell layer. Coating by endothelial cells is rare in cases of anterior communicating artery aneurysms, having been observed only

in 17 aneurysms of this localisation. On the other hand, in cases of middle cerebral artery aneurysms and endothelial cell-layer can be demonstrated in 20 vessel walls. However, the internal elastic lamina is more destructed than in other cases (Fig. 3b).

Each aneurysm contains erythrocytes inside all layers of the damaged vessel-wall as described above.

Discussion

Cerebral berry-aneurysms, systematically studies by electron microscopy, render following results:

Depending on the localisation of the aneurysms, there are differences between the inner and outer layer of the damaged vessel wall. In anterior communicating artery aneurysms and middle cerebral artery aneurysms, brain tissue is incorporated into the wall of the aneurysm. This can be explained by the lack of room in this areas, which does not allow expansion of the damaged vessel wall without destruction of the neighbouring brain tissue. This is repaired by astrocytic proliferation.

The varied condition of the internal elastic lamina in all aneurysms probably indicates the different stages of destruction of the elastic lamina. On the other hand, it can be explained by different causes damaging the vessel wall before the aneurysm is formed. CAJANDER and HASSLER (1976) have demonstrated enzymatic destruction of the elastic lamella at the neck of aneurysms. However STAUBESAND (1976) had demonstrated extracellular lysosomes inside mechanically damaged vessel walls. By this way, the presence of extracellular lysosomes is part of the uniform tissue reaction of the damaged vessel wall, and not a specific cause of aneurysm. Taking into account the reendothelisation only in middle cerebral artery aneurysms, the different conditions of the elastic laminae probably demonstrates that after the initial damage to the vessel wall, middle verebral artery aneurysm need more time than anterior communicating artery aneurysms to cause clinical symptoms. Additionally, the lack of endothelial cells in cases of anterior communicating artery aneurysms can be explained by mechanical factors. HASSLER (1961) rebuilt the typical areas of aneurysms localisation by using silicon-coated tubes. He found the hardest destruction of the silicon-coat following perfusion of the tubes in the area of the anterior communicating artery. This can explain the loss of endothelial cells in the anterior communicating artery aneurysms. However, it is not a satisfying explanation for the reendothelisation in middle cerebral artery aneurysms.

Inside the tunica media there are no essential differences in the pathological changes. All changes can be explained by the uniform tissue reaction of the damaged vessel wall. This tissue reaction is characterized by the change of the contractile myocytes into modified myocytes with mesenchymal functions, caused by the blood plasma penetrating following damage of the endothelial cells (KNIERIEM, 1970; MASSMANN, 1973; RIEDE and STAUBESAND, 1977). However, the list of causes of damage to the endothelial cells is innumerable. Some lead to widening of the vessel, others are repaired without symptoms (MEYERMANN, 1979).

The penetrating blood is demonstrated by erythrocytes in all layers of the aneurysmatic vessel walls. It can be assumed that blood reaches the subarachnoid space by this route without clinical symptoms.

Systematic studies of cerebral berry aneurysms provide additional information about the development of the pathological changes inside the vessel wall. However, these studies have to be completed by the development of an animal model to understand the time relations necessary for development of an aneurysm. Studying the aneurysms obtained at surgery as well as animal studies, are the two ways by which the morphologist can help the neurosurgeons to solve the clinical problems of prognosis and treatment.

Summary

The most successful treatment of cerebral berry aneurysms by surgical exclusion of the aneurysm from circulation has decreased the possibility to study these pathologically changed vessel walls by morphological methods. On the other hand, the improvement of surgical techniques provides the chance of removing the isolated berry aneurysms. By this way 141 berry cerebral aneurysms were studied by electron microscopy. The great number of examined aneurysms renders clear that different localization at the intracranial arteries leads to different ultrastructural changes in the damaged vessel wall. On the other hand, a uniform factor causative of the pathological changes can not be demonstrated. This is due to the fact that the damaged tissue of the vessel wall always reacts in the same manner, independently of the inducing process, which is hidden by the uniform tissue reaction when the pathologically changed vessel causes clinical symptoms and comes to morphological examination.

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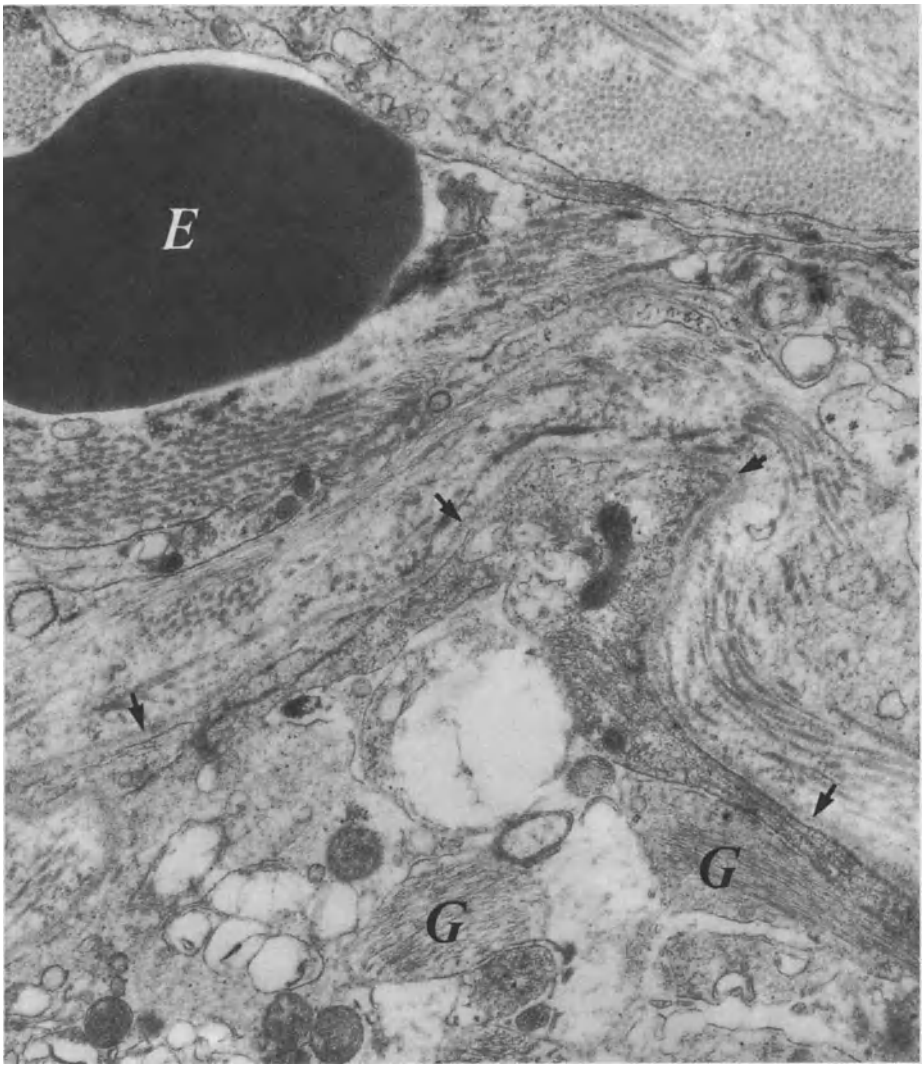

Fig. 1. Anterior communicating artery aneurysm. Inside the outer layer of the aneurysmatic vessel wall a network of glial fibres (G) is incorporated. The normal basement membrane of the brain tissue (arrows) separates the adjacent connective tissue of the arachnoid. E demonstrates an erythrocyte between the bundles of collagen fibrilles. Uranyl acetate. X 24,000

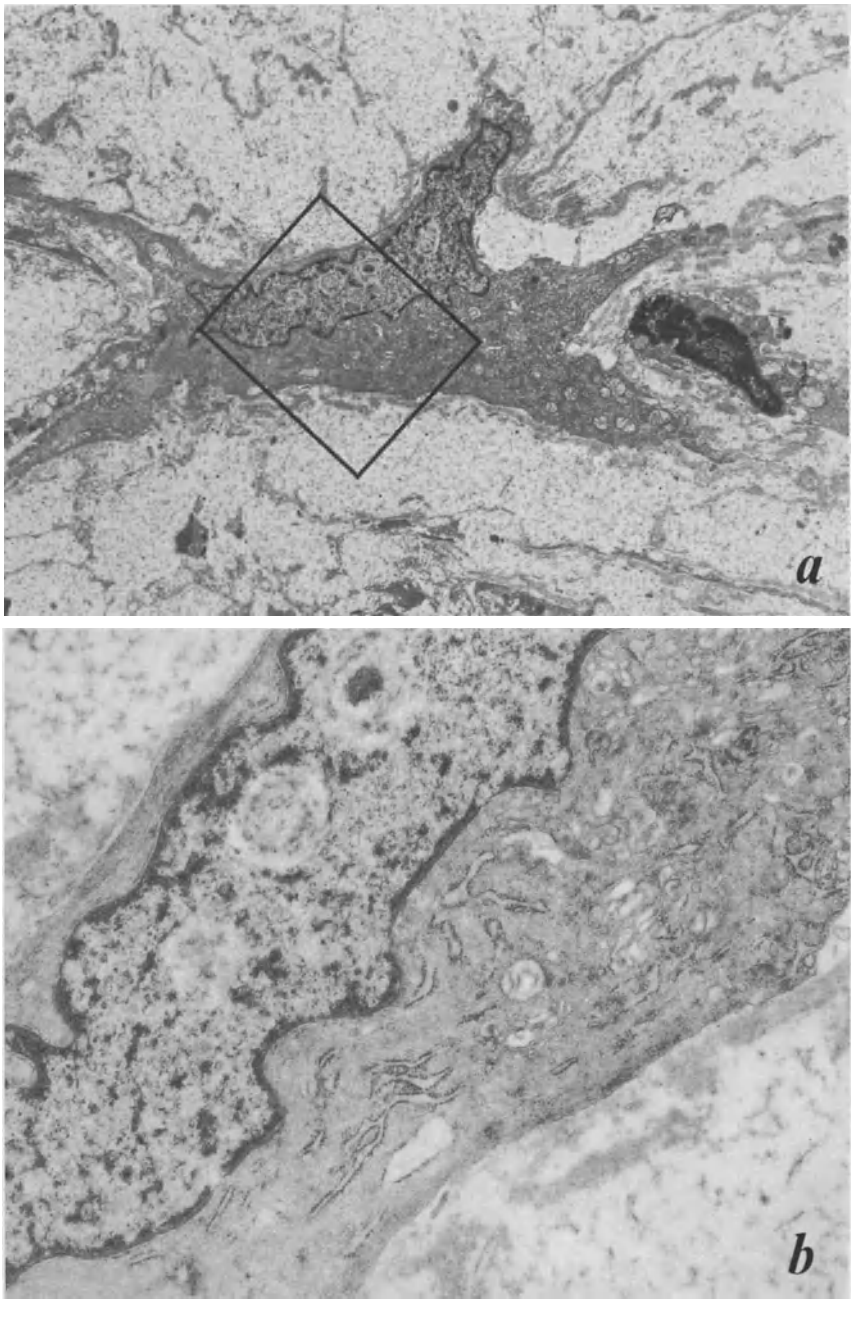

Fig. 2a,b. Internal carotid artery aneurysm. A typical large star-shaped modified myocyte with an increased number of cytoplasmic organelles, an enlarged endoplasmic reticulum and a decreased number of myofilaments. Uranyl acetate. a X 4750; b X 20,000

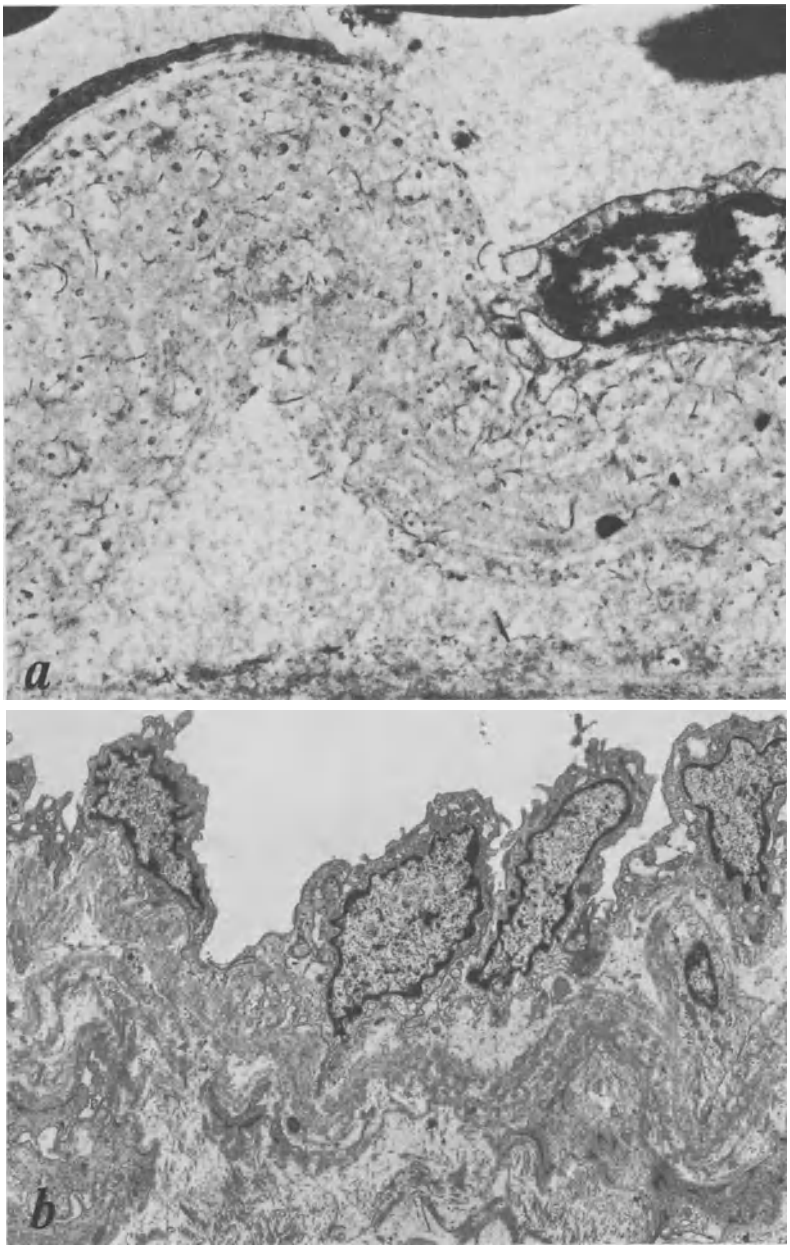

Fig. 3. a Anterior communicating artery aneurysm. Necrotic endothelial cells over a splitted and partially destructed internal elastic lamina. Uranly acetate. X 24,000. b Middle cerebral artery aneurysm. The closed endothelial cell-layer is located over a reticular basement membrane. The internal elastic lamina is nearly completely destroyed. Uranyl acetate. X 5,700

Theoretical Aspects and Therapeutical Concepts in Cerebro-Vascular Spasms After Subarachnoid Hemorrhage

A. HARTMANN

Additionally to acute communicating hydrocephalus and intracerebral hemorrhage cerebral vasospasms are only one of the major factors complicating the acute course of patients suffering from subarachnoid hemorrhage (SAH). At present it is well recognized that vasospasms might influence the outcome of these patients. The incidence of vasospasms following SAH ranges from 30-65%, depending on time of angiography, neurosurgical intervention and definition of vascular spasms (9).

Vascular constriction results in increase of vascular resistance and reduction of regional cerebral blood flow. Whether this decrease of blood flow leads to clinical symptoms and signs depends on the following parameters:

1. localisation of spasms in functional important or substitutional tissue,
2. development of collaterals,
3. ability of post-spastic vessels to autoregulate, i.e. to dilate and, thus, increase regional flow,
4. characteristics of the blood itself: reduction of viscosity improves blood flow and is able to neutralize the narrowing of the artery.

This may explain why only part of the patients presenting with excessive vasoconstriction on angiography shows clinical signs and symptoms corresponding to the spasms (Fig. 1).

This short review focuses only on hypotheses regarding the nature of spasms in subarachnoid hemorrhage and on concepts of therapy.

Cerebral vasoconstriction is an energy consuming process and not due to compression of small vessels. The depolarization in response to excitatory stimuli (such as mechanical irritation) or agents depends on the cytoplasmic concentration of free calcium, which determines the actomyosin ATPase activity. Extracellular and intracellular (protein-bound) calcium contributes towards activation of the contractile state by supporting free calcium (the "Activator Calcium") in the sarcoplasmic reticulum (24). The amount of free intracellular calcium available thus regulates the intensity of vascular constriction.

From the theoretical point of view, it should be possible to alter the diameter of arterial vessels by interfering with the calcium-storage or transport system between the extra- and intracellular compartments. ALPHA-adrenergic stimulation leads to release of intracellular calcium, which, then, is replenished by the extracellular pool (Fig. 2). Verapamil and other calcium-antagonistic inhibitors of excitation-contraction coupling result in peripheral vasodilatation by interfering with membrane calcium permeability (24).

It is not known whether the (debatable) effect of ALPHA-adrenergic blocking agents on cerebral vessels is due to their action on calcium-availability or to other factors, and it is not known whether Verapamil has in vivo effects on cerebral vessels under physiologic or pathophysiologic conditions.

Whereas the mechanism of physiologic concentration is well known, less has been evaluated about the relaxation of vascular systems. It is suggested that this is governed by lowering the level of "Activator Calcium" by different mechanisms:

1. energy-consuming pumping of intracellular calcium against the concentration gradient to the extracellular storage side,
2. binding of "Activator Calcium" to protein bound intracellular calcium or sarcoplasmic reticulum,
3. inhibition of extracellular calcium-influx.

BETA-adrenergic receptors might act as relaxation receptors on the cell membrane. The stimulation of these parts, for instance by isoproterenol, causes an increase in cyclic AMP via activation of adenyl cyclase (1, 2, 14) (Fig. 3). Cyclic AMP is broken down by phosphodiesterase.

Two therapeutic concepts are derived from this model:

1. Phosphodiesterase inhibitors such as papaverine, theophylline, caffeine, diazoxide or aminophylline are able to cause vaosidilatation by topic application. However, intracisternal or systemic administration of all of these substances results in severe arterial hypotension before the spasmolytic effect becomes evident (8). In the presence of damaged autoregulation this decrease of cerebral perfusion pressure might then cause more harm than vasodilatation does cause advantages.
2. Isoproterenol and other BETA-adrenergic stimulators lead to vasodilatation. Whereas the aforementioned phosphodiesterase-inhibitors cause increased cyclic AMP-turnover by inhibition of its degradation, stimulators of BETA-adrenergic receptors activate the formation of cyclic AMP by ATP (Fig. 3). This results in activation of specific phosphorylases with consecutive reduction of calcium-permeability (19). Topic application of isoproterenol relieves experimental vasospasms (20). This experience led to a concept followed by SUNDT and coworkers (22, 23). Of 30 patients with recognized vasospasms after SAH, 22 were considered to be considerably improved by repeated therapy with 0.4 to 0.8 mg isoproterenol in 150 ml 5% glucose for 8 h and 2 g lidocaine-hydrochloride in 450 ml 5% glucose plus 20 mEq potassium for 24 h. Lidocaine is given to prevent cardiac arrhythmias by the BETA-stimulator. CBF-studies and angiographic controls were not done. Before this procedure can be introduced into clinical practice, a controlled study with angiography and Xenon 133-studies has to be performed. FLAMM and coworkers used a slightly different regimen (5): isoproterenol (125 µg/h) and the canthine-derivative aminophylline as a phosphodiesterase-inhibitor (125 mg/h) are given as a continuous infusion up to 14 days in patients with spasm. Fifteen out of 27 cases improved. Angiography and Xenon 133-studies were not done routinely.

Some drugs which lead to vascular dilatation without interfering with the cyclic AMP system have been shown to relief experimental spasms: procaine, isordil, cyclospasmol, isosuxiprine, chlorpromazine, and nitroprusside (9). All these drugs are contraindicated in clinical therapy of spasms since they produce significant hypotension prior to spasmolysis.

CO_2, as a very potent cerebral vasodilator, has no effect on spasms and causes intracerebral steal. It should not be used against vasospasm (17).

According to the concept of KOSNICK and HUNT (10), artificial elevation of blood pressure by excess of blood to the intravascular system results in disappearance of neurological symptoms due to spasm. This overflow is dangerous in patients with unclipped aneurysms but is recommended by the authors after neurosurgical intervention if spasms occur. Expansion of intravascular volume also can be achieved by administration of low molecular dextrane, which, in addition, lowers viscosity. It has to be kept in mind that at the same time inhibition of platelet aggregation might favor rebleeding. In our opinion it is worthwhile to infuse low molecular dextrane in patients who develop spasms and correlated symptomatology after the aneurysm has been clipped.

All concepts mentioned so far derive from knowledge about the physiology of vascular smooth muscle. The following part deals with hypotheses based on chemical factors involved in the development of spasms.

The most spasmogenic among the blood constituents are the platelets. The role of their norepinephrine and epinephrine is not clarified as regards spasmogenesis. However, it is argued that local denervation of cerebral arteries following SAH results in reduced re-uptake of these catecholamines into presynaptic terminals (16) and increased concentration of catecholamines at local sites, leading to vasospasm. Therapeutic approaches with noradrenergic antagonists resulted in controversial conclusions. Whereas ALPHA-adrenergic blocking agents relieve spasms if applied topically (7), intracisternal or intraarterial (carotid artery) injection did not lead to convincing results (6, 12). Our own studies with the long-action blocker phenoxybenzamine showed some relief of spasms on angiography but no significant improvement of hemispheric blood flow (13). On the light of present experience, the author would not recommend either phenoxybenzamine or the short-action agent of this group, phentolamine. Both substances are not only noradrenergic blocking agents, but blockers of serotonin receptors as well. The spasmogenic potency of serotonin is well established (18, 25). Pretreatment with serotonin antagonist, such as kanamycin or reserpine, prevent development of vasospasm after SAH (26). ZERVAS claims that he was able to prevent development of late spasms by combined treatment with reserpine and kanamycin in a randomized study in patients with ruptured aneurysms. This regimen was not applied to patients who already had developed spasms (n:21).

Other serotonin inhibitors, such as the naturally occuring ergot alkaloids or methysergide, are more vasoconstrictive than spasmolytic. Thus, at present there is no convincing hypothesis for therapeutic approaches to counteract the strong spasmogenic effect of serotonin.

Research of the last years indicates that prostaglandins from platelets and brain tissue might play one of the key-roles in the development of cerebral vasospasms (3, 11). Particularly the prostaglandins $F2_{alpha}$ and E2 are able to produce prolonged vasoconstriction (4, 25). Since E1 of the same group leads to vasodilatation, it was used in one experimental design (9). Prostaglandins have not been used in clinical trials. The newly discovered prostaglandin-vasodilator, prostacyclin, has significant effects on normal cerebral and peripheral vascular regulation but has not been studied well enough to be introduced into clinical research. Breakdown products of erythrocytes might become important also (15).

Despite the fact that tremendous efforts have been undertaken to solve pathophysiological and biochemical questions in correlation to cerebral vasospasms, it must be conceded that, at the time of meeting, the cause of acute spasms has become clear. Nevertheless, late or prolonged spasms are still a mystery. Most of the therapeutic concepts have not convincingly proven their beneficial action. There is no regimen commonly accepted.

What we still lack is a substance which
1. has minimal side effects,
2. acts on prolonged, already existing spasms,
3. leaves normal, functioning cerebral vessels uninfluenced.

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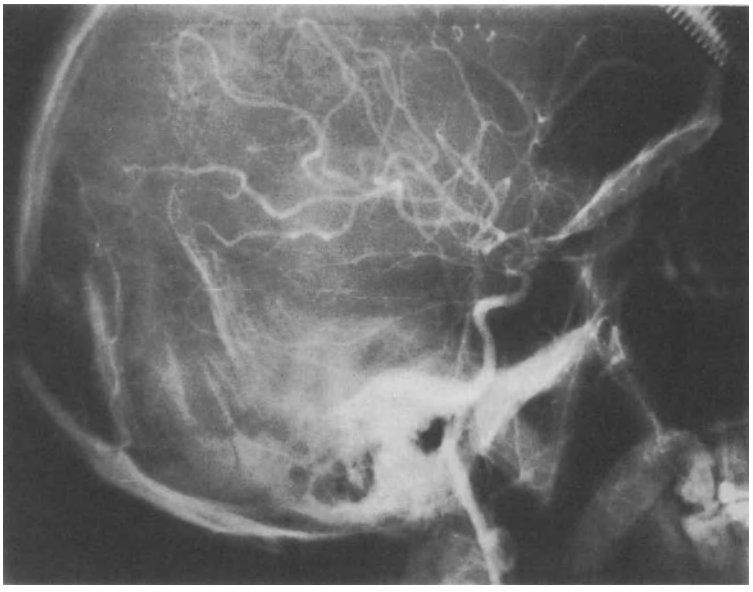

Fig. 1. Cerebral vasospasms. Angiography 8 days after SAH. Regional vasospasm at the base of the brain did not result in any clinical symptoms. The postspastic vessels are normally filled. Xenon 133-studies revealed normal perfusion

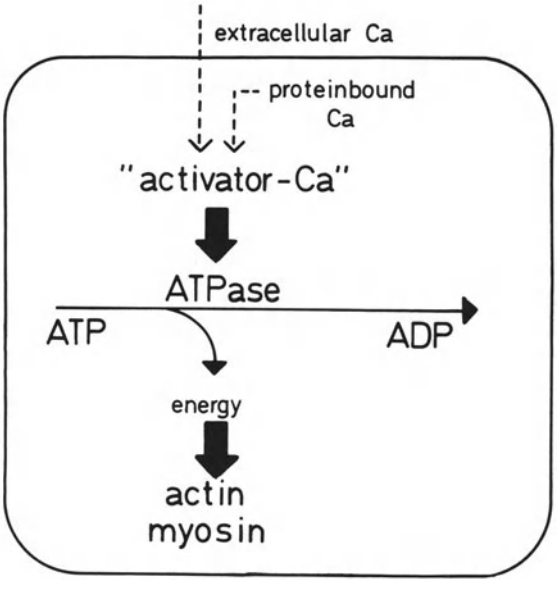

Fig. 2. Calcium and smooth muscle contraction. The intracellular free calcium ("Activator Calcium") is important for energy-dependent actomyosin-action. "Activator-Calcium" is closely correlated to the intracellular protein-bound calcium and to extracellular calcium. Interference with this balance influences actomyosin-action and, thus, vascular diameter

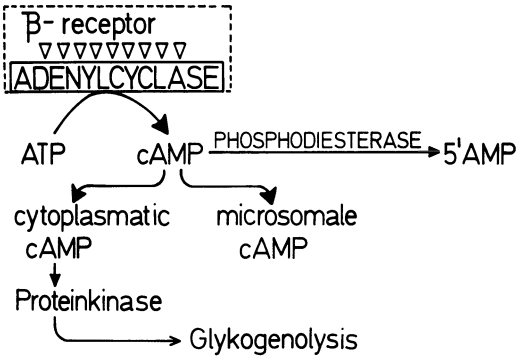

Fig. 3. Cyclic AMP-system and smooth muscle action. Increase in cyclic AMP reduces calcium permeability via activation of specific phosphorylases (not shown) and increased binding of proteinbound calcium by increase of microsomal cyclic AMP. This results in vascular smooth muscle relaxation. Increase in concentration of cyclic AMP can be achieved by BETA-adrenergic receptor stimulation (stimulation of adenylcyclase) or inhibition of phosphodiesterase

Early Operation of Ruptured Cerebral Aneurysms: The Role of Norepinephrine in Subarachnoid Hemorrhage and in Experimental Vasospasm

T. SHIGENO, K. MORI, I. SAITO, K. SANO, and M. BROCK

Introduction

It is now widely accepted that subarachnoid blood following aneurysm rupture plays a major role in the development of vasospasm. Then, *early surgery* with extensive removal of subarachnoid blood may have an advantage for the prevention of vasospasm. However, exact mechanisms to explain vasospasm have not been determined and are believed to be multifactorial. We are reporting on one of those factors, the adrenergic activity, by measuring *norepinephrine* (NE) concentrations in cerebrospinal fluid (CSF) from patients submitted to early aneurysm surgery, as well as by examining the arterial response to NE in *experimental vasospasm*.

Material, Methods and Results

Of 19 patients who underwent direct operation for ruptured aneurysms, 17 were operated upon within two weeks after subarachnoid hemorrhage (SAH) (1). Twelve were operated on within 3 days after SAH, prior to the occurrence of vasospasm. Most treated patients were in grade II or III according to HUNT (6), some being in grade IV, particularly those with intracerebral hematoma. Vasospasm appeared in 13 patients, in most of them postoperatively, and was divided into three patterns; type 1: local; type 2: multisegmental; type 3: diffuse. Our previous studies indicated that these patterns of vasospasm were closely related to prognosis (14, 15).

In cases of early operation, CSF was continuously drained for several days following surgery, through a catheter left in the basal cistern following operation. If intracranial pressure (ICP) was above 15 mm Hg, continuous drainage of ventricular fluid was carried out (16).

When surgery was performed prior to the occurrence of vasospasm, there was tendency to less severe vasospasm, presumably due to extensive removal of subarachnoid blood.

Ventricular, basal cisternal and lumbar CSF was collected in all of these patients at different desired intervals, according to the presence or absence of vasospasm. Concentrations of NE in CSF were determined using a newly developed automated fluorometric method for highly sensitive determinations of the order of 1 pg/ml (10).

In all three sites of CSF sampling, the values increased with the appearance of vasospasm, especially in cisternal CSF (Fig. 2). This was more clearly demonstrated when the pooled values were plotted according to the site of CSF sampling, showing that cisternal CSF contained significantly higher NE (0.246 $\pm$ 0.049 s.e. ng/ml, $p<0.001$)

in the presence of vasospasm. However, the increase was twofold or threefold, which is not considered to be a value high enough to constrict the cerebral artery, without presuming an increased sensitivity to NE in the arteries exposed to SAH.

To clarify the above points, the following experiments were carried out, consisting of two different sets of in vivo experiments. In the first animal model, arterial response to experimental vasospasm was directly observed. In rabbits, basilar artery was exposed transclivally 24 hours after SAH by injection of autologous blood into the cisterna magna (Fig. 3). Immediately after removal of subarachnoid blood from around the artery, vasospasm was always observed (5 animals). Thereafter, the basilar artery was irrigated with artificial CSF at 37^{o} C, leading to resolution of vasospasm to varying degrees. Then a series of molar concentrations between $1x10^{-10}$ and 10^{-2} of 1-norepinephrine hydrochloride (Sigma), dissolved in artificial CSF, was applied to the exposed basilar artery in a graded manner beginning with a low concentration. There was, however, no demonstrable concentration in the artery, which had shown vasospasm previously.

In an additional series of 6 rabbits, angiographic observations were performed using a new cisternal perfusion model. Blood induced vasospasm was caused through a transorbital intracisternal catheter. Twenty-four hours after SAH, bilateral retrograde axillary angiography revealed spasm of the basilar artery (Fig. 4). Then, artificial CSF was perfused through the cisternal catheter, by opening the cisterna magna without raising ICP. This procedure resulted in vasodilatation in most of the animals, if it was found at autopsy that the subarachnoid blood was successfully removed. However, subsequent perfusion with NE in different concentrations caused no recurrence of vasospasm.

Discussion

Vasospasm is one of the most important factors affecting prognosis of patients in the acute stage of SAH. There is still some argument about timing of aneurysm surgery, particularly in relation to the presence or absence of vasospasm. In our clinical experience, vasospasm was never observed angiographically within three days after SAH. Thereafter it begins to develop, always accompanying a variety of clinical manifestations (14, 15). Early surgery combined with cisternal drainage within three days after SAH partly prevents the progression of vasopsasm, because its primary cause is subarachnoid blood in contact with cerebral arteries.

Although many vasoactive substances have been proposed as a pathogenic factor in the development of vasospasm, NE still holds its value related to the sympathetic nervous system activity (4). Indirect evidence of the adrenergic hyperactivity following SAH, such as systolic hypertension and electrocardiographic changes, has been documented (5).

In contrast, there is little direct evidence, except for measurements of catecholamines in plasma and lumbar CSF associated with vasospasm, revealing a close relationship between higher content of NE and the presence of vasospasm (1, 2, 9, 12). However, until recently, there has been no report on a significant increase of NE concentration in cisternal CSF around the circle of WILLIS.

Therefore it is questionable, if such an adrenergic hyperactivity causes vasospasm or if it is only a direct result of SAH. There have been extensive studies on the cerebral arterial response to NE (18, 19). The concentration of NE in CSF found in patients with vasospasm, however, seemed to be far below those reported to produce significant vasoconstriction. This fact points forwards another possible mechanism in the pathogenesis of vasospasm, i.e., *denervation hypersensitivity*, meaning that the spastic artery is hypersensitive to low concentration of NE.

The presence of adrenergic nerve endings in the cerebral arteries of many species is well documented (3, 7, 11, 13). However, the pathophysiological significance of this innervation has not clearly been established. In denervation studies by IWAYAMA et al. (7), disappearance of NE fluorescence or degenerative chqnges on electron microscopy appeared as early as 24 h and were completed within 48 h. In experimental SAH, disappearance of fluorescence was also reported to occur in the very early period, lasting interference with the NE uptake mechanism leaves the receptor sites relatively unprotected or sensitized to NE circulating or locally present, i.e., prejunctional type of hypersensitivity (3, 13). This mechanism may readily explain the phenomenon of vasospasm in some aspects. First, prolonged vasospasm can be explained by the graudal progression of denervation following SAH. Second, the occurrence of diffuse vasospasm or its migration is readily explicable by a neural mechanism. Such an increased arterial sensitivity has already been observed in vitro following experimental SAH (8, 17). However, there has been no study using an in vivo model, and it is unknown whether such an increased contractile response in vitro corresponds to vasospasm. We observed no contractile response to any given NE concentration, although vasospasm was reversed by removing subarachnoid blood or irrigation with mock CSF, thus indicating the presence of vasoactive substances in the blood.

Conclusion

It is concluded that the sympathetic nervous system activity is increased in the presence of vasospasm, but that NE itself plays a minor role in the pathogenesis of vasospasm. However, irrigation of basal cisterns seems to prevent cerebral arterial spasm following early operation prior to its occurrence.

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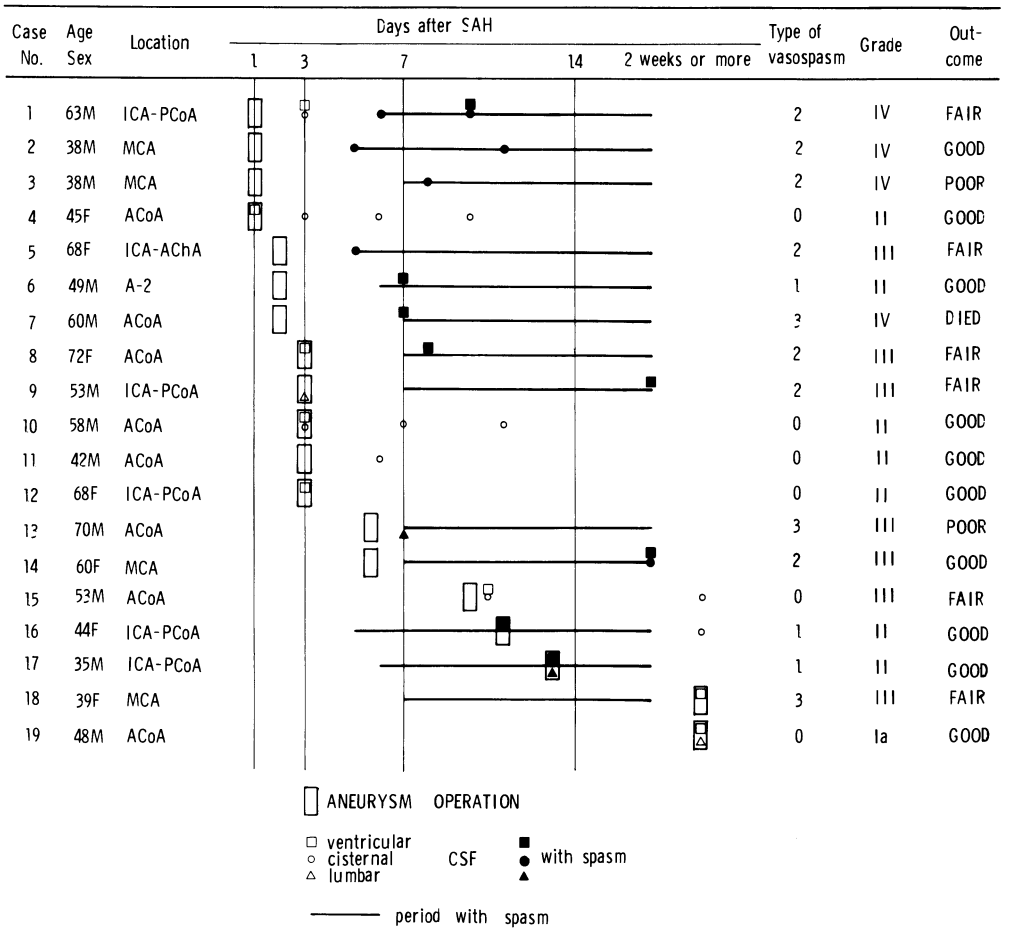


Fig. 1. Summary of the course in 19 patients and timing of CSF sampling for measurement of NE concentrations. Location of aneurysm: ICA = internal carotid artery; AChA = anterior choroidal artery; PCoA = posterior communicating cartery; MCA = middle cerebral artery; ACoA = anterior communicating artery; A-2 = portion of the anterior cerebral artery. Day 1 refers to the day of SAH. Type of vasospasm: 0 = absent; 1 = local; 2 = multisegmental; 3 = diffuse. Neurological grade: Hunt's grading at time of surgery

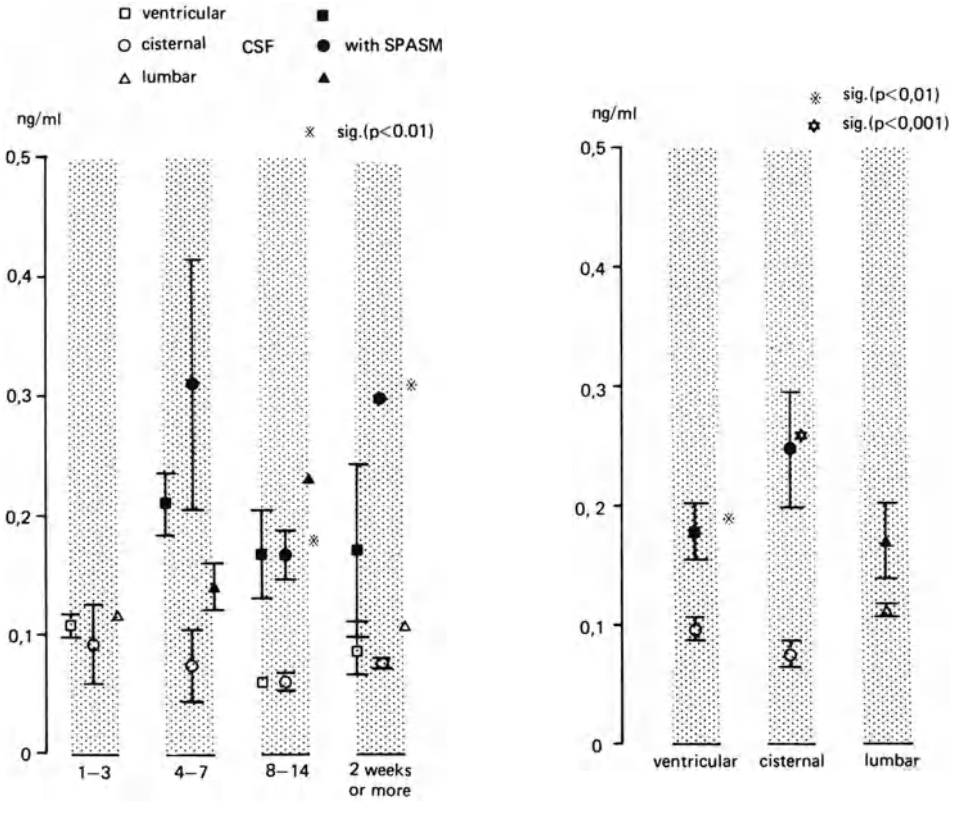


Fig. 2. Values of NE concentrations in CSF. *Left:* Changes according to days after SAH. *Right:* Pooled values according to the site of CSF sampling

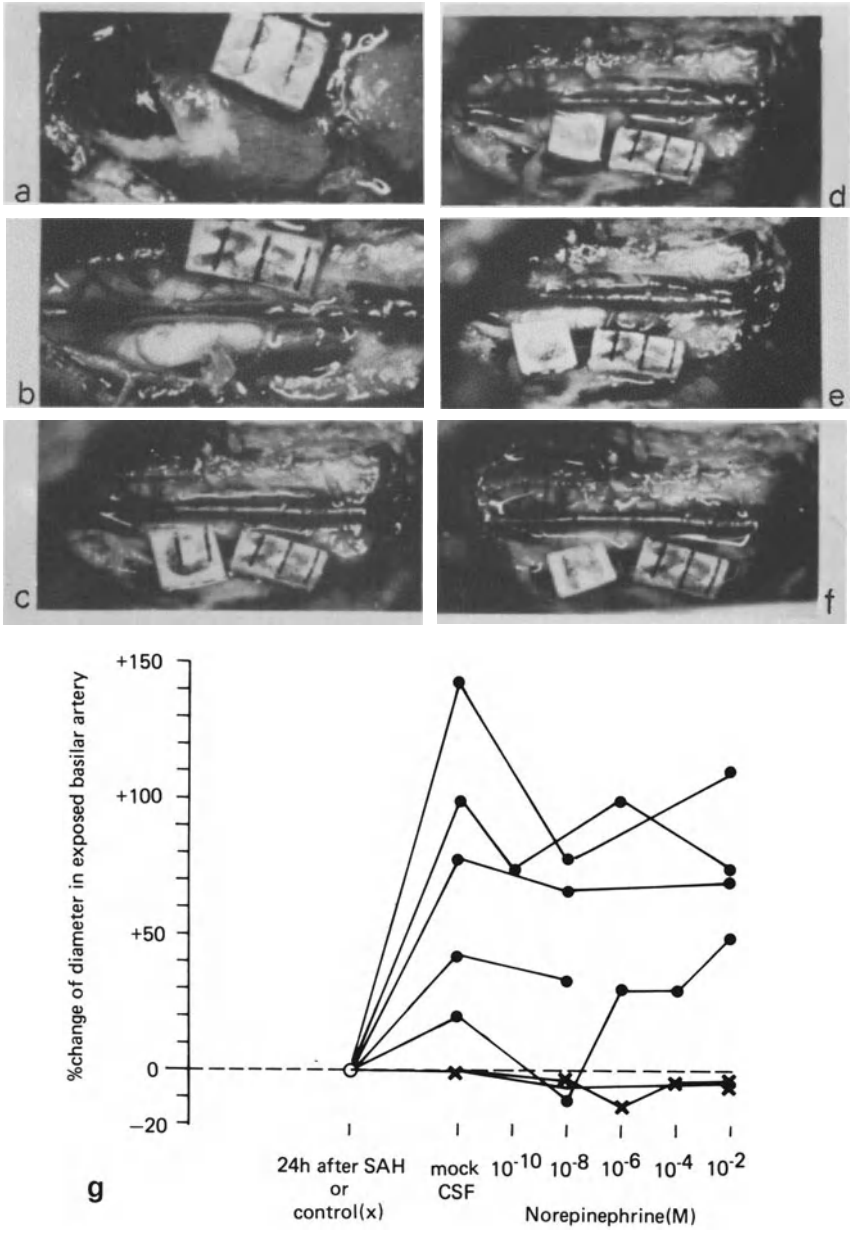
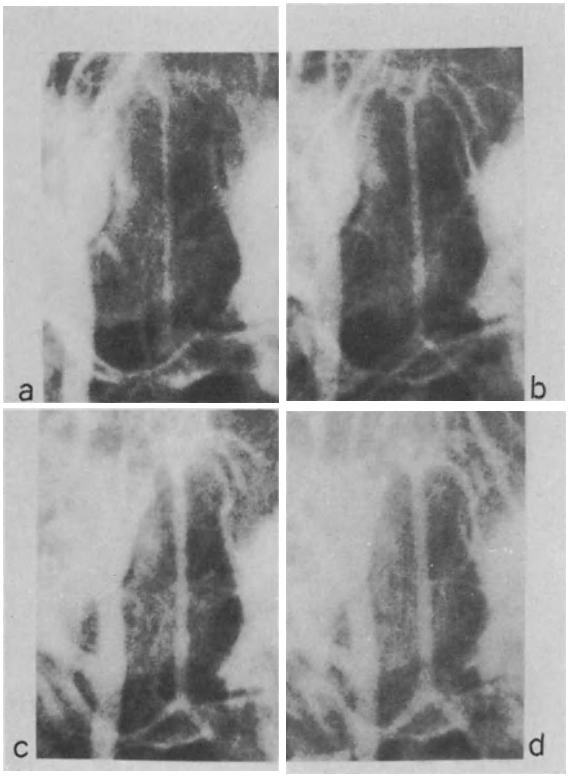


Fig. 3a-g. Direct observation of exposed basilar artery. a Subarachnoid blood beneath the dura mater 24 h after SAH; b vasospasm observed immediately after removal of blood; c reversal of vasospasm by irrigation with mock CSF; d no recontraction with application of NE ($1x10^{-9}$ M); e $1x10^{-4}$ M; f $1x10^{-2}$ M; g vascular response in 5 animals with vasospasm and 2 controls



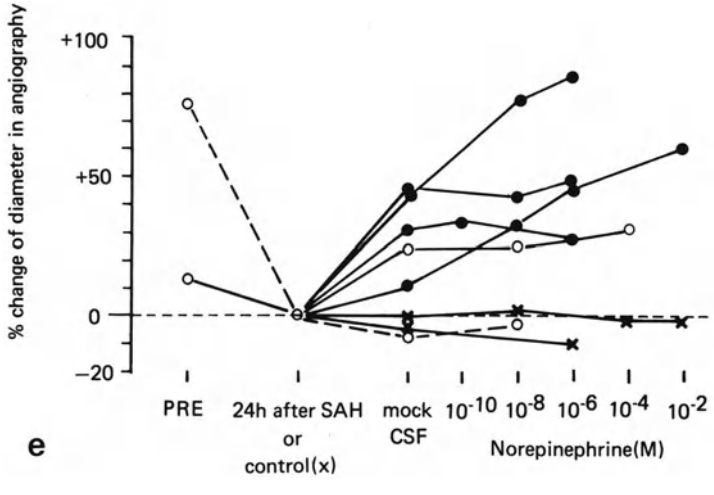


Fig. 4a-e. Angiographic observation. a Spasm of the basilar artery 24 h after SAH; b reversal of vasospasm following cisternal perfusion of mock CSF; c no recontraction with perfusion of NE ($1x10^{-8}$ M); d $1x10^{-4}$ M; e results of vascular response in 6 animals with vasospasm and 2 controls

Time Course and Clinical Significance of Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

J. HAMER, H. PENZHOLZ, and B. GÖTTE

Introduction

Within the first week following an aneurysmal bleeding, recurrent rupture and vasospasm with cerebral infarction and consecutive brain swelling are the most threatening dangers. To prevent a second subarachnoid hemorrhage (SAH), early clipping of the aneurysm has been advocated for those patients who are conscious, oriented and without severe neurological disturbances corresponding to grade I and II of the scale of HUNT and HESS (6). On the other hand, operation in the presence of cerebral vasospasm carries high risk and a markedly increased morbidity and mortality (1, 5, 9). Therefore, the clinical significance of angiospasm must be considered for the timing of operation. The present investigation contributes to the questions concerning incidence and time-course of cerebral vasospasm as well as the relationship between the degree of vasoconstriction and clinical grading.

Selection of Patients and Methods

This study includes 130 patients with an angiographically proven cerebral aneurysm (58 aneurysms of the anterior communicating artery, 44 infraclinoidal and posterior aneurysms, 25 of the middle cerebral artery and 3 of the vertebral-basilar junction). Depending on early and delayed referral of the patients to the neurosurgical department, panangiography was carried out between the first day and three weeks after the initial hemorrhage. 37 patients (29%) underwent angiography within the first 3 days, 50 (39%) between the 4th and 12th day, and 43 (33%) at the end of the second and in the third week. Cerebral vasospasm was classified into 3 groups according to previous investigations of SANO and SAITO (9): Type I represents diffuse angiospasm of both the basal and peripheral cerebral arteries, type II the multisegmental and type III the local vasospasm. The corresponding clinical findings at the time of angiography were correlated with the grading scale I-V of HUNT and HESS (6).

Results

Fortynine patients (38%) showed cerebral vasospasm. Type I was observed in 8 cases (6%), type II in 24 (19%) and type III in 17 patients (13%). Table 1 demonstrates that the rupture of a media aneurysm is more likely to be accompanied by vasoreactive constriction than bleeding of aneurysms with another localization. As to the distribution of the 3 types of vasospasm, there is no significant difference for the various sites of aneurysms. Table 2 shows that cerebral vasospasm occurs - in about 60% of all cases - in the middle and at the end of the first week

Table 1. Vasospasm and site of aneurysm

	No. of spasm	Vasospasm	Type I	Type II	Type III
Ant. comm. artery aneurysm n = 58	35	23 (40%)	4	8	11
Middle cerebral artery n = 25	13	12 (48%)	2	7	3
Internal carotid artery aneurysm and post. comm. artery aneurysm n = 44	30	14 (32%)	2	9	3
Vertebral and basilar artery aneurysm n = 3	3	-			

Table 2. Manifestation of vasospasm

Days since SAH	No. of patients	Vasospasm	Type I	Type II	Type III
1 - 3	37	8 (22%)	4	2	2
4 - 12	50	30 (60%)	3	16	11
13 - 21	43	11 (25%)	1	6	4

after primary SAH, and that the incidence of angiospasm is much lower versus the second and the third week. Diffuse vasospasm, the most dangerous type of vasoconstriction, however, appears mainly during the first days after aneurysmal bleeding: In 4 out of 8 patients, this type of angiospasm was observed in the first 3 days, versus 4 patients out of 41 with arterial spasm during the following two and a half weeks. Table 3 demonstrates that no patient with type I was clinically grade I or II, whereas about 50% of those patients with multisegmental or local vasospasm had no severe neurological symptoms. However, the morbidity in these cases was higher than in the group *without* vasoconstriction, where 73% of the patients were grade I or II. Among 130 cases, 9 patients (7%) died preoperatively due to recurring hemorrhage: Recurrent rupture occurred in 3 patients within the first 3 days after initial SAH, in 4 cases between the 4th and 12th day and in 2 during the third week.

Table 3. Clinical grading and vasospasm

Grade	No. of vasospasm n = 81	Type I n = 8	Type II n = 24	Type III n = 17
I	31	-	3	8
II	28	-	10	2
III	18	4	9	6
IV	4[a]	4	2	1

[a] Two patients with intracerebral hematoma.

Discussion

In larger clinical series, the incidence of cerebral vasospasm after rupture of an arterial aneurysm has been reported to be 35-40% (2, 7). The present findings are, thus, in good agreement with the observations of other neurosurgeons. Of more particular interest for timing of operation are, however, the *type* and the *time course* of vasospasm. Vasospasm occurs mainly in the middle and at the end of the first week after SAH and is then found in more than 50% of all cases. BERGVAL and GALERA (3) observed, in 70 patients, an incidence of 64% between the 6th and 12th day. WEIR et al. (10) reported a rate of 61% among 293 patients, and SANO and SAITO (9) found a frequency of 66% among 443 cases. Diffuse vasospasm is always accompanied with severe neurological symptoms some hours or few days after SAH. The more frequent types of multisegmental and local angiospasm are not necessarily linked with clinical disturbances. Here, additional pathophysiological factors such as low blood pressure, cardiopulmonary disturbances and paralysis of cerebral autoregulation may play an important role.

It has often been emphasized that cerebral vasospasm is elicited by spasmogenic substances which are released into the cerebrospinal fluid by the break-down of red blood cells during the first days after subarachnoid hemorrhage. This might explain why cerebral vasospasm occurs with some latency after the initial bleeding. These considerations and experiences with postoperative angiospasm have led Japanese neurosurgeons to a modified concept for timing of craniotomy: Whenever possible, operation with clipping of the aneurysm and washing out the blood from the basal cisterns should be performed within the first 3 days after primary bleeding. If this very early period has been surpassed, craniotomy should be intentionally postponed into the second week. In a large group of neurosurgical patients, HORI and SUZUKI (5) have shown that operative mortality was 4% between the 8th and 14th day. It rose, however, to 19% in cases operated on within the first 7 days after initial SAH. The main cause for this markedly raised lethality was postoperative vasospasm. Similar results have been previously reported by other neurosurgeons (1, 9). On the other hand, the risk of early fatal bleeding must be weighed against the rate of operative mortality due to ischemic brain swelling. In the largest clinical series of conservatively treated patients with aneurysmal SAH (4, 8), the mortality rate for recurrent rupture has been 4-6% for the first week after hemorrhage. Our findings are very consistent with these figures. Considering the present observations and the results of other neurosurgeons, there are good reasons to accept the Japanese concept for timing of operation.

Conclusion

Cerebral vasospasm is a very common phenomenon following aneurysmal SAH. Angiospasm occurs mainly in the middle and at the end of the first week after the initial bleeding. Therefore, very early angiography may not reveal spasm, and the possible danger of ischemic brain swelling may not be appropriately taken into account. Diffuse vasospasm is always accompanied by severe neurological disturbances. Local and multisegmental vasoconstriction has a somewhat better prognosis, but, nevertheless, marked clinical symptoms are here more frequent than in cases without vasospasm. The present results support the Japanese concept for timing of operation with either a very early clipping within the first 3 days or with an intentionally delayed craniotomy during the second week after primary hemorrhage.

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Clinical Importance of Vascular Spasms After Subarachnoid Hemorrhage

J. NEUMANN

In the last years a great number of papers has been published on the influence of angiographic vasospasm after subarachnoid hemorrhage (SAH). The opinions are still controverse, some authors finding them to be the cause of severe cerebral ischemia and postoperative complications, others considering them meaningless for the timing of operation (1, 2, 3, 4, 5).

We reviewed 94 cases which died in the course of the disease with or without operation and correlated the clinical angiographic and necropsy findings.

Clinical Findings

There was no predominance of one sex, the age peak was 50 years. Neurological deficits were seldom. When occulomotor paresis was present, the cause was mostly an aneurysm of the internal carotid artery. Nearly all patients with vasospasms in the arteriogram were conscious on admission, with a more or less severe organic psychosyndrome (grade I or II). Only a few were unconscious or comatous (grade III to IV).

Arteriography

Fifty angiograms of patients who later underwent autopsy were reviewed. Most aneurysms were located in the anterior part of the circle of WILLIS (Table 1). They were usually small, only two being of the giant type. Half of the cases showed typical vasospasms (obvious reduction of vessel caliber involving the segments in the vincinity of the aneurysm). Figure 1 shows the timing of angiograms in the presence of vasospasm.

Table 1

A. com. a.	39%	(n = 64)
ICA, ACA, MCA (left side)	27%	(n = 44)
ICA, ACA, MCA (right side)	25%	(n = 42)
Multiple	5%	(n = 9)
Other location	4%	(n = 7)

Spasms can be found immediately following SAH, but more often after the second day. This indicates that they may need some time to develop. They can be demonstrated up to three weeks after SAH. There is no dependence from the age of a patient.

In this connection, it is remarkable that we did not find any source of bleeding in 25% of our patients who underwent angiography because of SAH, but we saw vasospasms.

Pathomorphological Findings (gross examination)

Out of 94 patients 47 underwent aneurysm surgery. The cause of death was mostly cerebral (Table 2). Only y few patients came to death because of complications others than cerebral. Twenty-five patients showed no spasms at the time of angiography (Fig. 2). Thirteen of them underwent surgery. Ten had a postoperative brain infarction, which led to herniation. In some cases the neuropathologist could demonstrate the clip on the supplying vessel. One additional patient had an intracerebral hematoma, two others died because of a solitary intracerebral hematoma and could not be saved by means of an operation. One patient died during the operation.

The 12 remaining cases were not operated on. Ten died because of a space-occupying intracerebral hematoma, in six of them the blood penetrated the ventricular system. One patient died due to edema, another showed no cerebral cause.

Twenty-five other patients had vascular spasms in the angiograms. Thirteen of them underwent operation and died in the further course. Eight had vast brain infarctions, involving the territories of the ACA or MCA.

Six times the area of infarction was that of the aneurysm-bearing artery. In one patient an intracerebral hematoma was additionally present, and in one case there was a MCA thrombosis due to arteriosclerosis and a clipped AComA aneurysm.

Two other cases died because of other postoperative complications: one had an epidural hematoma in the posterior fossa, another had severe edema. No cerebral cause was found in two patients. One died 17 days after surgery, from an intraventricular hemorrhage.

Twelve patients with spasms at the time of angiography were not operated on. Eight died because of sequelae of the hemorrhage (space occupying lesion, intraventricular penetration, edema). Three had infarctions in the area of the aneurysm-bearing artery. One of them, addi-

Table 2. Gross findings at autopsy

a) Infarction,ACA, MCA	23 (8)
b) Intracerebral hematoma with penetration into the ventricles	9 (18)
c) Intracranial hematoma	1 (10)
d) Edema due to SAH, herniation	5 (9)
e) No cerebral cause	6 (1)

Operated and (not operated) patients.

tionally, had a space-occupying hemorrhage. One died because of infarction as a complication of arteriography.

In three cases an aneurysm was not demonstrated prior to autopsy:

1. Aneurysm of the ICA, severe spasms, death after a second hemorrhage several months later.
2. AComA aneurysm, angiogram not available, death one month after SAH, infarction (ACA).
3. AComA aneurysm, severe spasms, death 11 days after SAH.

Discussion

We reexamined the causes of death in our aneurysm patients operated and not operated on. Patients who died after surgery more often had a large infarction in the area of a major vessel regardless if there were spasms present or not. We regard this as a complication of surgery.

In 3 patients we found brain infarctions despite the fact that they were not operated on. This finding may be related to the hemorrhage and/or spasm, since all of them had severe spasms.

Most patients who did not have surgery died because of herniation due to the cerebral hemorrhage, there being no relation to spasm. In some cases we could not find the aneurysm on the angiogram, a fact which might be caused by spasms.

Serotonin and a certain type of prostaglandine liberated from the thrombocytes of the clot are accused to be the cause for vascular spasms (6, 7, 8). This is in agreement with the fact that in our patients without spasm and without operation we found preferrably an intracerebral hematoma without spreading of blood into the subarachnoid space.

The time when spasms are to be seen widely overlays with the time of the highest danger of a second hemorrhage. To wait until spasms are naturally resolved may therefore be harmful. We consider the ischemic complications to be rather an (undesired) effect of operation than the sequela of spasm. Spasms cause no defined clinical picture (9, 10). They are only an angiographic finding, and should not be overestimated for the timing of surgery.

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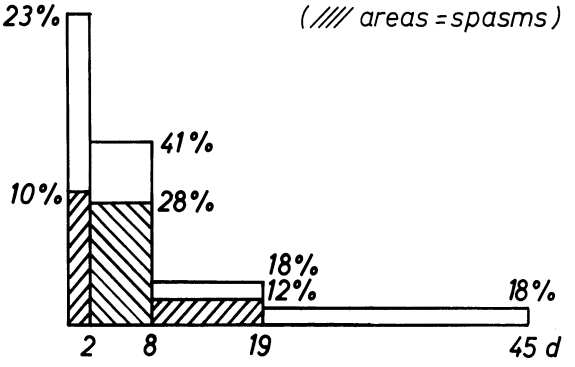

Fig. 1. Time of angiography and presence of spasms

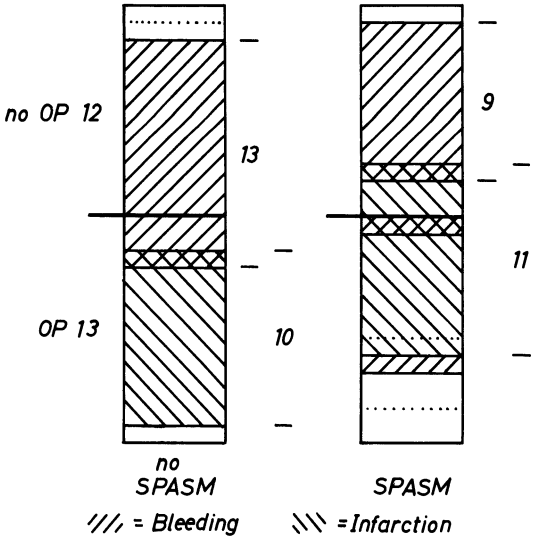

Fig. 2. Operated and not operated patients with and without spasms, cause of death. There is a slight increase of deaths because of infarcts in the group with spasms

Therapeutic Considerations on Vasospasm in the Aneurysm Patient

H. TANNENBAUM, M. NADJMI, P. GRUSS, and J. BOCKHORN

Introduction

Spasm of cerebral vessels represents a dangerous complication of aneurysmatic subarachnoid hemorrhage. Large-scale statistic studies have cited the frequency of vasospasm to be in the range of 15-40%, whereby 8% of patients suffer postoperative vasospasm, accompanied by various degrees of neurologic deficit. The exact causes of this phenomenon remain unclear, although alterations of the cerebrospinal fluid (CSF) within the basal cisterns, caused by the presence of blood and its breakdown products, appear to play an important role. In the regions supplied by the involved vessels vasospasm causes ischemia proportional to its severity. Surgical treatment of an aneurysm is incapable of influencing the accompanying vasospasm. Vasospasm disappears spontaneously following restoration of a normal CSF. An operation should be performed only when the additional trauma of surgery does not exceed the vascular compensation mechanisms of the brain.

Material and Approach

During the past ten years 209 aneurysms have been treated at the Neurosurgical Clinic of the University of Würzburg. Evaluation of possible vasospastic alterations was based on clinical findings, angiography, computerized axial tomography (CT) and measurements of regional cerebral blood flow (rCBF)[1].

Case Reports

Case I, preoperative spasm: The patient was a 38 year-old female with a left-sided aneurysm of the middle cerebral artery accompanied by speech disturbances and right-sided hemihypesthesia. The angiogram revealed spastic fluctuations in vessel diameter and CAT scan revealed a luxury perfusion in the teritory of the left middle cerebral artery (Fig. 1). After the clinical signs of ischemia had disappeared, a control CAT scan showed no abnormal findings. Surgery was subsequently performed. There were no postoperative complications nor was there evidence of vasospasm.

Case II, postoperative spasm: The patient was a 31 year-old female who had gone through two episodes of hemorrhage from a right-sided anterior communicating aneurysm. During the preoperative period there was no clinical or CAT-evidence of vasospastic ischemia. The aneurysm was clipped following a right-sided subfrontal exposure. Postoperatively

1 The rCBF measurements were supported by the "Stiftung Volkswagenwerk".

the patient was conscious and responsed to verbal communication. No neurologic deficits were noted. On the second postoperative day the patient became obtunded and developed aphasia and pronounced right-sided hemiparesis. The CAT scan (Fig. 2) revealed two areas of ischemia; one in the right fronto-parietal region, the other in the left temporo-parietal region. After treatment involving barbiturate sedation, anti-edematous medication, volume-substitution and administration of low molecular weight dextranes, the patient's condition improved considerably. Hemiparesis had decreased, and the patient's level of consciousness improved. Control CAT two weeks later showed no improvement in relation to the clinical picture. The patient made a complete recovery after two years. CAT scan at this time still clearly exhibited the regions which had sustained infarction.

Case III, postoperative spasm: The patient was a 45 year-old male with an anterior communicating aneurysm who had sustained two hemorrhagic episodes. He did not present any preoperative neurologic defict. The preoperative CAT scan revealed the presence of blood in the basal cisterns but no evidence of ischemia.

Clipping of the aneurysm was performed via a left subfrontal approach. On the fourth postoperative day the patient was awake, fully conscious and had no motor deficits. He then became increasingly somnolent and presented a right-sided hemiparesis. A CAT scan depicted a zone of ischemia in the left fronto-parietal region which extended to the median plane (Fig. 3). Measurement of rCBF revealed a marked decrease in perfusion and a focal pathologic finding in the region of the left anterior cerebral artery. Due to the severity of the course of the illness, treatment with a Ca-antagonist was attempted. One hour after oral administration of the substance, a bilateral 10% increase in blood flow was recorded. The foacl pathologic finding in the left anterior region, however, remained (Fig. 4). One week later CAT revealed that the ischemic zone had expanded despite all therapeutic measures. The patient died three weeks later.

Discussion

Although the exact causal mechanism of vasospasm remains unclear, the clinical consequences are often severe. Sevéreal modalities of treatment exist with variable degrees of effectiveness. The vasic therapeutic goal is to limit the extent and degree of damage caused by ischemia due to vessel spasm, and to keep neurologic deficit to a minimum so as to favor reversibility.

Regarding therapeutic regimens, we recommend sedation with barbiturates with simultaneous assisted ventilation, anti-edematous medication, volume stabilization and monitored administration of low molecular weight dextranes. We also recommend the monitoring of intracranial pressure, CAT controls and measurement of rCBF. Depending upon the patient and the indication, careful trials with vasoactive substances may be attempted.

The CAT scan, in particular, has proven to be a great aid in the evaluation of the patient since it is a non-invasive procedure which places no additional burden on the vascular system, and which may be repeated with greater frequency than angiographic studies. In the CAT vasospasm as a zone of ischemia which corresponds to the anatomical region supplied by the vasospastic vessels. As a rule, this zone is seen as a hypodense focus. Less frequently, vasospasm appears as luxury perfusion after the administration of contrast media (Fig. 1, 2, 3).

CAT often also offers information concerning the amount and distribution of blood in the subarachnoid space (1, 2, 3, 4).

Conclusion

In accordance with previous findings and results, vasospasm appears to be due to pathologic alterations of CSF in the basal cisterns, initiated by subarachnoidal hemorrhage. Primary neurosurgical treatment is not able to alleviate acute vasospasm. A self-healing tendency is apparent upon restoration of a normal CSF. Recovery is impeded either by leakage or by a further episode of subarachnoid hemorrhage. The proper time to perform surgery is determined by the facts outlined above. The initial treatment of vasospasm, therefore, remains symptomatic to ensure best possible protection against ischemia of the brain.

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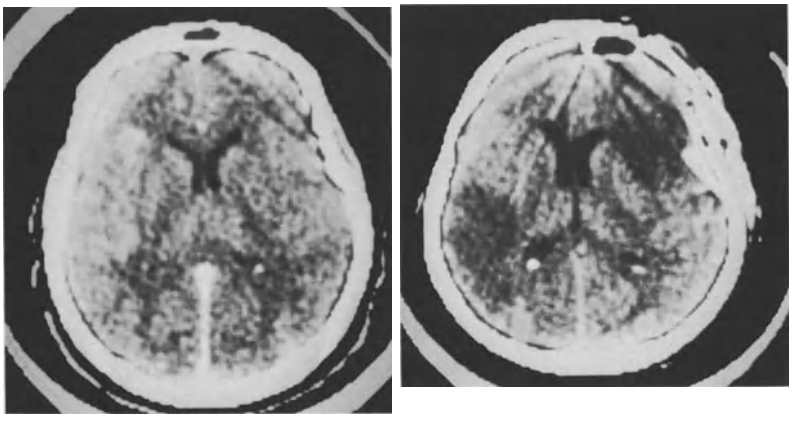

Fig. 1. *Left:* "Luxury perfusion" in the territory of the left middle cerebral artery after administration of contrast media (case I)

Fig. 2. *Right:* Postoperative vasospasm with two areas of ischemia, one in the right fronto-parietal region, the other in the left temporo-parietal region (case II)

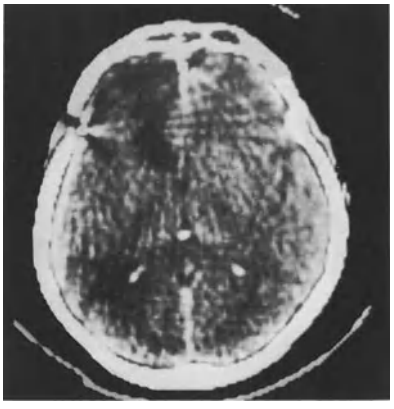

Fig. 3. Postoperative vasospasm: a zone of ischemia in the left fronto-parietal region extending to the median plane (case III)

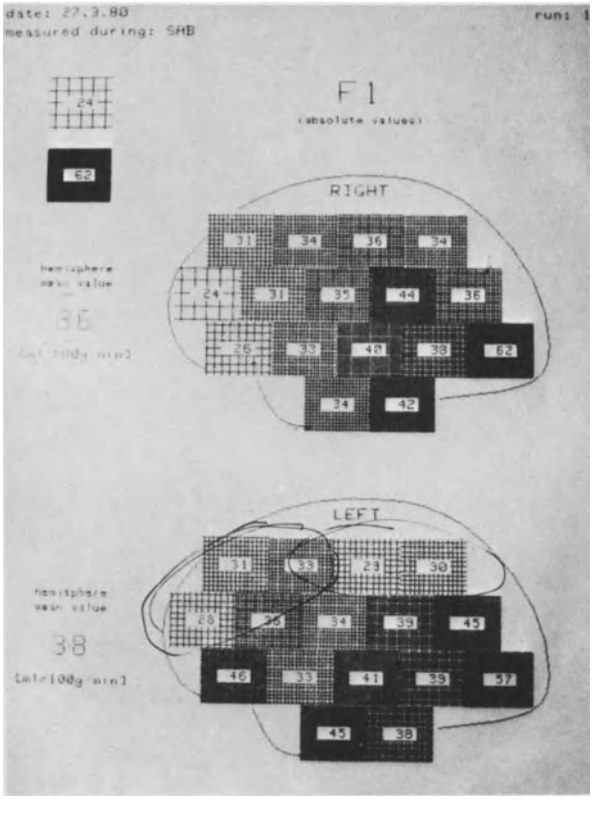

Fig. 4. Measurement of rCBF in a case of postoperative vasospasm. Marked decrease in perfusion and a focal pathological finding in the region of the left anterior cerebral artery (case III)

Biochemical and Clinical Alterations in the Presence of Spasm of Cerebral Arterial Aneurysms

H. KOSTRON, K. TWERDY, and J. FISCHER

Introduction

Diagnosis, therapy and timing of operation of intracranial aneurysms have already been discussed and an agreement been reached. Less known are the biochemical changes which initiate vasospasm. In a previous paper (4) we suggested to subdivide the vasospasm into three phases based on biochemical and morphological facts: (1) acute biochemical, (2) prolonged biochemical morphological, (3) chronic morphological. This method seems to be the best for drawing therapeutic conclusions. Furthermore we summarized the stages of the spasm into a scheme depending on the most effective stimulation present. Naturally all the phases do not show clear time limitations.

We examined in 124 patients, operated upon for cerebral aneurysms as regards preoperative conditions, vasospasm and postoperative outcome (5). Preexisting generalized vasospasm with neurologic deficit (BOTTFRELL grading) leads to bad operative results (Table 1). Also young patients show a higher tendency to vasospasm and brain edema.

Results and Discussion

The following assumption is based on preliminary results of our clinical investigations. Further work is being performed to prove the proposed facts.

First, a short outline of the vasoconstricting mechanism of vasospasm: contraction is modulated by the Guanylat-Cyclase-System through noradrenergic transmitters, dilatation by the Adenylat-Cyclase-System through cholinergic and purinergic transmitters. Vasoconstricting substances, which occur under pathologic circumstances, (i.e. 5-Hydroxytryptophan (5-HT), Prostaglandin, Histamine, Kinines, Norepinephrine (NE)) act mainly on direct receptors in the vessel wall and with

Table 1. Postoperative outcome of 124 patients, operated on for cerebral arterial aneurysms within the last 10 years

	Generalized spasm (%)	Without spasm (%)
Died	48	6
With neurological deficit	31	14
No neurological deficit	21	80

some stimulation of cGMP (Fig. 1). In most instances the initial moment for the spasm is a mechanic trauma such as the rupture of an aneurysm, or head injury with tweezing and stretching of the basal arteries. This trauma can also be the direct surgical manipulation of the vessel. The neuromuscular junction is damaged by trauma and the neurotransmitter NE is set free causing acute localized vasospasm. This is the reason for the supersensitivity of this part of the vessel, so that further spasmogenic factors derived from blood and platelet disaggregation can cause the spasm and are responsible for the prolonged vasospasm. At the same time endothelial micro-lesions are set where platelet aggregation takes place, which in its turn also causes high concentration of vasoconstricting factor. This acute phase, which may last for one hour to one day, is followed by the prolonged phase, caused mainly by Dopamine released from brain tissue and above mentioned substances. The first morphological changes, necrosis of the smooth muscle cell, can be found within hours. Spasm lasting longer causes further necrosis with fibrosis of the media and endothelium, which blocks the dilatating system. This fibrosis is the expression of the destruction of the physiological structures, the increase of metabolites and reduced nutrition of the vessel's wall. At this point of spasm the enzymes regulating dilatation and constriction, Adenylat-Cyclase and Guanylat-Cyclase show the same concentration as in the normal vessel. This means that the chronic spasm is only based on morphological changes of the vessel wall.

The clinical appearance of vasospasm is varied. Spasm causes a temporary functional stenosis followed by underperfusion of the corresponding brain area. Initially spasm changes only the biochemistry of the vessel wall, spasm lasting longer causes neurologic deficit and disturbances of metabolism of brain tissue. The neurologic symptoms depend upon localization, time and generalization of the vasospasm, and may vary from a short unconsciousness to dysfunction of brain areas and death. We have also seen spasm without neurologic deficit. The reflex action of the central adrenergic neurons which follows the initial trauma causes ischemia by vasospasm affecting mainly the parenchymatons vessels, according to the localization of these adrenergic neurons. Naturally this ischemia causes the most marked effect on the basal structures.

The correlation between clinic and biochemistry is difficult. The BOTTERELL grading does not always show a positive correlation to the concentration of spasmogenic factors in blood and cerebrospinal fluid (CSF) (Table 2). During the acute phase of spasm, NE is localized mainly in the vessel wall. But in the advanced stages of vasospasm, in the prolonged and chronic form, and also in the presence of increased intracranial pressure (ICP), we find extremely high concentrations of catecholamines (3). In the prolonged form of spasm, high concentration of vasoconstricting agents can be measured, caused by ischemia and disaggregation of blood and platelets. Ischemia produces free radicals and causes disturbances of the cell membranes and release of cytotoxic enzymes. This is followed by brain edema and high ICP. As a form of repair mechanism, Dopamine will be released by brain tissue to stabilize the cell membranes. But Dopamine itself now affects directly the presensitized vessel and, on the other hand, is synthisized by Dopamin-Beta-Hydroxylase (DBH) to NE (1). Depending on the degree of ischemia, the concentration of Tryptophan, which is a precursor for 5-HT, is raised in CSF (6). The function of this release of 5-HT is not yet known. Serotonic neurons are possibly involved. Also, the level of Homovanillic-Acid and Hydroxyindolacetic-Acid is increased as sign of the higher activity of biogenic amines (2). The catecholamines NE and Epinephrine show a positive correlation to ICP (3). Thus, chronic

Table 2. Spasmogens in relation to spasm and clinical condition. Norepinephrine (NE), 5-Hydroxytryptamine (5-HT), prostaglandins (PG), intracranial pressure (ICP)

	NA	5-HT	PG	Histamin	Free radicales	Dopamin	ICP
Acute phase 1-24 h	+++	---	---	---	---	---	---
Prolonged phase 4-8 d	++	+++	++	++	++	+++	++-+++
Chronic phase 10 d -	+++	---	---	---	---	+	++
BOTTERELL-grades:							
I	---	---	---	---	---	---	---
II	+	+	---	++	---	+	+
III	+++	+++	++	++	---	+++	++
IV	+++	---	---	---	+++	+++	+++

spasm results from the high catecholamine concentration caused by the raised ICP. It seems raised ICP is not the primary reason for the chronic spasm. This conclusion may also be drawn from morphologic changes, which are similar to those associated with Pheochromozytoma, Tetanus and the Apallic Syndrome.

Further spasmogenic factors result from the synthesis of Prostaglandines from Arachidonic Acid and from the breakdown to Thromboxan. Thromboxan and prostaglandines react as vasoconstrictors only in combination with other spasmogenic factors.

Surgery and exposure of the vessel and the aneurysm, even when done as carefully as possible, always causes biochemical changes of the brain tissue and release of various spasmogenic substances, mainly Dopamin. Iatrogenic subarachnoid bleeding (SAB) leads, again, to disaggregation of blood and platelets. The advantage of an early operation with washing of the SAB and prevention of further blood disintegration must be considered alternatively with all the above mentioned consequences. To avoid the potentiating effect of the new trauma one should wait for desensibilisation of the vessel and normalization of blood and CSF.

The main guideline should be the neurologic condition of the patient. The biochemical normalization can hardly be determined since the normal values, for example of catecholamines and 5-HT, show a high individual variation. However, these values correlate with the clinical improvement and can be ascribed prognostic value.

Conclusion

There is no perfect correlation between biochemical and clinical datas in patients with SAB, except in cases of severe neurologic deficit. Presensitization by rupture of the aneurysm, which causes the supersensitivity of the vessel wall to all following vasoconstricting substances, is necessary for spasm to take place. Due to this, biochemical values and the clinical condition should be normalized prior to operation, which, in itself constitutes a renewed trauma to the vessel and produces spasmogens again.

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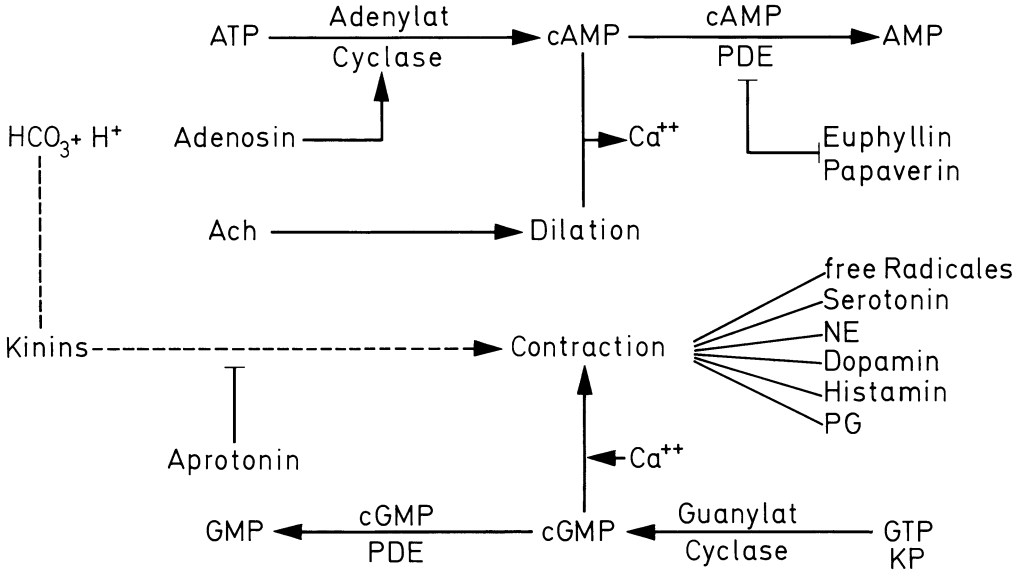

Fig. 1. Physiological and pathophysiological mechanisms of dilation and constriction. Adenointriphosphate (ATP), Adenosinmonophosphate (AMP), Guanointriphosphate (GTP), Guanosinmonophosphate (GMP), Kreatinphosphate (KP), cAMP-Phosphodiesterase (cAMPPDE), cGMP-Phosphodiesterase (cGMPPDE)

Enhanced Fibrinolytic Activity in Patients with Subarachnoid Hemorrhage

E. OTT, G. BERTHA, G. LADURNER, K. MARGUC, and H. LECHNER

Introduction

The most common causes of subarachnoid hemorrhage (SAH) are ruptured intracranial aneurysms, arterio-venous malformation and cranio-cerebral trauma. However, the percentage of unattributable cases of SAH varies between 20% and 50% (4). On the other hand indicators of activated fibrinolysis such as high levels of fibrinogen degradation products (FDP) have been found in the cerebrospinal fluid (CSF) of patients with SAH and it has been suggested that enhanced fibrinolytic activity (EFA) may be one of the many possible causes of rebleeding (1, 2, 7).

The present investigation describes fibrinolytic mechanisms in patients with SAH due to ruptured intracranial aneurysms and in those, in whom no cause of the SAH could be detected at angiography. Preliminary results of this study have been reported previously (6).

Patients and Methods

In 32 patients (8 males, 24 females) with a mean age of 54 years (range 38-65) who were admitted because of clinical symptoms due to SAH, the evidence of enhanced fibrinolytic activity (EFA) was 2-4 days following the onset of the acute symptomatology using the fibrin stabilizing factor (FSF), fibrin degradation products (FDP), antithrombin III (AT III), fibrinogen and platelet numbers as indicators. Clinical diagnoses have been verified in all patients by CSF lumbar puncture and by cerebral four vessel angiography. The laboratory techniques for estimating EFA have been described elsewhere (5).

On the basis of the laboratory findings, two groups of patients with SAH were distinguished: 21 patients with SAH and EFA and 11 patients with SAH and normal fibrinolytic activity. The values thus obtained in the patients with SAH were compared to those found in 20 patients of comparable age and sex distribution with recent cerebral ischemic infarction. At the time of the laboratory examinations, none of the patients received antifibrinolytic treatment.

Results

As can be seen on Table 1 normal fibrinolytic activity (NFA) was evident in 11 patients with SAH but was found to be enhanced (EFA) in 21 patients with SAH when compared to the control patients. Patients with EFA tended to have lower fibrinogen levels and platelet numbers than patients with NFA (Table 2). It can be noted from Table 3 that in patients with SAH and EFA there was a high incidence of normal

Table 1. Normal (NFA) and enhanced fibrinolytic activity (EFA) in patients with SAH

	FSF (%)	FSP (µg/ml)	AT III (mg/100 ml)
SAH - NFA (n=11)	85.7 ± 9.8	4.1 ± 0.6	22.3 ± 1.2
SAH - EFA (n=21)	55.8 ± 7.3[a]	7.8 ± 2.1[a]	30.4 ± 2.8[b]
Control group (n=20)	90.0 ± 9.5	2.4 ± 0.8	24.6 ± 1.0

[a] $p < 0.05$. [b] $p < 0.01$.

Table 2. Fibrinogen levels and numbers of platelets in patients with SAH and normal (NFA) or enhanced (EFA) fibrinolytic activity

	Fibrinogen (mg/100 ml)	Platelets (10^3)
SAH - NFA (n=11)	375 ± 49	236 ± 34
SAH - EFA (n=21)	318 ± 38	218 ± 36
Control group (n=20)	350 ± 46	234 ± 33

Table 3. Angiographic findings in patients with SAH and normal (NFA) and enhanced (EFA) fibrinolytic activity

	Angiography	
	Positive	Negative
SAH - NFA (n=11)	11	0
SAH - EFA (n=21)	5	16[a]

[a] $p < 0.01$ (CHI-square Test).

angiograms whereas in all patients with SAH and NFA, cerebral four vessel angiography revealed a ruptured intracranial aneurysm as the cause of the bleeding.

Discussion

On the basis of the results presented in the present communication, it has been confirmed that EFA can be present in patients with SAH. There is no evidence to suggest that EFA might have been the sequel of SAH since 11 patients with SAH showed NFA although determinations of laboratory tests were performed in both groups of patients with SAH at comparable time intervals following SAH. Moreover, NFA was evident in patients with SAH due to ruptured intracranial aneurysms confirmed at angiography. On the other hand, it is a striking finding that in only 24% of the patients with SAH and EFA, the cause of the intracranial bleeding was detected by angiography whereas 76% of these patients had normal angiograms. However, it has to be admitted that cerebral angiography can miss microaneurysms or aneurysms which have already been occluded by a local thrombus.

Nevertheless, EFA in patients with SAH has also been reported by other investigators as a possible cause for rebleeding (1, 2, 7) so

that it can be concluded from the present results that in patients with SAH without angiographically verified aneurysms, EFA might have been the cause rather than the sequel of SAH.

Conclusion

The source of the bleeding in patients with SAH cannot always be detected by cerebral angiography. In these patients enhanced fibrinolytic activity should be considered as a possible cause of SAH.

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Grading and Timing of Operation of Cerebral Aneurysms

H. W. PIA

The progress in microsurgery, neuroanaesthesia, pre- and postoperative intensive care has resulted in a considerable improvement of the mortality and morbidity of cerebral aneurysms. The operation itself, therefore, became devoid of risks. This situation is reflected in the negligible mortality and morbidity in patients operated in grade I and II and with only 5% in patients in grade III. The importance of *primary and/or secondary impairment of cerebral function* following rupture of the aneurysm for the prognosis is particularly evident when considering the high mortality and morbidity of patients who are in grade IV and particularly in grade V (Table 1) (PIA et al., 1979 (2)). It remains unclear which prognostic effect, negative or positive, is brought about by the operation itself and what effect does the operation have upon the already existing cerebral lesions. Favourable therapeutic development led to the discussion about the *timing of operation*. In contrast to grading which generally reflects the degree of impairment of cerebral function, the two most important sequelae of aneurysm rupture, namely vasospam and secondary bleeding, cannot be measured and estimated exactly. Vasospasm and particularly rebleeding can be prevented through correctly timed, i.e. early operation. The serious consequences of vascular spasm and recurrent bleeding as well as the very limited help offered by conservative therapy are so well-known, that statistical evaluation does not seem necessary here.

Surgery of aneurysms has two aims: rapid therapy and prophylaxis. These aims cannot be achieved through the policy of *operation after an interval* of three weeks or later after the first bleeding. Excellent operative results of operations performed after such a long interval show only the positive side of the aneurysm surgery. A considerable number of patients, who represent the negative selection, died during this interval because of recurrent bleeding, vascular spasm and other sequelae of aneurysm rupture.

Consequently, the concept of *early operation* timed at the beginning of the second week after the first bleeding has been developed. This concept was accepted during the Symposium in Bad Nauheim in 1977 (PIA et al., 1979 (2)). It is a possible and realistic way of treatment and has been accepted as the optimum management for patients in grade I and II, with some restrictions for patients in grade III, but not for patients in grade IV and V. The concept was based on the fact that recurrent haemorrhages usually occur later and that stabilization of central regulation may be assumed approximately one week after the bleeding.

The *immediate operation* shortly after the haemorrhage is a further logical step in fulfilling the therapeutic and prophylactic aims. The elimination of the source of bleeding and removal of blood from the subarachnoid space seem to prevent the development of damaging

Table 1. Grade of risk and mortality

	Total	I	Deaths	II	Deaths	III	Deaths	IV	Deaths	V	Deaths
YASARGIL	505	124	1	155	1	140	3	74	8	12	7
GUIDETTI	200	70	-	50	4	35	4	30	8	15	10
PIA	261	84	1	84	1	58	4	28	8	2	2
SANO	403	252	5	69	3	49	4	27	4	6	5
SYMON	150	7	-	53	3	55	-	33	8	2	1
SUZUKI	1000	491	15	240	13	212	21	55	10	2	2
KEMPE	857	149	2	315	2	257	6	136	15	-	-
Total	3364	1177	24	966	27	806	42	383	61	39	27
			2%		2,8%		5,2%		15,9%		69,2%

phenomena of vascular spasm and recurrence of the haemorrhage. First series published (GUIDETTI (1), SANO (3), SUZUKI (4, 5)) seem to support the concept of immediate operation.

Our personal experience with immediate operation based on the policy of immediate referral of the patient with subarachnoid hemorrhage into a neurosurgical centre brought about questions and problems which should be discussed when speaking upon timing and grading of aneurysms.

The first result of such a policy was an increase in the number of not operated patients (Table 2). In the years 1953 till 1968, the number of such patients was small. These were patients who either refused the operation or in whom the surgery was considered to be technically not possible. Since 1969 the number of patients not operated upon increased considerably, particularly during the last three years. Closely related is the increase in early admissions (Table 3). In the last ten years early admissions constituted approximately one-third of patients with aneurysms. At present the percentage of patients admitted immediately after the haemorrhage increased to 40 per cent of all patient with aneurysms.

At present our policy is as follows: patients with subarachnoid hemorrhage in grade I, II and III have a computerized tomogram done on the day of their hemorrhage or admission, an angiography within 24 h and surgery is performed on the following day. An increasing number of patients in grade IV, particularly with intracerebral haematomas is now managed along the same lines.

Table 2. Cerebral aneurysms. Gießen 1953 - 1979 (n = 630)

			No operation			
			1953-1968		1969-1979	
	n	Operation	n	Dead	n	Dead
Internal carotid a.	185	149	12	1	24	10
Anterior cerebral a.	200	152	15	11	33	24
Middle cerebral a.	86	59	14	7	13	9
Vertebro-basilar a.	42	25	7	2	10	7
Multiple aneurysms	117 (58)	90 (31)	20 (7)	4	7 (3)	2
Total	630		55	25 45%	83	52 63%

Table 3. Time of admission (%)

	n	Immediately	1. Week	2. Week	3. Week	Later
1953-1968	152	11	14	11	14	50
1969-1979	320	19	12	16	10	43

Patients with two or more subarachnoid hemorrhages and with insufficient or inadequate angiographic examination as well as othe accompanying pathology present particular problems. In such patients the complication rate following angiography and surgery is relatively high and

the timing of investigations and surgery must be individually chosen. Location and size, as well as number of aneurysms are often the decisive factors and demand careful analysis in each individual case. Apart from these restrictions, I would like to present two cases representative for success and failure of the immediate operation.

Case 1: 40-year-old female patient R.U. 170939/882/1719/80 was admitted 48 hours after her first subarachnoid hemorrhage. Angiography had already been performed. It showed a ventro-cranial aneurysm of the anterior communicating artery and a second aneurysm at the junction of the pericallosal and calloso-marginal artery. Computer-tomography indicated a trace of blood in the right ambient cistern. Clinically - grade II. The patient was operated upon on the 4th day after her bleeding. Both the aneurysms were clipped. The postoperative course was uneventful and the angiogram performed 10 days later showed normal cerebral circulation (Fig. 1).

Case 2: 33-year-old female patient H.W. 150446/902/1756/80 was admitted 24 hours after her first subarachnoid hemorrhage. The angiogram showed a cranio-ventral aneurysm, 1.2 x 0.6 cm in diameter, of the anterior communicating artery and aplasia of the left A_1-segment of the anterior cerebral artery (Fig. 2a). Computerized tomography showed blood in the subarachnoid space (Fig. 2b). Clinically - grade II. Surgery on the 4th day after the bleeding. Uneventful clipping of the aneurysm. The patient recovered with delay from the anaesthesia and developed a bilateral infarction within the perfusion area of the anterior cerebral artery on the 3rd postoperative day, right-sided infarction in the area of the posterior cerebral artery and a secondary brain stem lesion. These caused the death of the patient within a few days (Fig. 2c).

In spite of the lack of vascular spasm in the preoperative angiograms, there is no doubt about extensive secondary spasm. It was also obvious that the timing of the operation influenced the development of this complication.

The analysis of 50 operations performed within the first week after the subarachnoid hemorrhage (Table 4) showed a relatively high operative mortality (20%) distributed over all days, similar to the other early results. The numbers are small, however, there is nothing to suggest that the operation performed after the third or fourth day is more dangerous. On the contrary, favourable postoperative courses are more frequent.

Table 4. Acute operation on cerebral aneurysms

	n	Results Excellent	Good	Fair	Poor	Dead	
1. Day	6	1	-	2	1	2	IV, III, IV
2. Day	10	2	4	2	-	2	IV, V
3. Day	8	5	-	2	-	1	V
4. Day	8	1	2	3	-	2	III, IV
5. Day	5	5	-	-	-	-	
6. Day	2	1	-	-	-	1	IV
7. Day	11	5	2	2	-	2	III, IV
Total	50	20	8	11	1	10	

Global analysis may lead to simplified and false conclusions such as in the analysis of immediate, early and late operations after 1, 2, 3 and more weeks after the bleeding (Table 5). In our material the largest number of bad, fair results, and cases of death, occur in patients operated in the first week. The figure of such results is smallest among patients operated in the third week after the bleeding and during the interval. The distribution of cases with excellent and good results showed an inverse proportion in this respect.

The relation between the *timing of operation and grade* upon the prognosis was analysed for the unfavourable results (Table 6). It appears that the grade of impairment of cerebral function is of greater importance for the prognosis than the timing of operation. Out of 37 patients in whom early results were fair, there was 1 patient in grade I, 6 patients in grade II, 18 patients in grade III and 9 patients in grade IV. Out of 14 patients who remained with severe deficits: 2 were originally in grade II, 7 in grade III, 5 in grade IV. Out of 27 patients who died, 1 was in grade V at the time of operation, 9 in grade IV, 11 in grade III and 6 patients in grade II.

Table 5. Timing of operation on cerebral aneurysms (%)

	n	Results Excellent	Good	Fair	Poor	Dead
1. Week	50	40	16	22	2	20
2. Week	45	49	29	11	3	8
3. Week	37	73	5	11	3	8
>3 Weeks	160	58	18	11	7	6
Total	292	55	18	13	5	9

Table 6. Time of operation, grade of risk and results

	n	Results Fair grade	n	n	Poor grade	n	n	Dead grade	n
1. Week	11	II	3						
		III	7				10	III	3
		IV	1	1	IV	1		IV	6
								V	1
2. Week								II	1
	5	III	4	1	III	1	4	III	2
		IV	1					IV	1
3. Week	4							II	1
			1				3	III	1
		IV	4		IV	1			
>3 Weeks	17	I	1						
		II	3	11	II	1	10	II	4
		III	6		III	6		III	5
		IV	7		IV	3		IV	1

The fact that apart from the timing of operation, other factors play an important role in the final outcome is particularly evident when

analysing patients, who have only slight or moderate impairment at the time of operation. These factors include the location, size and number of aneurysms, single or recurrent haemorrhages, vascular spasm, hydrocephalus, presence of intracerebral haematoma, extracerebral factors and age. All these factors must be analysed and considered for a meaningful analysis of the influence of timing of the operation upon the final results. Furthermore, the operative techniques during the acute stage of bleeding, oedema and congestion of the brain, intraoperative rupture of the aneurysm, and adequate anaesthesia must be taken into account. For example, the assumption that arterial hypotension does not produce additional hypoxaemic lesion during this phase of a disturbed blood-brain-barrier and local cerebral circulatory disturbances, is neither proved nor disproved.

At the present stage of the development of aneurysm surgery, it is possible to manage the aneurysm through an early operation, partly with spectacular successes, however, there is still no proof that the early or immediate operation is less risky than an operation at a later stage, and that the number of patients, who are actually cured, is larger.

The number of cases in our series is too small to speak strongly in favour of an early operation. Our figures seem to suggest that the early operation is a procedure with better results, almost identical with the results of operations performed with considerable delay.

This concept of the timing of operation, seemingly realistic and feasible, cannot be considered as an optimal one because it does not take into account the secondarily deteriorating patients during the phase before the operation.

Convincing conclusions, which are not based on individual findings can be achieved only through a cooperative study such as the recently initiated study on the acute operation within the first three days. Other problems such as the management of patients with recurrent hemorrhages, optimal time for the referral of the patient, optimal time of angiography, causes of secondary deterioration, etc. should be investigated in the same way.

I hope that such studies will take place. We have achieved enormous progress in the surgical treatment of aneurysms, however, a further effort is necessary to assure its optimal application.

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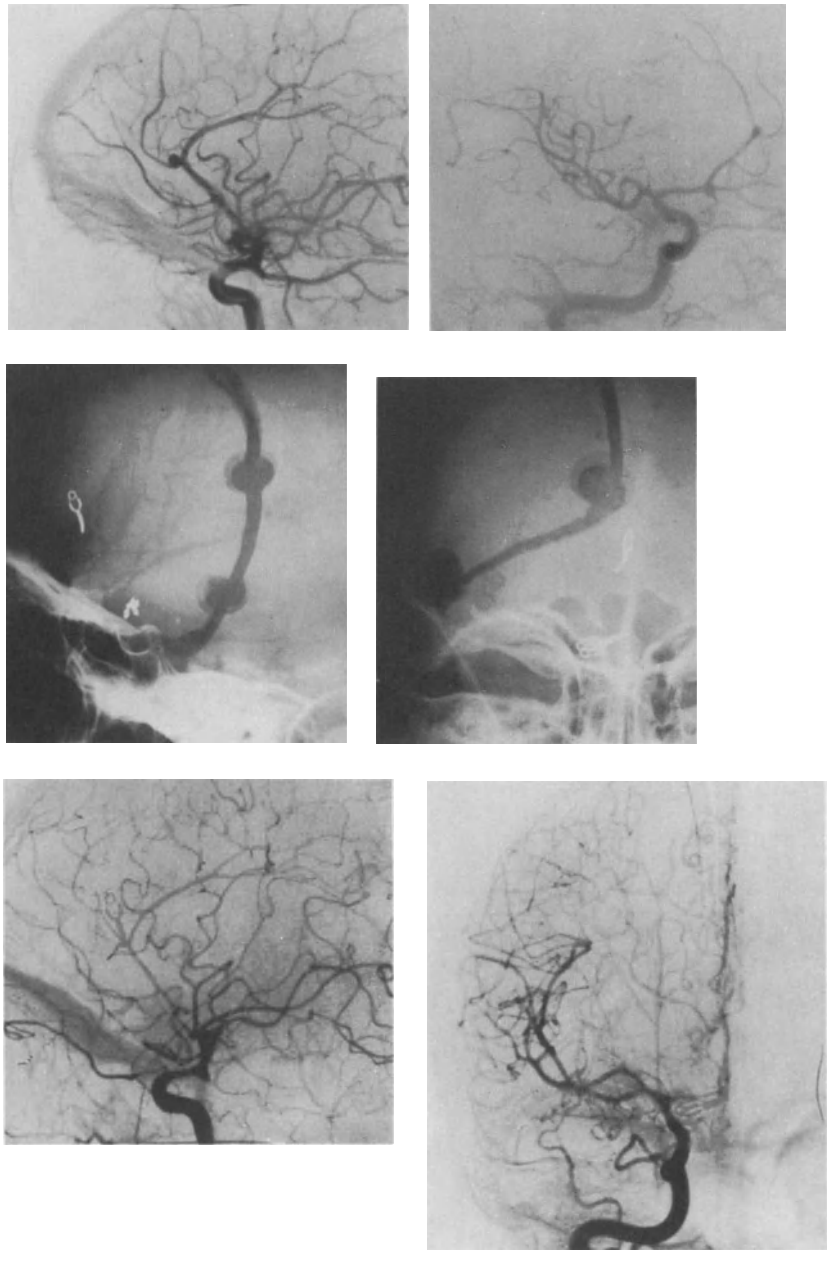

Fig. 1. Female 40 years, acute SAH. Multiple aneurysms: ACOA and peric. A. Operation 4. day. Normal course. Preoperative angiograms, postoperative skull X-rays and angiograms

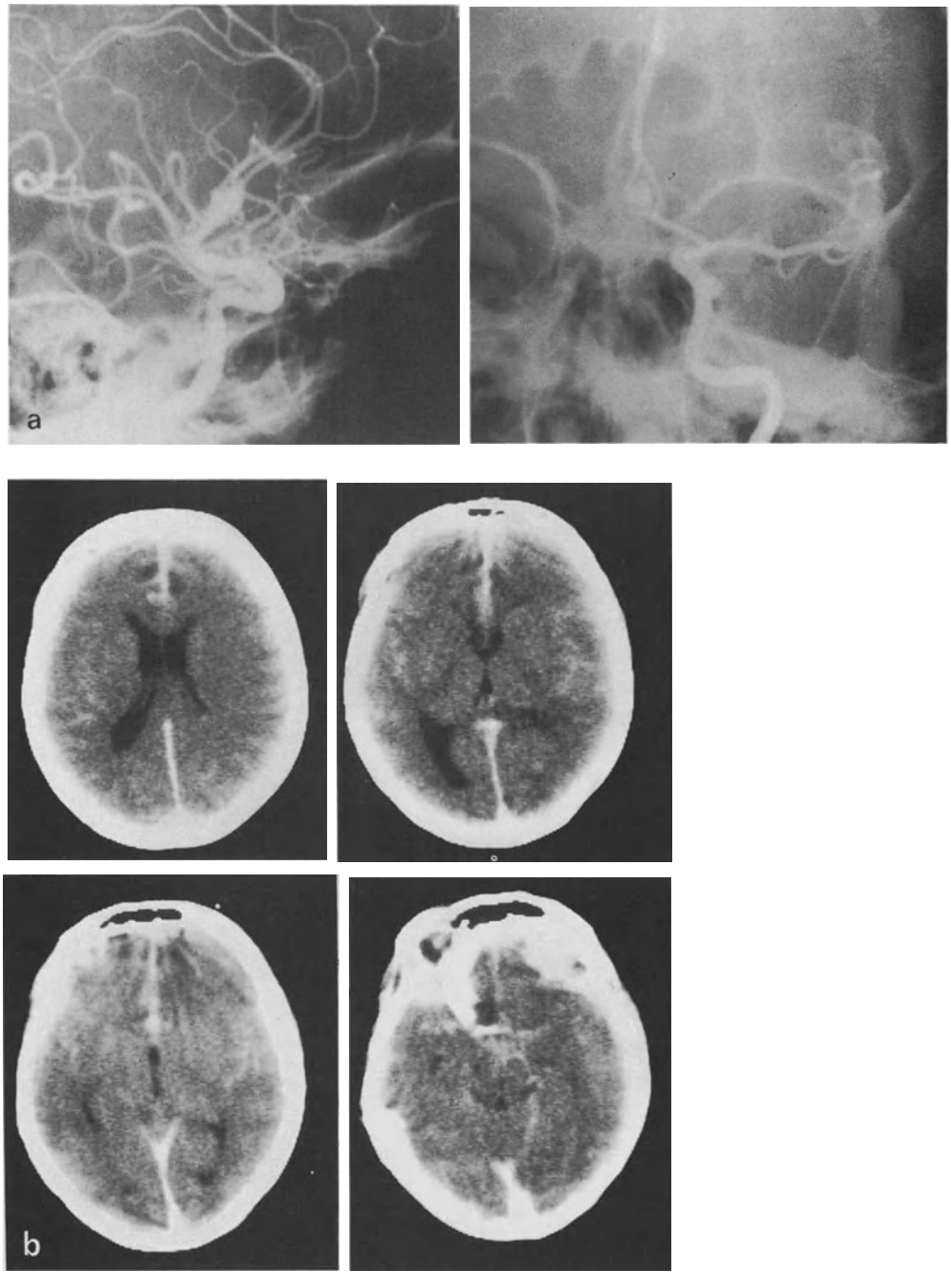

Fig. 2a-c. Female, 33 years, acute SAH, aneurysms of ACOA. a CT-Scan 2. day: SAH especially on the right side. Operation 4. day. Clipping of the neck without complications. After 3 days total infarctions of both ACA - and right-sided PCA, secondary brain stem lesion (c) and bulbar death

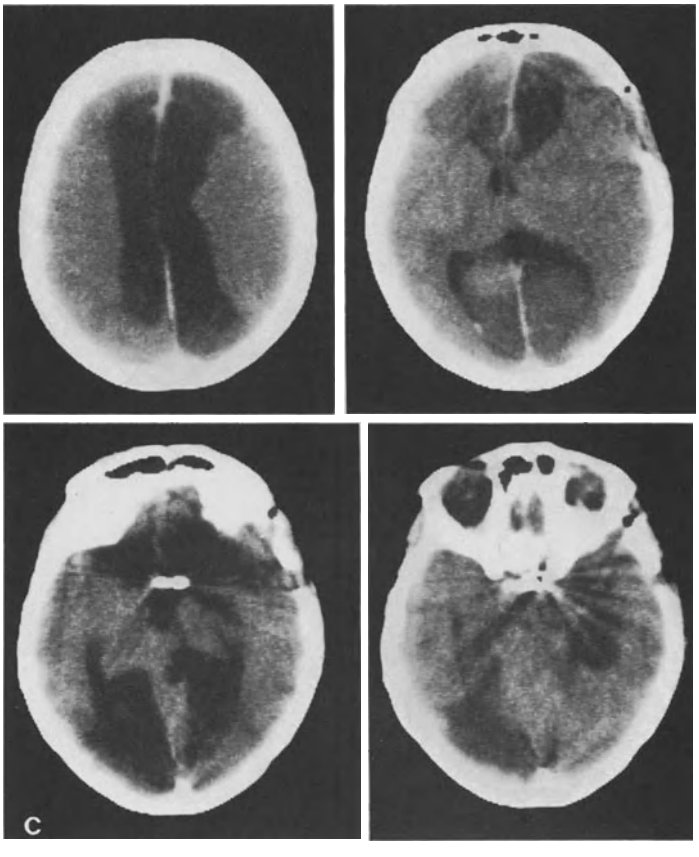

Fig. 2c

Relative Importance of Prognostic Factors for Operations of Intracranial Aneurysms

R. A. FROWEIN, W. SLATINOPOULOS, A. STAMMLER, and B. Richling

The prognostic importance of such factors as kind and duration of cerebral functional disturbances and the age of the patient has been demonstrated in investigations of severe head injuries (i.e. FROWEIN et al., 1980).

We have now also analysed 674 intracranial aneurysms treated in the Neurological and in the Neurosurgical Clinics of the University of Cologne (Fig. 1). 572 operations were carried out in the 29 years between 1951 and the end of 1979: of these, 280 were performed in the 19 years between 1951 and 1969. The overall mortality rate, calculated for five year periods, ranged from 20-35%. The 292 cases operated on in the past 10 years with the operating microscope showed a constant overall surgical mortality of 21%. The mortality rate for the remaining 102 patients treated in this period, who were not operated on was 75%. Twenty-seven of these patients died of rebleeding, this point should be kept in mind.

The positive effects of the use of the operating microscope become evident if we compare our early and late statistics (YASARGIL et al., 1975; ADAMS et al., 1976; PIA, 1978; PIA et al., 1979). From a surgical point of view, the following aneurysms are most important: aneurysms arising from the internal carotid artery, the anterior communicating artery and the middle cerebral artery. In the earlier period the operative mortality for these aneurysms was between 20% and 38% for all age groups if we exclude those cases who were in coma at operation or had a giant aneurysm (PIA 1980). In the later period the average mortality was about 15%.

Age

Figure 2 shows the age distribution of the patients with the most important aneurysms (excluding cases of giant aneurysms or those in coma). As we might expect, operative mortality tends to increase with increasing age. The largest number of patients was found in the group between 30-50 years; the mortality of patients in this age group operated on between 1951 and 1969 was about 29%, in the cases operated after 1970 it was about 15%.

Time of Operation

Figure 3 brings together for the period since 1970 three of the most important prognostic factors in aneurysm operations: age of the patient (up to 30, 31-50, 51-60, over 60); state of consciousness (coma, clouding of consciousness, full consciousness); and the time of operation in relation to the onset of the subarachnoid hemorrhage (SAH).

The 10-year-period has been divided into 3 shorter periods: 1970-1973; 1974-1976; 1977-1979. From 1970-1973 the great majority of operations were performed more than 2 weeks after the subarachnoid hemorrhage SAH. Later there was an increasing tendency to operate at an earlier stage; until 1976 these earlier operations were largely critical cases with clouding of consciousness or coma; but in the last 3 years we have operated 31 fully conscious patients between the third and the fourteenth day after SAH; 10 of these were operated in the first week.

One difficulty which arises in attempting to assess statistically the chances of survival of 2 groups of patients with the same syndrome and in the same age group - one group operated on soon after SAH and the second group later - is the very small number of early operations contained in our sample. Another problem which complicates statistical analysis is the unequal distribution of the 3 states of consciousness in the different time periods following SAH.

The attempt to operate comatose patients was almost always unsuccessful. This was so in acute, subacute and chronic stages, and in all age-groups. Out of 15 operated cases, only 2 survived; preoperatively these 2 had been in coma I without paresis.

Of the 35 patients with clouding of consciousness, only 5 survived an operation in the first week. Patients over 50 years of age with clouding of consciousness are more likely to survive an operation when the period between the SAH and operation is longer than a week. The mean mortality of the 35 patients in this group was 57%.

The mean mortality of patients who were fully conscious preoperatively was 9%. Because of the same number of operations in the first and second weeks after the SAH, the mortality rate for this period is very approximate and can only be expressed as a sliding mean value. The mean mortality calculated in this way for the second week is about 15%. For operations performed during the third week and later it is about 8%.

Age, however, is a factor which influences mortality more than does the time of the operation (Table 1). The operative mortality for the 40 fully conscious patients up to 30 years was 5% and for the 120 patients from 30 to 50 years it was 4%. It was 18% for those between 50 and 60, and 30% for those over 60. Thus our observations of fully conscious patients showed that age was a far more important prognostic factor than the time of operation.

Table 1. Intracranial aneurysms in patients, fully conscious before operation. Postoperative outcome in relation to the age of the patient

Age-group	No. of patients	Survivors	Deaths	%
> 61	11	8	3	30
51-60	51	42	9	18
31-50	120	115	5	4
-30	40	38	2	5
Total	222	203	19	

State of Consciousness

The great importance of state of consciousness as a prognostic factor can be seen yet again in Fig. 4. It shows the distribution of all fatal courses in relation to the main age groups, the preoperative states of consciousness and the main time periods following the SAH. The deaths which occurred in the first three days were in all age groups and almost always patients who had been comatose before the operation.

Between the third and the tenth day, the deaths occurred largely in somnolent patients. After the tenth day, the largest number of deaths occurred among preoperatively conscious patients. This fact does not reflect a high mortality rate but results from the greater number of operations in this category.

Diameter of Cerebral Vessels

In Figure 5 the size of the cerebral vessels is shown in relation to the age of the patients and the time of operation. Angiographic findings were available for 167 of the 292 patients.

In comatose or somnolent patients between the ages of 30 and 50 with fatal courses, who were operated on in the first three weeks, there was always a general or focal narrowing of the vessels near the aneurysm. But this was also true of more than half of the survivors in the same age group, who were operated on in the same period. It is clear, then, that even in cases where the operation takes place soon after SAH, as long as the patient is free from disturbances of consciousness, narrow vessels will not preclude survival. Our experience suggests that the prognostic value of a local narrowing of vessels is lower than that of disturbances of brain function or high age.

The cause of the narrowing is often a dense arachnoid sheath around the vessel feeding the aneurysm. If this sheath, which gets increasingly tight in the course of time, is cut open with micro-scissors, the vessels spread out so that the diameter of the vessel increases. During this procedure we have never observed vasospasm without concomitant coagulation of the vessel.

Rebleeding

Because of the high operative mortality of patients in coma (87%) and of those with clouding of consciousness (57%), operations are usually contraindicated in these cases.

In our discussion of the operative mortality of fully conscious patients - 15% in the first 10 days, 8% in the second week and later - we have not mentioned the incidence of fatal rebleeding among patients waiting for operation. Twenty-seven such cases have been observed in the Neurological and Neurosurgical Clinics in the last 10 years. In fact, the mortality rate from rebleeding, at least from the fourth day on, should be added to the operative mortality figures, so that overall mortality of conscious patients with a latency of more than three weeks is really 18%.

For this reason a fully conscious patient should be operated as soon as possible after the fourth day following SAH.

Summary

An analysis of the effects of various factors on the course of 394 patients with cerebral aneurysms treated in our clinics between 1970 and 1979 is presented. It showed that the most important factor in survival after operation is the recuperation of brain function following SAH and before operation. The age of the patient is the second most important factor. Less important is the period between SAH and operation. Vasospasm observed at angiography had no prognostic significance.

Because of the danger of rebleeding we recommend that the operation of the aneurysm in fully conscious patients be carried out as soon as possible after the fourth day following SAH.

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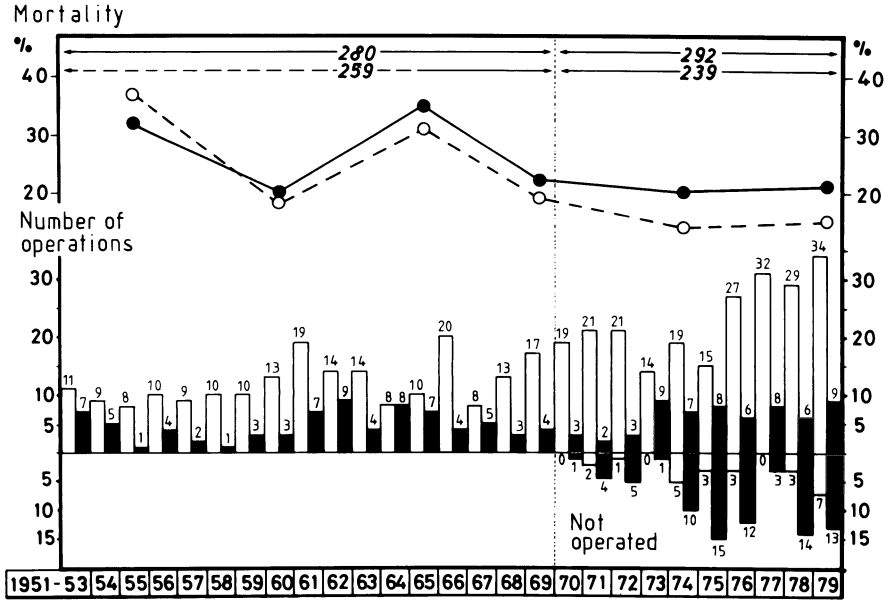

Fig. 1. Intracranial aneurysms, Cologne 1951-1979. □ = survivors, ■ =deaths. Postoperative mortality: ●——● all types of aneurysms. o---o aneurysms arising from the internal carotid artery, anterior comm. artery and middle cerebral artery (excluding cases of giant aneurysms or those in coma)

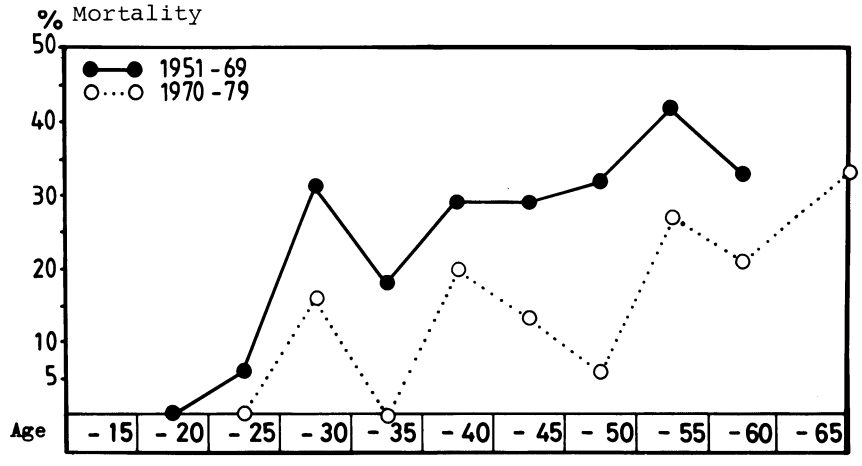

Fig. 2. Intracranial aneurysms: operated cases. Correlation of age and mortality. Aneurysms of the internal carotid, anterior communicating and middle cerebral artery (excluding giant aneurysms or patients in coma)

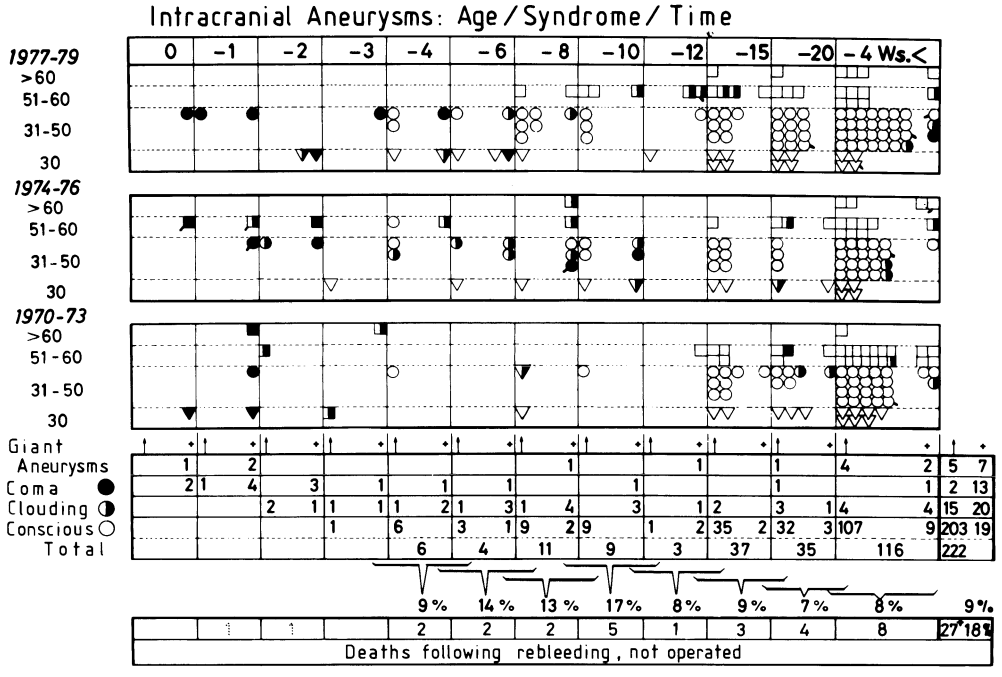

Fig. 3. Correlation of age, preoperative syndrome and time after SAH. ● patients in coma; ◑ clouding of consciousness; o consciousness

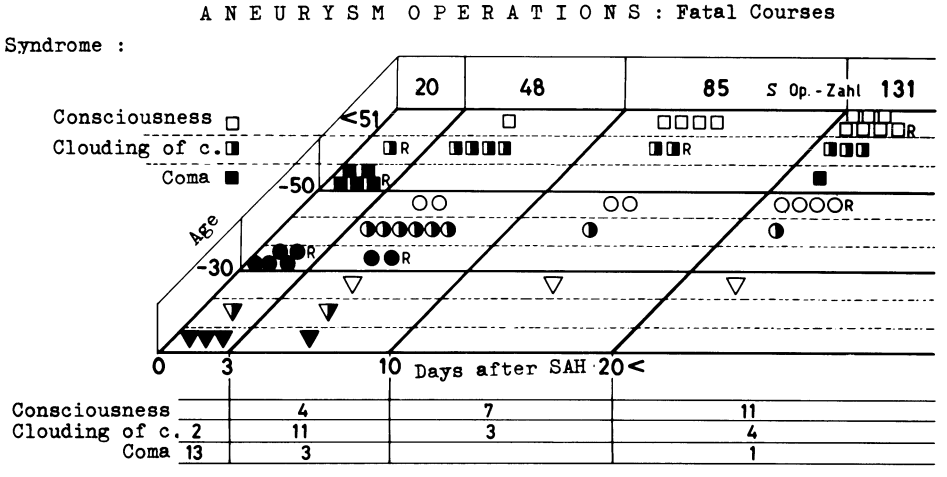

Fig. 4. Correlation of syndrome, time after SAH and age in fatal courses. R, giant aneurysms

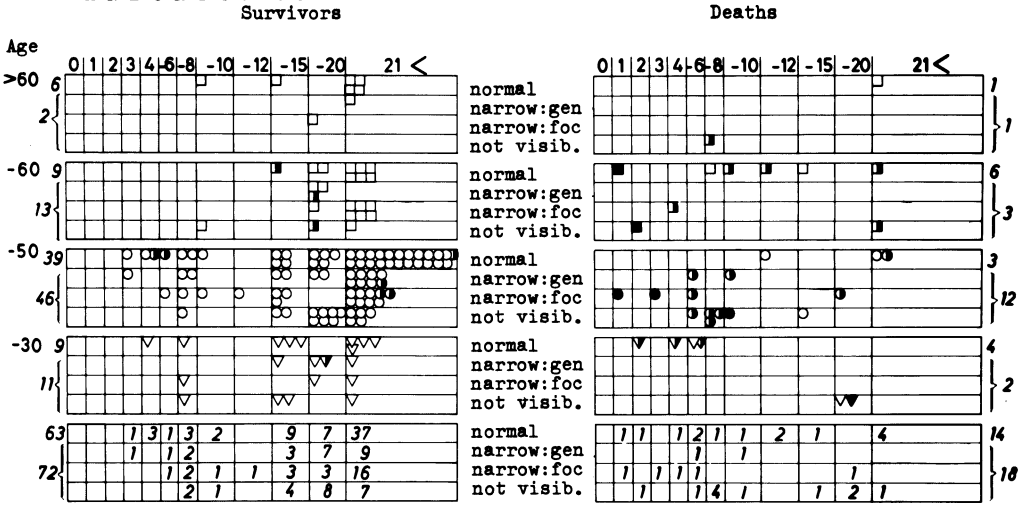

Fig. 5. Diameter of cerebral vessels in correlation to time after SAH and age. Narrow vessels will not preclude survival after early operation

Timing of Aneurysms of Cerebral Vessels – Documentation of 200 Patients in a Retrospective Study

O. HEY and K. SCHÜRMANN

In recent years, various authors were able to show convincingly the influence of favorable time of operation on the treatment results in aneurysms (3, 4, 6, 9, 11, 12). This is essentially determined by recurrent hemorrhage and vasospasm. The first recurrent hemorrhage mostly occurs on the third to 11th day, with a peak on the seventh day (7). The period of predilection for vasospasm is between the fifth and 13th day after a subarachnoid hemorrhage (SAH) (4, 11, 12). The time factor thus plays an important role in the treatment of aneurysms. We analyzed our patient material with regard to the time factor.

Material

200 patients with aneurysms of cerebral vessels were analyzed in a retrospective study. It was investigated to what extent a delayed diagnosis, recurrent hemorrhage, vasospasm and preoperative finding (BOTTERELL grading) influence the time up to operation as well as the results of treatment. All patients were classified in the grades 1-5 according to BOTTERELL on the basis of their preoperative symptoms (1). The grade is raised one step when the patient is older than 50 years old and/or there is severe cardiac, pulmonary, hepatic or renal disease. This gives rise to seven grades. 178 single aneurysms, 13 multiple aneurysms and nine patients with additiondal findings (two angiomas, seven brain tumors) were then evaluated. The operation period was from 1956 to June 1978. A further 47 patients (treated from July 1978 until February 1980) were not included in this investigation, although their treatment results will be communicated.

Results

1. Delaying factors from the onset of SAH up to admission into a hospital: only 2/3 of the patients (118 patients) were directly referred to *any* hospital on the day of hemorrhage by the family doctor. The remainder were referred later, in an extreme case even 120 days after the first hemorrhage (Table 1).

2. Only 19 patients were primarily admitted to the Department of Neurosurgery; 181 patients were primarily admitted to another clinic. In the latter group, the patients were transferred in the first week in 25% (44 patients) and in the remainder (75%) only from the second week onwards, in an extreme case even 511 days later. In the patients transferred late (i.e. from the second week onwards), the recurrent hemorrhage in the outside hospital had occasioned the transfer in the majority of cases.

Table 1. Interval between SAH and admission

Interval between SAH and admission	No. of cases	%
1 Day	118	65,9
2 Days	8	4,5
3 Days	10	5,6
4-7 Days	22	12,3
2nd Week	8	4,5
3rd Week	5	2,8
4th Week	2	1,1
> 4 Weeks	6	3,3
Total	179	100,0

Thus at the time of admission to the Department of Neurosurgery, 114 patients had suffered *one* SAH and 73 patients (36,5%) had suffered *several* recurrent hemorrhages (Table 2).

3. Corresponding to the time periods described, there was a substantial delay in angiographic diagnosis. Angiography was performed in the outside hospital in 54.9% of the patients (Fig. 1). Analysis for the time between SAH and angiography revealed that 50.1% underwent angiography up to the second week, and the remainder later.

4. Influence of preoperative grade on the results of treatment: the majority of our patients show the higher grades 3, 4 and 5; the highest mortality rate is found in grades 4 and 5 with 25.9% and 50% respectively, with an unfavourable preoperative initial situation (Table 3). The preoperative mortality is 3%, the postoperative mortality 22.5% (45 patients).

Table 2. Influence of SAH on the results of treatment

Incidence of SAH	Dead Preoperative	Postoperative	Survival	Total
Without	0 -	4 -	9 -	13 -
One	2 (1,8%)	20 (17,5%)	92 (80,7%)	114 (100%)
Multiple	4 (5,5%)	21 (28,8%)	48 (65,7%)	73 (100%)
Total	6 (3,0%)	45 (22,5%)	149 (74,5%)	200 (100%)

5. Influence of vasospasm on the results of treatment: there is no significant difference in the mortality between the group "with" and "without" vasospasm (Table 4). This is because not all 200 angiograms were available for evaluation. However, the vasospasm influenced the results negatively via the resulting elevation of grade.

6. On the other hand, the influence of recurrent hemorrhage on mortality is clear. We find a higher mortality (28,8%) in the group with "multiple SAH" relative to the comparison group with 17,5% (Table 2).

Table 3. Influence of gradings (BOTTERELL) on the results of treatment

Grade	Dead		Survival	Total
	Preoperative	Postoperative		
1	0 -	0 -	1 -	1
2	0 -	6 (18,7%)	26 (81,3%)	32 (100%)
3	0 -	6 (8,2%)	67 (91,8%)	73 (100%)
4	1 (1,7%)	15 (25,9%)	42 (72,4%)	58 (100%)
5	3 (9,4%)	16 (50,0%)	13 (40,6%)	32 (100%)
6	1 -	1 -	0 -	3
7	0 -	1 -	0 -	1
Total	6 (3,0%)	45 (22,5%)	149 (74,5%)	200 (100%)

Table 4. Influence of vasospasm on the results of treatment

Vasospasm	Dead		Survival	Total
	Preoperative	Postoperative		
Verified	3 (4,6%)	18 (27,7%)	44 (67,7%)	65 (100%)
None	1 (1,2%)	22 (26,2%)	61 (72,6%)	84 (100%)
Total	4 (2,7%)	40 (26,8%)	105 (70,5%)	149 (100%)

Discussion

In a study of more than 1000 operated cases with aneurysms of cerebral vessels, SUZUKI reports that the mortality of surgery is under 5% (12). This applies to cases when an early operation was performed within one to three days after an SAH, i.e. before the predilection period for vasospasm and recurrent hemorrhage. It further applies to patients with a favorable preoperative grade (4, 11, 12). When one waits longer before operating, the incidence of recurrent hemorrhage rises (3, 8, 9, 10). A further factor, the genesis of vasospasm between the fifth and 13th day, results in deterioration of the prognosis (4, 11, 12). This is the case especially when the spasm is accompanied by a diminution of cerebral blood flow (2, 5). Poorer preoperative grades result from this.

Our results confirm the dependence of the success of surgical treatment on the preoperative condition. It was shown that the prognosis of a patient becomes poorer the higher his preoperative grade (mortality in grades 3, 4 and 5 was 8.2%, 25.9% and 50% respectively). Furthermore, a high incidence of preoperative recurrent hemorrhage (36.5%) is found, This is explained from the fact that substantial time delays occurred from the onset of SAH up to operation. Immediate hospitalization by the family doctor occurred in only 2/3 of the patients on the day of the SAH, and in the remaining patients very much later (Table 1). Only 19 patients were admitted directly into the Department of Neurosurgery in the first instance. The patients admitted to other hospitals were treated conservatively there for too long. As a rule, these patients suffered a severe recurrent hemorrhage after a shorter or longer interval. This recurrent hemorrhage in turn had an unfavorable effect on the result of operation. Thus the mortality in patients with recurrent hemorrhages was 28.8%, and those with *one* SAH 17,5%.

According to our results, the negative influence of the preoperative vasospasm has been shown mainly in the preoperative mortality rate (Table 4). In addition, the vasospasm brought about a rise in grade.

If one can succeed in achieving a better timing up to operation, patients will come earlier to the Department of Neurosurgery with fewer recurrent hemorrhages, less vasospasm and a better preoperative state. As we have shown, the results are markedly affected by this, so that better results are to be expected in the future.

First proof of this is shown by the evaluation of 47 patients in whom this requirement was met (operated on from July 1978 until February 1980). Here, the mortality is 8.6% compared to 22.5% in the comparable group (Table 5). These results are in almost complete agreement with those of other authors (4, 11, 12).

Table 5. Results of treatment of 247 aneurysms

Time	Dead		Survival	Total
	Preoperative	Postoperative		
1956 - 6/1978	6 (3,0%)	45 (22,5%)	149 (74,5%)	200
7/1978 - 2/1980	2 (4,3%)	4 (8,6%)	43 (87,1%)	47

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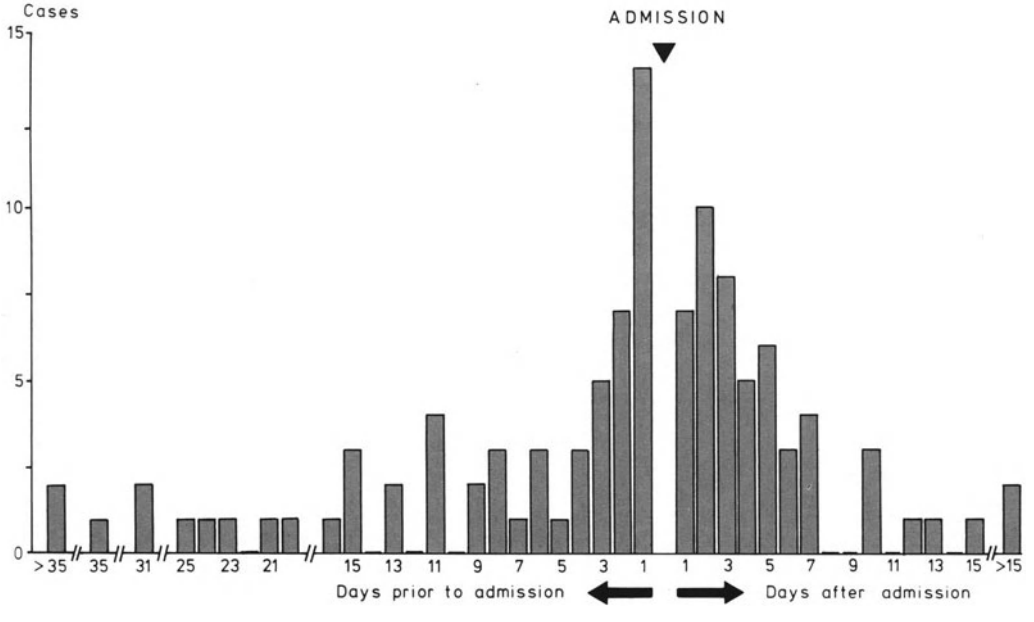

Fig. 1. Time of angiography related to day of admission in a neurosurgical clinic. The columns on the right side represent: angiography performed in a neurosurgical clinic. The columns on the left side represent: angiography performed in another hospital

The Timing of Surgical Treatment of Patients in the Acute Stage After Aneurysm Hemorrhage

H. KNEISSEL and W. KOOS

In the department of Neurosurgery, University of Vienna, about 700 patients with intracranial arterial aneurysms have been operated since autumn of 1964. The distributions of age, sex and the localization of the aneurysms correspond exactly to the international statistics.

According to all important publications and our own experience, the 2 most important factors which determine the surgical mortality are:

1. the condition of the patient at the time of the operation (clinical neurological condition stage I-V) according to HUNT and HESS (1968);

2. the length of time elapsed since the subarachnoid hemorrhage (SAH).

It is evident that the brain damaged by the SAH cannot be healed by the operation alone. The operation is a prophylactic procedure which prevents a secondary hemorrhage with further traumatisation of the brain by clipping the aneurysm.

According to our experience, the danger of pre-operative hemorrhage is enormous. In a series of 334 cases with recurrence of bleeding, 33% (110 cases) occurred between the third and the seventh day after the primary hemorrhage.

The question arises, when and in which clinical-neurological stage the prophylactic operation can be carried out.

An operation brings about increased risks of brain edema and blood-filled cisterns which may reduce the chance of survival for the patient.

Table 1 shows our timing schedule for patients in group I-V. According to the grading of the patients with SAH corresponding to the surgical risk, the patients in grades I and II present no problems. They should be operated as soon as possible. The surgical mortality lies far below 10%. Patients in grade IV should quickly be checked under X-rays but an operation should only be carried out in case of a life-endangering expanding intracerebral hemorrhage.

From the neurosurgical point of view, grade V seems to be rather hopeless. As comprehensive statistics show, the patients in grade III (according to SYMON about 47%) with neurological deficits and more or less impaired consciousness have about 2 weeks of life expectancy without operation. Of the patients in this group about 6.6% per day are going to die.

In accordance with statistics by HUNT (1967) (Table 2) the state of the patients improve in 55% of the cases, but 45% remain in the same condition or even deteriorate. Therefore 20% of the whole group of

Table 1. Classification of the patients according to the surgical risk (stage I-V). Subarachnoid hemorrhage

Treatment plan	Stages					
	I	II	IIIA	IIIB	IV	V
Immediate referral to hospital	+	+	+	+	±	-
Early angiography (all cerebral vessels)	+	+	+	+	±	-
Early operation	+	+	+	-	+ (only intracerebral hematoma)	-

Table 2. Change in the clinical condition of patients in stage III (HUNT, 1967). Significance of waiting policy regarding patients rated grade III at time of admission

Status of patient	%
Improved to grade I	20
Improved to grade II	35
Remained at grade III	11
Deteriorated to lower grades	34

patients are the most important ones for the neurosurgeon with respect to the fate of the patient and the timing of the operation.

In Fig. 1, we compared our surgical results with a co-operative study by ALVORD (1972), who reports on 5000 non-operated patients, who had had a SAH as a result of an intracranial aneurysm.

The lowest curve shows that after 8 weeks only 40 out of 100 patients would still be alive without operation. The subsequent curves show the respective life expectancies of those patients who survived the primary hemorrhage by one, seven, ten days etc. For the assessment of the overall mortality of aneurysmal hemorrhages, only the lowest curve containing all cases including all grades can be used. All other curves show the course of the illness of a selected group of patients.

In Fig. 2 our surgical results are projected in the form of cumulation curves upon the ALVORD curve. Accordingly all operated patients of all grades after single and multiple hemorrhages were included without any selection, i.e. all cases from the time before microscopic surgery as well as those who were operated by means of the surgical microscope. Therefore a comparison between operated and non-operated patients is permissible at least theoretically and graphically.

In case of emergency surgery within the first 24 hours, the results are discouraging: the operative mortality is above 90%. From the steep rise of the cumulation curves we can conclude that the operative mortality quickly decreases even below the natural mortality when about the fourth day 60% of the operated patients survive. More than 50% of these patients were in grades III and IV.

The curve to the right shows the course of the illness of all patients, the curve to the left those cases with only one SAH, in the grades I-IV.

After the seventh day, both curves show only a very slight rise since the cumulation curve, which is based on 700 cases, is not altered significantly by sporadic cases added later on. If the curve for the grade I and II cases was deducted from the overall curve, it would run a course below 10%. However, we intend to evaluate only the overall statistics in this paper.

If we consider the surgical mortality in cases with primary hemorrhage in all grades to be about 20% than the following considerations must be discussed:

Out of 100 patients about 10% die without having reached a condition where operation would have been possible. With a surgical mortality of 20%, 72 of the remaining 90 patients could be saved including those patients operated in the first days already. If an operation was carried out after the sixth day, the neurosurgeon would theoretically be faced with only 60 surviving patients out of 100 due to the natural mortality. Therefore, only 51 patients can be saved due to the better operation results after the seventh day with a mortality rate of 15%. There is a calculated difference of 21 patients, who would probably be saved by an operation within the third and the seventh day after the hemorrhage.

One reason for this could be the frequent rebleedings especially within this particular period. This recurrence of bleeding can be prevented by early operation.

The other reason could be the fact that by delaying surgery, 45% of the grade III-patients do not improve but deteriorate instead.

It is evident that the neurosurgeon will decide according to the patient's clinical condition and especially on his or her state of consciousness whether to operate or not. If we also take statistical facts into consideration, a certain number of patients can be saved by an operation carried out within the third to seventh day after the SAH.

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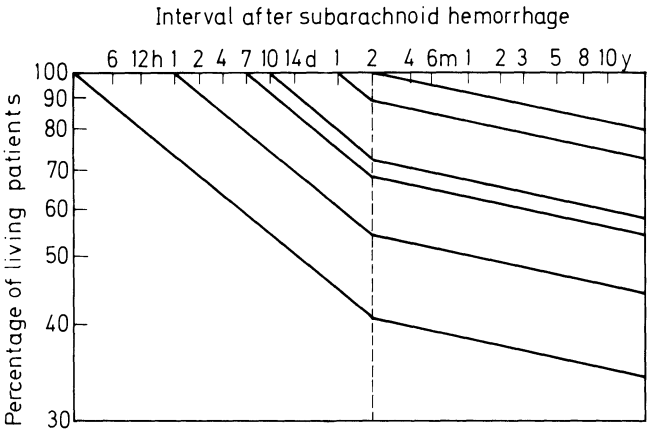

Fig. 1. Natural mortality of non-operated patients (ALVORD, 1972)

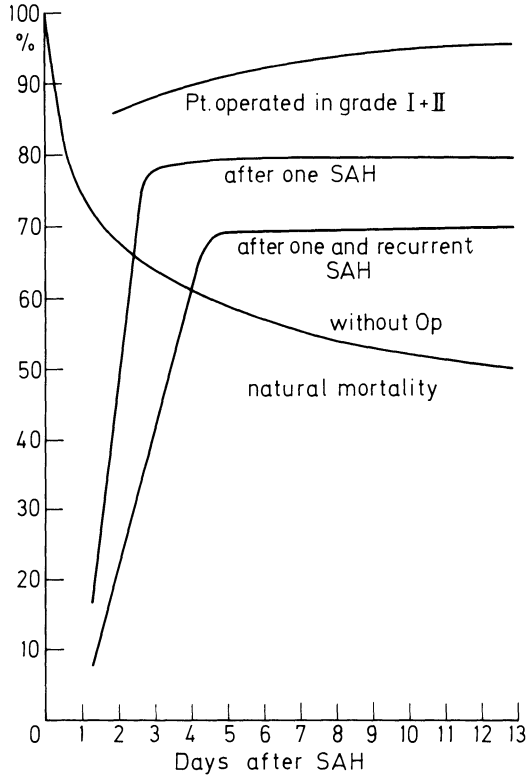

Fig. 2. Correlation of natural mortality with surgical mortality

Timing of Aneurysm Surgery After Spontaneous Subarachnoid Hemorrhage

H. M. MEHDORN, W. GROTE, and B. TENFELDE

Introduction

Subarachnoid hemorrhage (SAH) usually occurs in otherwise healthy persons. The risk of death or disability from rebleeding is particularly great in the first 2 weeks following SAH (18), but continues to be a serious hazard after 3 weeks (2). Therefore early surgical treatment with the aim of obliterating the bleeding source seems logical. However, early experience in aneurysm surgery showed that operation on patients in poor neurological and clinical condition resulted in excessive mortality (HUNT and HESS, 1968) (8). Most neurosurgeons therefore prefer to delay surgery until the patient's neurological and medical status are stable usually at an interval of 1-3 weeks after SAH. There have been a few recent encouraging reports on early aneurysm surgery (16, 20). Early surgery has several theoretical advantages over delayed surgery: Prevention of rebleeding; amelioration of vasospasm; prevention and treatment of ischemic complications; ease of operation - dissection of the aneurysm; prevention of medical complications. In order to compare the beneficial and detrimental effects of early or late surgery on the final outcome of patients, we analysed the clinical course of 154 patients who underwent a direct surgical approach to an intracranial aneurysm between January 1, 1976 and December 31, 1979. These patients were mostly referred to us from other hospitals where they had been treated medically for various intervals after SAH. The patients' neurological and medical status were classified according to the Co-operative Aneurysm Study (CAS) Scale (9) at different points throughout the period beginning in the referring hospital and ending at a follow-up examination 3-51 months after the operation. The patients were usually operated upon under controlled hypotension using magnification. The policy of timing of surgery was kept relatively uniform over the entire period: patients in a good grade were operated upon as soon as possible after arrival in the department, whereas patients with poor grading were allowed some delay in the hope of improving before the operation was performed.

The series consists of 96 female and 58 male patients with an age range from 1-76 years, the maximum incidence occurring in the 6th decade. There were 48 aneurysms of the internal carotid artery (ICA), 41 of the anterior communicating artery (ACoA), 33 located on the middle cerebral artery (MCA), 16 in the proximal part and two in the distal part of the anterior cerebral artery (ACA), 8 in the posterior communicating artery (PCoA) and the posterior cerebral artery (PCA) and 8 in the vertebrobasilar circulation.

Results

The classification of all patients over the clinical follow-up period is shown in Fig. 1. Overall improvement of the groups' classification from admission in the referring hospital and referral to our institution continued until the operation at which date 48 patients were classified in grade I, 40 in grade II, 54 in grade III, 11 in grade IV and 1 in grade V. During the first 5 days after the operation, 9 patients died of central dysregulation; at the time of discharge, the number of deaths had increased to 14, making an immediate p.op. mortality rate of 9%. The remaining 5 patients who died while still under our care, died of pneumonia (2 cases), pulmonary embolism (1 case), and gastro-intestinal complications (ileus, GI-bleeding) (2 cases). The mortality rate related to surgery itself was therefore 5,8%. At time of the follow-up exam, 43% of all patients were free of symptoms, 18% complained of minor headaches or psychopathological alteration, and 26 patients had died. Three of the 12 patients, who had died since discharge, had succumbed to GI-complications, one to a chronic subdural hematoma and one to brain infarction due to recurrent bacterial endocarditis. The cause of death was not known for the remaining 7 patients.

One of the important factors influencing the outcome after SAH is the localisation of the aneurysm (Fig. 2). Aneurysms of the ICA, the ACoA and the MCA have a rather favorable late outcome with 28 out of 48 ICA-aneurysm patients classifying for grade I or II, 22 out of 41 ACoA and 17 out of 33 MCA-aneurysm patients. This was combined to a long-time mortality rate of 16,6% for ICA-aneurysms, 10% for ACoA-aneurysms and 18% for MCA-aneurysms.

The influence of the referral interval on late outcome is illustrated by Fig. 3. Twenty-one patients were referred to our institution within the first 3 days after SAH, 52% of them in grades IV to VI. The late mortality in this group was 8 out of 21 patients. This indicates that many patients in very bad condition were referred to our institution at an early date. 54% of these 21 patients improved finally, compared to 46% who become worse when comparing the final outcome to the grade upon admission in the referring hospital. This is the highest percentage of patients becoming worse; however, nearly, one-third of these patients were in grade V and VI. Later intervals between SAH and admission to our institution are associated with a higher percentage of improving patients. However, one must consider that to among those patients admitted to our institution in the 3rd week after SAH, 52% had already initially been in grade II.

The time interval between the first significant SAH and admission to our institution also affects the time interval between the last SAH and operation. In Fig. 4, this interval is related to late outcome. Two patients underwent surgery within 3 days after SAH, one in grade V with a space-occupying intracranial hematoma - who subsequently died - and another one who regained good functional activity but kept a neurological deficit. Besides these 2 emergency cases, five patients were operated upon within the first week after SAH, with a preoperative grading of I-III. All improved or - in grade II - remained unchanged. This is in sharp contrast to the results experienced in patients operated upon in the second week after SAH. 40% were made worse, among which 20% had originally been grade I or II. 50% improved, 27% of them originally belonging to grades III to V.

Further improvement in the surgical results was obtained in those patients who underwent operation in the 3rd week after SAH, 44% of them

from grades III to V. This must be compared to a worsening of 12%. The figures derived for the interval longer than 22 days after SAH show a minor decline of the percentage of patients who improved, while the percentage of the patients who were classified to be worse at the follow-up examination increased to 20%. These results are even more important as this very late group consists of 55% of the patients, who were classified to be in grades I and II at the time of surgery.

Discussion

Surgical treatment of intracranial aneurysms after SAH has significantly reduced the mortality of this entity. Series of conservatively treated patients report mortality rates ranging from 44.5% (12) to 52% (13) and to as much as 70% for aneurysms of the ACA (1). However, timing of aneurysm surgery has always been a controversial issue. POOL was probably the first to suggest that "early" operation in patients in good neurological condition may offer results at least equal to late operation while giving the advantage of decreasing the risk of rebleeding (14). This point was further elucidated by HUNT and HESS (8) and later by YASARGIL (11, 19) and SUZUKI and YOSHIMOTO (17). "Early" means, within the first 48-72 hours after SAH (6); surgery within this period would prevent lasting vasospasm and reduce the risk of cerebral ischaemia.

Our series of 154 consecutive patients operated upon for ruptured aneurysms consists of patients treated in different ways in the referring hospitals; the referring colleagues adhered either to a conservative point of view, that means medically treating the patients over a rather prolonged period of time; others prefer to admit the patients to our institution, often for the sole purpose of CT-scanning, while keeping their good grade patients under long medical treatment.

Our data suggest that it is safe to perform early surgery in good grade patients (in contrast to a recently reported study (15)). The worst results were obtained in those patients transferred to our institution within the first 3 days after SAH and operated upon in the second week after SAH, usually when the patients' neurological grading did not improve or turned worse and when it was thought that surgery would be of some benefit. Later surgery had an improvement rate somewhat smaller than that of early surgery. This again suggests that it might be safe to perform early surgery. Data recently presented showed that with the use of antifibrinolytic agents still approximately 18% of the patients will be damaged due to another hemorrhage within the first 2 weeks, and that additional 15% will die or become disabled (4). These data have to be taken into account when one advocates late surgery.

From a practical point of view, one must consider that most of our patients come from referring hospitals; therefore the major part of the time schedule will be planned by others. We think that our data are sufficient to suggest that very early referral should become an advisable goal in order to allow the operating surgeon to decide freely about the date of the operation. Obviously, this policy includes a change of attitude towards early angiography, preceded by CT-scanning. The latter is a major tool to post-SAH-diagnostics, since it may help to predict the occurrence of vasospasm (3). The risk of very early angiography is not higher than when it is delayed (5, 7, 10). Further improvement of pre- and postoperative attention to cerebral perfusion may help to further reduce the surgical mortality rate of 5,8% and improve the functional results.

Conclusion

On the basis of data collected in our series, aneurysm surgery within one week after SAH carries the lowest risk of mortality and deterioration. Data to be collected in the International Cooperative Study on Timing of Aneurysm Surgery should provide more detailed information concerning the question of timing of surgery.

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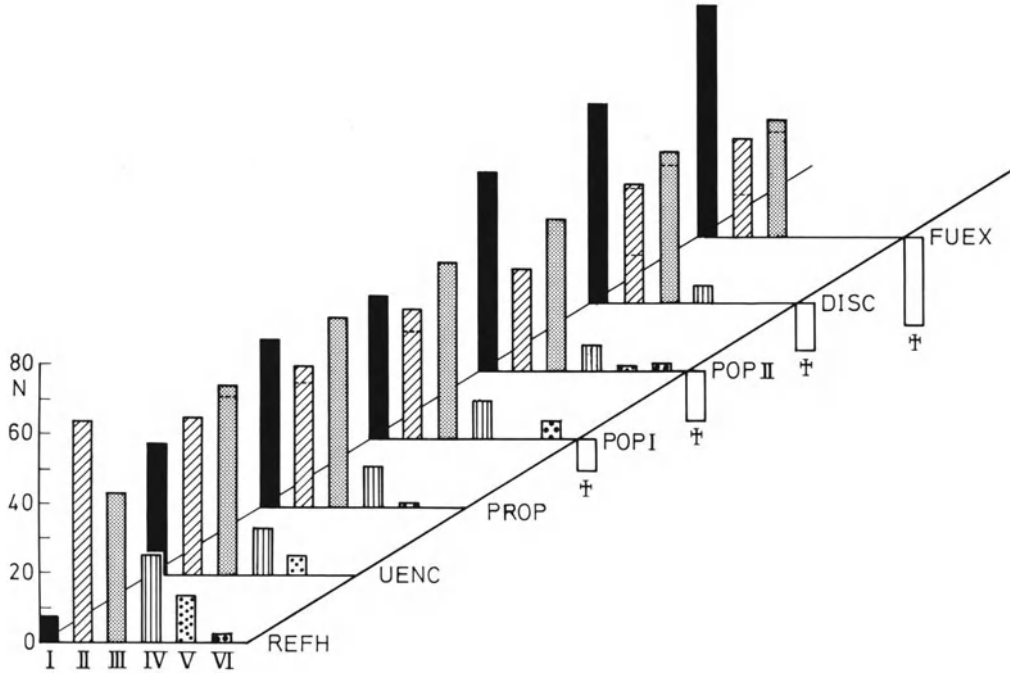

Fig. 1. Patients' symptomatology according to CAS classification (n = 154). REFH, referring Hospital; UENC, admission, Dept. of Neurosurgery; PROP, immediately preoperation; POP I, day 1-5, postoperative; POP II, day 6-14, postoperative; DISC, at time of discharge; FUEX, at follow-up examination

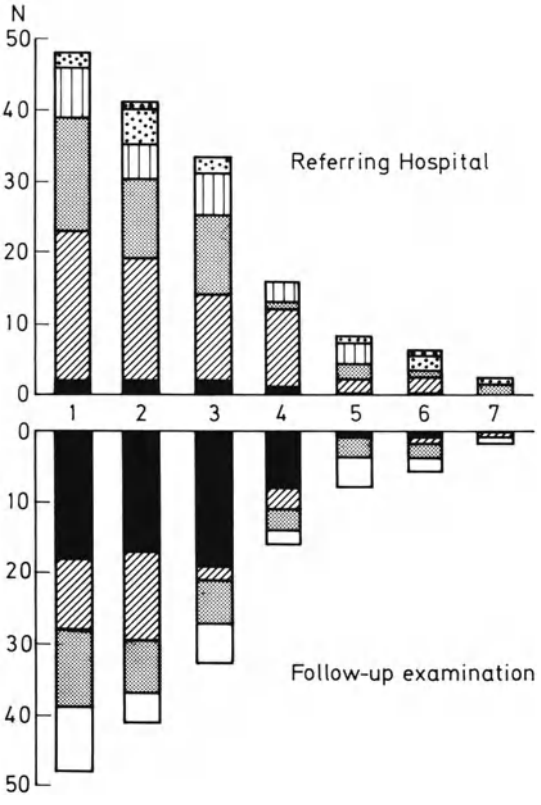

Fig. 2. Comparative results related to localization of aneurysms. Localization: 1 = internal carotid a.; 2 = anterior commun. a.; 3 = middle cerebral a.; 4 = anterior cerebral a., prox. part; 5 = posterior commun. a.; 6 = vertebrobasilar a.; 7 = anterior cerebral a., dist. part

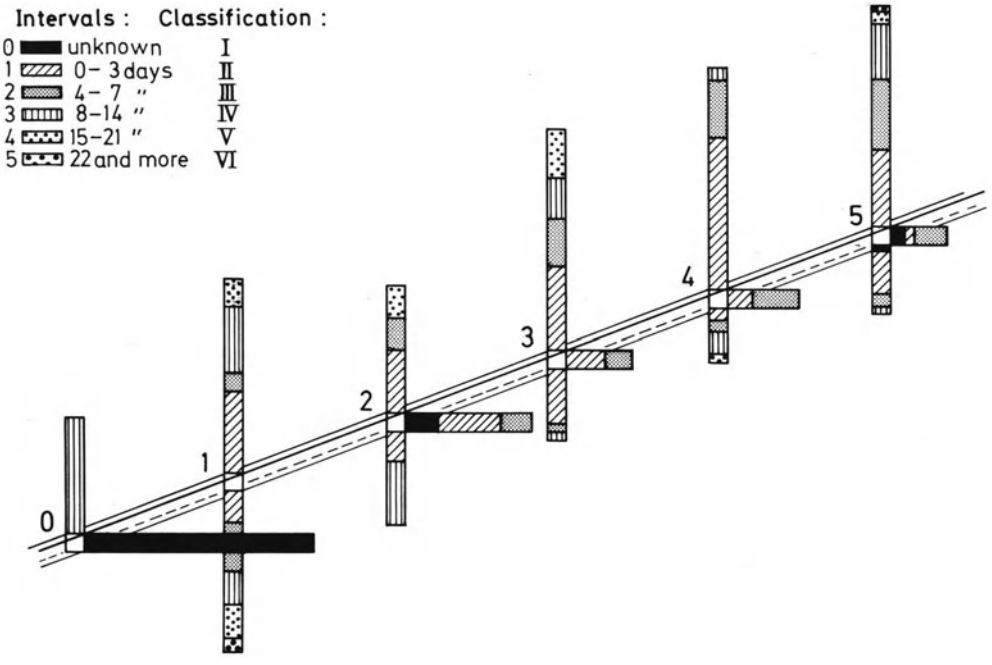

Fig. 3. Variations of symptomatology according to CAS classification from referring Hospital to follow-up examination according to time interval from first SAH to admission

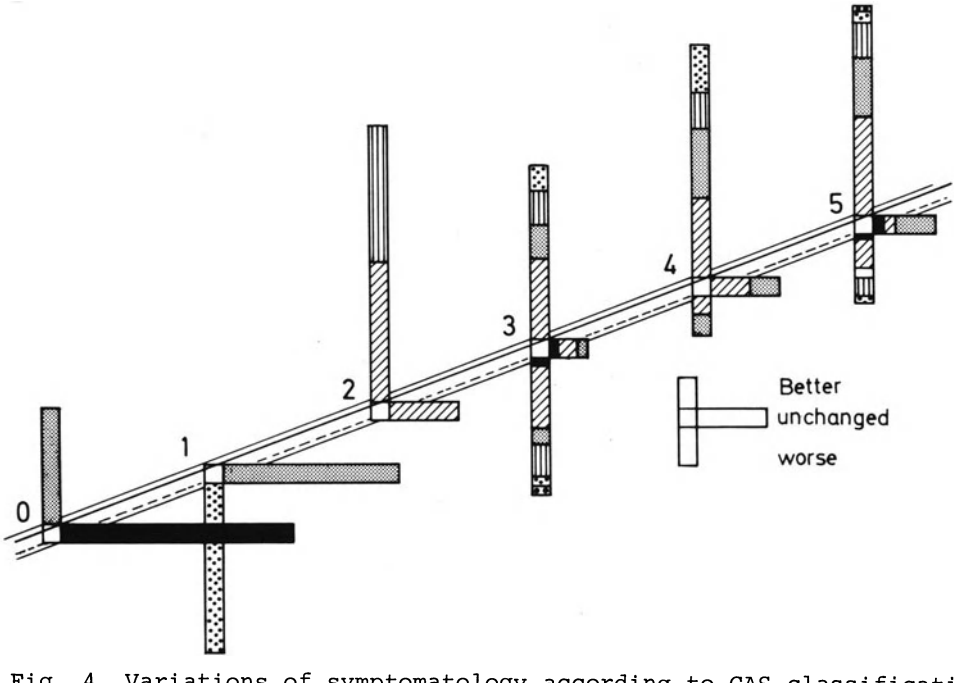

Fig. 4. Variations of symptomatology according to CAS classification from referring hospital to follow-up examination according to interval from SAH to operation

Subarachnoid Hemorrhage (SAH) and Intracranial Aneurysm – Spontaneous Course and Surgical Treatment in 227 Patients

L. M. AUER, B. GALLHOFER, G. LADURNER, F. HEPPNER, and H. LECHNER

Introduction

Timing of intracranial aneurysm surgery has been a matter of investigation, extensive statistical evaluations and debate for many years. Opinions as well as surgical techniques have changed and therefore, a re-evaluation is justified. The present paper contains the results of a joint neurological and neurosurgical study. The aim of this work was a more precise interdisciplinary treatment of patients with subarachnoid hemorrhage (SAH) and more optimal timing of operation of the aneurysms responsible.

One of the main points of discussion in the literature of the last few years has been the decision whether to operate upon a patient in good clinical condition during the first week after SAH. This problem is also of primary interest in this presentation.

Material and Approach

The histories of 227 patients were evaluated. All patients had suffered a SAH during the years 1960-1979 and were admitted to one of the two investigating units (Neurochirurgische Univ. Klinik, Neurologische und Psychiatrische Univ. Klinik, Graz).

An intracranial aneurysm was found by angiography in all cases. Of these patients, 118 were treated surgically by clipping, trapping or wrapping of the aneurysm. The last 20 cases were operated with microneurosurgical techniques. The second group, 109 patients, remained on conservative treatment for various reasons. Of the total number of 227, 100 were men and 127 were women. The neurological picture on admission was determined according to the grading scale of HUNT and HESS (6). CT-Scans were performed in the last 37 cases, these are described in detail elsewhere (8). Rebleeding was classified as "early" when it occurred within an interval of 30 days. Rebleeding after more than 30 days was defined as "late".

Mortalities were evaluated from survival rates during the stay in hospital. Survival and rebleeding rates from unoperated patients were calculated in order to compare their prognosis with that of operated patients. Taking into consideration the incidence of rebleeding as a function of time and of neurological grading, the timing of surgery for patients in different clinical conditions is defined.

Results

1. Conservative Treatment

Absolute numbers of early and late rebleeding are given in Table 1. Figure 1 shows percentages of rebleeding and the respective survival rates, separated into two groups of neurological grading (I-II and III-V). The general frequency of rebleeding was 30%. Grade I-II patients rebled much more frequently, totalling 55% compared with 20% in grading-group III-V (even among the survivors of the first SAH in grading-group III-V, the incidence of rebleeding was markedly lower than in the grade I-II group, namely 38,5%). The condition of 94% of the patients in whom there was rebleeding deteriorated as a result of the recurrent SAH, 31% of them never again achieving an operable condition. Table 1 indicates the earlier incidence of rebleeding in grade I-II patients than in grade III-V, which is also graphically demonstrated on Fig. 2. The mean interval is 11 days for grades I-II and 18 days for grades III-V. In grade I-II patients, seven days after the first SAH, 41% of rebleeding had occurred, 60% on day 10, 70% on day 14 and 95% on day 21.

The general mortality was 54%, 30% in grade I-II, 68% in grade III-V. All grade III-V patients, who rebled, died compared with 55% of grade I-II-patients. After an interval of 30 days, rebleeding occurred in 4,6% of cases, with a probability of a lethal outcome in 2%.

2. Postoperative Course

Late surgical treatment accounts for the high preoperative rebleeding rates on Table 1.

The general surgical mortality was 18%, 13% after an operation before rebleeding, 30% if rebleeding had occurred before surgery. The neurological condition was the second decisive factor: the mortality was 11% in grade I-II patients and 17% in grade III-V without rebleeding (Fig. 3). In patients with grade I-II and successful clipping of a saccular aneurysm, the mortality was 5,9%. In the subgroup of microsurgically treated patients, the general mortality was 10%. No grade I-II patient died following clipping.

Table 1. Numbers of patients with rebleeding

	Surgical group		Conservative group	
	Early	Late	Early	Late
Grade I-II	21	4	18	4
Grade III-V	5	2	12	1
Total	26	6	30	5
Average interval to rebleeding in days				
Grade I-II	10,3		11,4	
Grade III-V	13,2		18	
Total	11		15	

Discussion

The above results are in accordance with data from the literature regarding the incidence of rebleeding and mortality rates in the natural history of SAH due to an aneurysm (2, 4, 5, 9, 10, 12), especially when considering the high and early incidence of rebleeding in grade I-II patients (1, 7, 10, 11).

Comparison of surgical results with the prognosis in unoperated patients supports the value of surgery.

The main point in the optimal timing of an operation depends on the risk of fatal rebleeding in the different groups of clinical conditions. However, considerations in recent studies frequently excluded this problem and drew conclusions only from operative mortality rates following operation after various time intervals after the SAH (6, 11). For grade I-II-patients, the lowest mortality rates were found on day 1-2 and after day 10. Therefore, operations was recommended either within 48 hours, or after day 10. Within the rest of the first week, mortality rates of up to 15% were found. In our series, however, 60% of all rebleedings had already occurred by day 10, with a mortality rate of 18% in the whole group (Table 2). Adding mortality rates of operated surviving patients who rebled and those operated who did not rebleed a total mortality rate of 28% (Table 2) results, compared with 15% when operating on any of the "high risk days" during the first week after SAH (11). There seems no question, therefore, that operation in grade I-II patients should be performed as early as possible following the SAH.

Grade III-IV patients, on the one hand, rebleed significantly later and less frequently. On the other hand, many of these cases improve markedly within 14 days. Therefore, waiting for stabilisation or even improvement would seem justifiable. Mortality in grade V patients has been found and described as 100% (2, 3, 6). Transportation as well as operation are contraindicated for that reason.

Late surgery after an interval of 30 days is not to be recommended in the light of our own results as well as those of others (13).

Table 2. Patients with grade I-II

Mortality following surgery within first week after SAH	Mortality after waiting until day 10 after SAH	%
	Mortality from rebleeding	18,0
ca. 15%	Operative mortality of surviving patients with rebleeding	2,5
	Operative mortality of patients without rebleeding until surgery	7,4
		27,9

Conclusions for Timing of Surgery

1. Grade I-II patients should be investigated and operated at the earliest possible opportunity without a waiting period.

2. Grade III-IV patients should be operated when stabilization or improvement of the clinical picture has occurred (usually after 2 weeks). Early surgery within 24 h is rare.

3. Grade V is a contraindication for surgery.

4. Late surgery is most critical and needs very thorough consideration.

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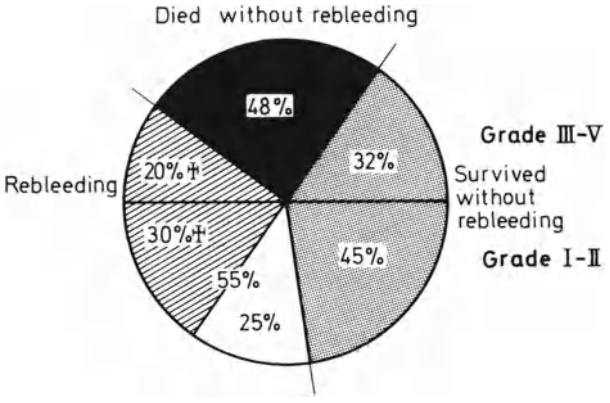

Fig. 1. Percentages of rebleeding and lethal outcome in conservatively treated patients with intracranial aneurysms and SAH. *Lower half:* grade I-II, *upper half: grade III-V*

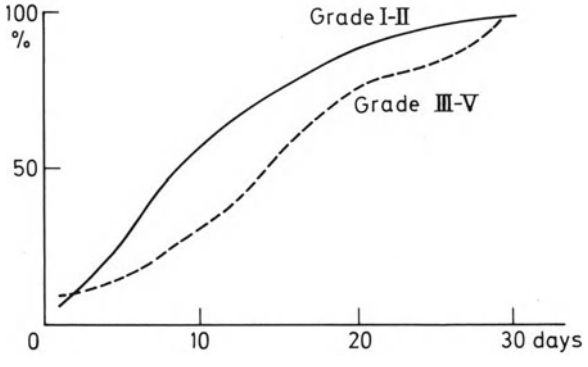

Fig. 2. Interval from first SAH to rebleeding. Percent of conservatively treated patients plotted against time in days. *Upper curve:* patients with grade I-II; *lower curve:* patients with grade III-V

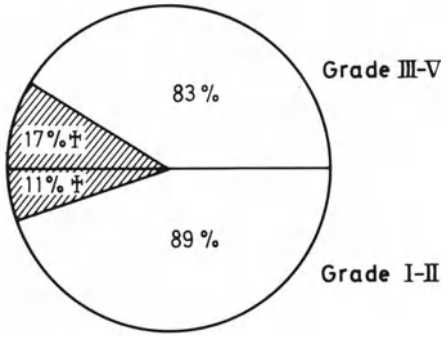

Fig. 3. Postoperative mortality rates of patients with no rebleeding and grade I-II *(lower half)* and grade III-V *(upper half)*

Treatment of Acute Subarachnoid Hemorrhages

U. MUHTAROGLU, H. KLINGE, and M. RAUTENBERG

During the years from 1975-1979 we treated 241 patients with subarachnoid hemorrhages. Aneurysms were found to be the source of bleeding in 139 patients and angiomas in 47 patients, while the cause could not be determined in 55 cases.

In recent years increasing numbers of patients have been admitted shortly after the onset of the hemorrhage, with the result that we were able to treat some severe cases on the day the hemorrhage began already (Table 1).

Local conditioning factors must also be taken into consideration in the "timing" of the diagnostic and therapeutic management. Thus, diagnoses could be made in over 70% of our cases within the first 24 h after admission (Table 2).

We detected 170 aneurysms in 139 patients. Mutiple aneurysms were subjected to surgery only when they could be reached by the same craniotomy.

Surgery was undertaken on 102 patients with 107 aneurysms (Table 3). Among the non-surgically treated aneurysms, there were also some autoptically verified aneurysms of patients, who were admitted *in extremis*.

Patients in grave danger, especially those with large space-occupying intracerebral hematomas, were operated immediately as a rule, so that in spite of the high risk, a number of patients of grades IV-V according to HUNT were treated by surgery in the first 24 hours. Patients in grades I-III were often operated on after only one or two weeks, especially if arterial spasm was suspected at arteriography and because of the clinical state, and also if the patient showed clinical improvement.

Regarding the question of the optimum time for surgery, we have continued to base our decisions on the individual cases and have not as yet been able to fix a certain program. This implies the risk of rebleeding of course, which we have had to observe in several of our patients.

According to case histories and clinical reports, we had 91 cases with multiple hemorrhage. Most of these patients were not brought to our clinic until re-bleeding had occurred.

Taking all our results into consideration (Table 4) we see the best results in patients of grade I-III, which is to be expected.

Table 2: see pp. 258 and 259

Table 1. Interval from SAH to admission

Grade	n	-1 Day	-3 Days	-7 Days	-2 Weeks	-3 Weeks	-4 Weeks	Over 4
I+II	72	///// ///// ////	///// ////	///// //	///// ///// ///// //	///// ///// /	/////	///// ////
III	56	///// ///// ///// //	/////	///// /	///// ///// /////	///// //	////	//
IV	56	///// ///// ///// //	/////	///// /	///// ///// /////	//// //	/	/////
V	57	///// ///// ///// ///// ///// ///// //	/////	///	////	///// /		/
Total	241	(36%)	(22%)			(42%)		

Table 3. Interval from diagnosis to surgery

Grade	n	-1 Day	-3 Days	-7 Days	-2 Weeks	-3 Weeks	-4 Weeks	Over 4
I+II	●39	●●●●●	●●○	●●●●●	●●●●●	●●●●●	●	●
		○		●●	●●●●○	○○		
					○			
	○ 6							
III	●21	●●●○○	●●●●○	●●●●●	●●●●○	●○	●○	●
			○	●●	○			
	○ 8							
IV	●18	●●●●●	●●●●○	●●●○	●○	●●	●	
		●●○○○	○					
		○○○○○						
		○						
	○13							
V	●24	●●●●●	●●	●●	●●			
		●●●●●						
		●●●●●						
		●●●○○						
		○○○○○						
	○ 7							
Total	●102	33	21	19	16	8	3	2
		32,3%	20,6%	18,6%	15,7%	7,8%	2,9%	1,9%
	○ 34	19	5	1	5	3	1	○
		55,8%	14,7%	2,9%	14,7%	8,8%	2,9%	

●, aneurysms; ○, angiomas.

Table 2. Interval from admission to diagnosis by CT and angiography

Grade	n	-1 Day	-3 Days	-7 Days	-2 Weeks
I+II	●49	●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ○○○○○ ○○○○○ ○○○○○	●●●●● ●●●●● ●○○○○ ○○○	●●●●● ●○○	●
	○22	○○			
III	●40	●●●●● ●●●●● ●●●●● ●●●●● ●●○○○ ○○○○○ ○○○○	●●●●● ●●●●● ●●○○○	●●○	●
	○16				
IV	●48	●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ○○○○○ ○○	●●●●● ●●●●○	●●●○	●
	○ 9				
V	●49	●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●●●●● ●○○○○	●○		
	○ 8	○○○			
Total	241				

●, aneurysms and angiomas; ○, no vasc. malf.

Even in the group of severe cases, who were in grades IV-V preoperatively, we were able to discharge 6 patients (10%) in good condition and 20 patients (almost 30%) in satisfactory condition, so that we feel justified in treating such patients by surgery despite the high risks involved.

Reference

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Table 2 *(continued)*

-3 Weeks	-4 Weeks	Over 4
	●	●
●●	●	
	●●	

Table 4. Preoperative condition and operative results on discharge

Grade	n ●	o	-1 Day	-3 Days	-7 Days	-2 Weeks	-3 Weeks	-4 Weeks	Over 4
I+II	31	2				| | |	| | | | |	| | | | |	| | | ⊖⊖
							| | | | |	| | | | |	
	3	1					| | | | ⊖	|	
							⊖		
	5	1					--	-	⊖
				+	+	++⊕			+
III	11	6				|	| | ⊖⊖⊖	| | | | |	⊖⊖
								| | | ⊖	
	9	3					----⊖	-----	-⊖⊖
	2	-			+	+			
IV	4	-					|	|	| |
	10	6				-⊖	-	--⊖	-----
				+⊕⊕	⊕⊕	++⊕	+⊕⊕		-⊖⊖⊖⊖
	4	7							
V	1	1					|		⊖
	3	1				-	-		-⊖
			+	+++++	+++++	++++⊕		⊕	+++⊕
	19	6		⊕⊕	⊕				
Total	102	34							

● Aneurysms o Angiomas

|	⊖	good
-	⊖	fair
+	⊕	dead

Surgery of Intracranial Aneurysms: Indications and Timing

G. LAUSBERG

During the past few years, the so-called right time for surgery of intracranial aneurysms has increasingly approached the time of the first subarachnoid haemorrhage, the ideal period being the first and second week following the initial haemorrhage.

To this effect, our clinical histories were analysed under the aspect of hospitalization following the first subarachnoid haemorrhage, and determination of the resulting time for surgery as well as the symptoms of the first subarachnoid haemorrhage, depending on the localization of aneurysm.

A review of our own patients (Table 1) in the Neurosurgical Clinic Bochum-Langendreer revealed 162 cases with subarachnoid haemorrhage and aneurysm treated from 1976 to March 1980. This figure does not include traumatic and angiomatous haemorrhages.

In 37 cases, no aneurysm was found as a cause for the subarachnoid haemorrhage and only in 4 cases was an angiographic diagnosis omitted in view of the poor condition of the patients. Of these, 13 died, the remaining patients survived but were affected by considerable neurological disturbances.

In 30 cases with identified aneurysm, no surgery was undertaken for various reasons yet to be discussed. 15 out of these cases died. In 93 cases, surgery was performed in the case of verified aneurysm. These included 95 patients with a history of one or several subarachnoid haemorrhages. In 6 cases giant aneurysms were found and 8 times there was no history of a haemorrhage. From this group of operated patients, 21 died. In 2 cases, an aneurysm was found incidentally during the cerebral diagnosis although there had been no haemorrhage. In both instances, no surgery was performed.

Table 1. Spontaneous SAH and aneurysms (without angioma). Neurosurgical Clinic, University of Bochum-Langendreer (1976-1980/March)

	n	Deaths
SAH without aneurysm	37	13 (35,1%)
SAH with aneurysm - no operation	30	15 (50,0%)
SAH with aneurysm - operation	85	20 (23,5%)
Aneurysm without SAH - operation	8	1 (12,5%)
Aneurysm as an incidental finding - no operation	2	-
Total	162	49 (30,2%)

The classification of the 93 operated patients (Table 2) shows the preferred involvement of the anterior communicating artery in a total of 42 cases. These included 8 giant aneurysms, 2 with a history of mild symptoms of a subarachnoid hemorrhage. These originated from the internal carotid artery 5 times and in 3 instances they were localized in the suprasellar region with corresponding visual disturbances and psychic changes. A double aneurysm was present in 12 of the 93 aneurysms.

An analysis of the time interval between the first subarachnoid haemorrhage and hospitalization in the Neurosurgical Clinic shows a mean value of 17.6 days in 144 cases. A breakdown into the various groups yields an average of 25.7 days for operated aneurysms, 9.5 days for non-operated aneurysms and of 5.9 days for subarachnoid haemorrhages without a verified aneurysm. What emerges from these figures is that the group of the non-operated aneurysms is affected by a poorer overall health condition with a high mortality rate of 50 and 35.1%. A breakdown into survivors and fatalities of the respective group indicates that the interval between subarachnoid haemorrhage and referral to the clinic was lower by 1/3 up to 1/2 within the respective group with a fatal outcome.

A total of 74 cases were referred from the department of internal medicine, 49 from a neurological centre and 19 cases were referred to us directly by the family physician or by emergency physicians. In the group of the operated aneurysms, the referral to the hospital was made 33 times by a department of internal medicine and 43 times by a neurological department. By contrast, the non-operated aneurysms were referred to the hospital 22 times by specialists for internal medicine and 11 times by the family physician directly. The high number of referrals from neurological clinics for the group of the oper-

Table 2. Aneurysms operations. Neurosurgical University Clinic Bochum (1976-1980/March)

Localization		n	Giant aneurysm among them	Double aneurysm among them
Internal carotid artery	right	17	1	2
	left	10	4	2
Anterior communicating artery	right	18	-	1
	left	24	2	1
Anterior cerebral artery (knee)	right	-	-	1
	left	2	-	2
Middle cerebral artery	right	11	-	3
	left	9	-	
Others		2	1	
Total		93	8	12

ated aneurysms explains the relatively long period of 25.7 days between the subarachnoid haemorrhage and referral to the neurosurgical department. This is due to the fact that the angiographic diagnosis is made by the neurological clinic itself in some cases. The patient remains there until angiography is undertaken and he is then referred to a surgical department.

A breakdown of the first symptoms furnished by 163 single and multiple bleedings in 123 cases of aneurysm shows disturbances of consciousness 88 times (54%) and primary brain stem sypmtoms 18 times (11.1%) with a particularly high incidence rate in the case of aneurysms involving the middle cerebral artery which showed an increased incidence of intracerebral haemorrhages. In 92 cases, headache and/or vomiting were the first symptoms of haemorrhage, whereas in 11 cases the subarachnoid haemorrhage presented with an epileptic seizure.

A review of the localization of the aneurysms and their relationship to multiple subarachnoid haemorrhages (Table 3) reveals the highest incidence of subarachnoid bleeding (40%) in aneurysms of the middle cerebral artery with an average interval of nine days and of only five days for the patients who died. The second highest incidence with 28.8% goes to the aneurysms of the anterior communicating artery with a mean interval of 25 days between the haemorrhages for the survivors and 13 days for those who died. The lowest recurrence rate (21.9%) for subarachnoid haemorrhages was found with aneurysms of the internal carotid artery, with 42 or 18 days intervening between the subarachnoid haemorrhages.

Table 4 shows the breakdown of the various causes for avoiding surgery in 30 cases of verified aneurysm with subarachnoid haemorrhages.

There were 5 aneurysms involving the region of the internal carotid artery and 10 aneurysms of the middle cerebral artery as well as the anterior communicating artery. Two of the patients were in a poor condition, but survived the bleeding. Three patients were not subjected to surgery because of a vascular spasm with a left-sided hemiparesis persisting for weeks. One patient recovered completely from the severe neurological and psychic disorders during a follow-up period of 2 years. In another case, slight hemiparesis on the right side remained and in the third case of recovery, the patient was left with moderate aphasia. Eleven cases presented with brain stem symptoms, 10 of them died and one survived with a mute autism syndrome. Six patients were not operated because they constituted risk cases due to

Table 3. Aneurysm localization and multiple SAH (n = 38)

Localization	Total number of aneurysms	Multiple SAH	Mean value (days) survivals	Deaths
Internal carotid artery	32	7 (21,9%)	42	18
Anterior communicating artery	52	15 (28,8%)	25	13
Middle cerebral artery	30	12 (40,0%)	9	5
Others	9	4	14	1
Total	123	38 (30,8%)	23	9

Table 4. Non-operated aneurysms with SAH (n = 30)

Localization		Poor state of health	Hemispheric failure	MBS/ BBS	Prior to operation (deaths)	Increased risk	Surgery rejected	Total
Internal carotid artery	Survivals	-	2	-	-	1	-	3
	Deaths	-	-	1	1	-	-	2 > 5
Anterior communicating artery	Survivals	1	1	-	-	1	3	6
	Deaths	-	-	3	1	-	-	4 > 10
Middle cerebral artery	Survivals	1	-	1	-	1	-	3
	Deaths	-	-	4	2	1	-	7 > 10
Others	Survivals	-	-	-	-	2	1	3
	Deaths	-	-	2	-	-	-	2 > 5
Total	Survivals	2	3	1	-	5	4	15
	Deaths	-	-	10	4	1	-	15 > 30

localization of their aneurysm and additional unfavourable factors such as age and internal diseases. Five cases survived in a good state, a female patient with an aneurysm of the middle cerebral artery died. Four cases died prior to the planned surgical intervention on account of a recurrent subarachnoid haemorrhage. In two of these cases the aneurysm involved the middle cerebral artery again. In one case, the second fatal subarachnoid haemorrhage occurred four days after the first bleeding, in the 3 other cases death supervened because of recurrent bleeding after 13 days once and twice after 21 days. The primary haemorrhage was accompanied by coma in each case. One of the patients died in the night preceding surgery, another patient died immediately after her transfer from the primary clinic. In 4 further cases, surgery was rejected by the patients, one of them had been afflicted by haemorrhage for the third time in 18 years.

From the group of subarachnoid haemorrhage without confirmed aneurysm, 13 out of 37 patients died, with the primary brain stem symptoms being present in 7 cases, while 5 cases had suffered a second subarachnoid haemorrhage with instantaneously ensuing brain stem symptomatology and one patient died due to pneumonia after the second subarachnoid haemorrhage.

Finally, a study of the symptoms associated with eight giant aneurysms shows that mild multiple subarachnoid haemorrhages had occurred in only two cases. The symptoms were usually visual disturbances in 6 cases and personality changes in 3 cases. Unilateral amaurosis was present twice for 5 years and once for 10 years.

In summary, the analysis of the 93 aneurysms which were treated by operation shows that the time of surgery was 36 days after the first haemorrhage on the average. Although the fatal course in 21 of the operated cases cannot be directly related to the interval between the first subarachnoid haemorrhage and the operative intervention, an attempt must be made to bring the time of operation much closer to the time of the first subarachnoid haemorrhage. The reason for this is that from the group of the 30 non-operated aneurysms, 4 cases died of a second subarachnoid haemorrhage within an average period of 13 days before surgery could be performed. It can be assumed that the fatal recurrent haemorrhage could have been avoided if the patients had been referred from the primary clinics at an earlier data, thus offering the possibility of timely surgery. Recurrent haemorrhages showed the highest incidence (40%) for aneurysms of the middle cerebral artery with a mean interval of 15 days for suvivors and of only 5 days for those who died. These are followed by aneurysms affecting the anterior communicating artery with 28.8% recurrent haemorrhages and the internal carotid artery with 21.9%. When giant aneurysms are present, the space-occupying characteristic stands to the fore, while subarachnoid haemorrhage play a subordinate role and, as a result, it is rather rare that the time of surgery is determined by acute symptoms.

Recurrent Subarachnoid Hemorrhage During Hospitalisation

D. VAN ROOST, P. OLDENKOTT, D. RINKER, and S. TODOROW

Introduction

In order to point out the risk of an early second subarachnoid hemorrhage after the patient's admission to the hospital, we analysed the data of *all* patients who entered our Tübingen neurosurgical department because of a subarachnoid hemorrhage (SAH) in the last 3 years.

Material and Approach

Of the 70 patients in this group - 40 males and 30 females (3) - 61 (87%) underwent angiography and 37 (52%) were examined by computer tomography (CT). In 70% of the cases, the etiology of the SAH was an aneurysm, in 14% an AV malformation. In one single case a tumor (LINDAU tumor) was found to be the cause of the SAH. In about 20% of all SAH, the etiology remained unclear. Thirty-four patients (48%) had suffered a SAH recurrence prior or after their admission to our hospital. The diagnosis of a recurrent hemorrhage was not always proven by a second lumbar puncture. Sometimes it was based on convincing anamnestic and clinical signs. Forty-two patients (60%) were operated on. The general mortality of the SAH patients during hospitalisation was 19/70 (27%).

Figure 1 shows the age distribution of the SAH-patients in our series in a histogram. Compared with larger studies (7), the age peak of SAH is moved to the left, towards a younger age. Most probably this is explained by our higher percentage (70%) of aneurysms (2, 6, 9).

Discussion

Searching for factors with prognostic value regarding the risk of a recurrent subarachnoid hemorrhage, we compared the primary with the recurrent SAH on 3 points:

1. on the presence of arterial hypertension, migraine, coagulopathy or diabetes in the history;
2. on the assessment of the clinical neurological state on the day after the first bleeding, as graded by BOTTERELL (1), and
3. on the etiology of the subarachnoid hemorrhage.

In 28% of the primary SAH and 26% of the recurrences, we found migraine in the history. A previously known hypertension occurred in both groups at the equal rate of 26%. A coagulopathy was seen in only 3 patients with primary SAH.

The incidence of several diseases was twice as high in patients with recurrences. These were *diabetes*, or the combination of *diabetes with hypertension*, or *hypertension with migraine*.

Comparing the patients' clinical findings soon after the SAH, no important difference was noted between the two groups, i.e. primary and recurrent SAH. The apparently paradox situation of small divergences in grade 1A and 4 (classification by BOTTERELL), namely a higher incidence of recurrences in the mildest cases may be explained as follows. In cases of dramatic post-hemorrhagenic states, intensive diagnostics and therapy are introduced much earlier than in cases with lighter and less differentiated symptoms.

The middle cerebral artery was found to be involved in a first SAH in 20% of the cases and in only 12% of the recurrences. Thus the MCA aneurysm seemed to tend to rebleeding (3) less than the average. The other origins of SAH did not present such a difference. A possible explanation for the smaller recurrence incidence of MCA aneurysms could be once again, that they lead to more prominent neurological symptoms and consequently *treatment* is initiated more quickly. A further factor may be a more solid tamponade of the aneurysm.

Figure 2 shows the incidence of SAH recurrences, grouped into time classes after the first bleeding. According to other authors (3), we found the highest risk of rebleeding between the *4th and the 14th day*, whereas the first 3 days represented a relatively *free interval*. Two weeks after the primary SAH, 54% of all recurrent hemorrhages had already taken place. Among the 10 post-angiographic recurrences, 4 occurred in the first 2 days after angiography, so that the question of causal relationship between angiography and rebleeding arises. Such a correlation is unlikely, however, (3) since the average time interval between primary SAH and angiography was found to be 12 days. This is usually performed in the most dangerous period, as far as recurrence is concerned. Anyway the interval between bleeding and angiography/operation became smaller as the grades of posthemorrhagic clinical condition became poorer (8). On the other hand, we observed a man, who suffered a sudden loss of consciousness in the street, and on whom immediate angiographic investigation was performed because the CT was not functioning. This showed an intracranial saccular aneurysm on the right internal carotid artery, which obviously rebled during this so early angiography as marked by an extravasation of contrast medium into an intracerebral hematoma (ICH) as well as into the ventricles.

While SAH mortality correlates directly with recurrences (2), morbidity, depends largely on vasospasms and ICH (11). In Fig. 3 the relationship is shown between the severity of initial symptoms and the presence of an ICH (in CT or in angiography).

We did not find a similar relationship between initial symptomatology and vasospasms, in spite of the generally assumed causal relationship between ICH-vasospasms (Fig. 4). The global percentage of vasospasms in our series was 41% (5). We try to explain the fact that the severe grades contain relatively few spasms by the earlier angiography in these cases, some are performed in the early posthemorrhagic period where spasms need not be expected (4, 11).

The CT findings of ischemia or edema each seemed to correlate to 60% positively with the presence of vasospasms in angiography. In 40% there was a false positive or false negative relationship.

Conclusions

1. The history of diabetes and the combination of hypertension with diabetes or with migraine seemed to be risk factors in the prognosis of a recurrent subarachnoid hemorrhage.

2. A good clinical status of the patient on the day of the primary SAH has a relatively higher recurrence risk, probably because of a delay in the diagnostic and therapeutic measures.

3. Inversely, the more obvious aneurysms of the MCA show a lower rebleeding risk. A more solid aneurysm tamponade in this region might be a second reason for this phenomenon.

4. The low rebleeding risk until the 3rd day after the primary SAH, and the markedly higher risk until the end of the 3rd week, should lead to a more rapid performance of diagnostic and therapeutic measures, as this has been the case in our series. The first hours after the primary SAH nevertheless remain unsuitable for angiography, and should be left to CT investigation.

5. The severity of the initial condition seemed to correspond definitely with the presence of an ICH, but not with vasospasms. These obeyed almost obligatory rules in their occurrence.

6. Between the CT finding of cerebral ischemia or edema and the angiographic finding of vasospasms, we found a slight positive correlation.

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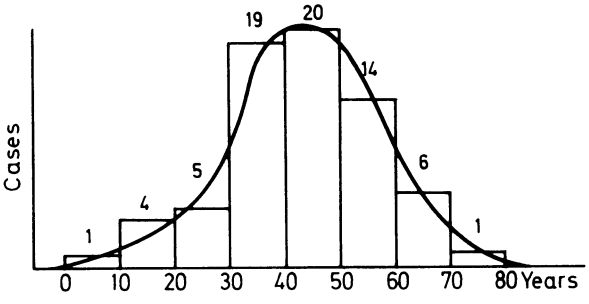

Fig. 1. Age distribution of SAH

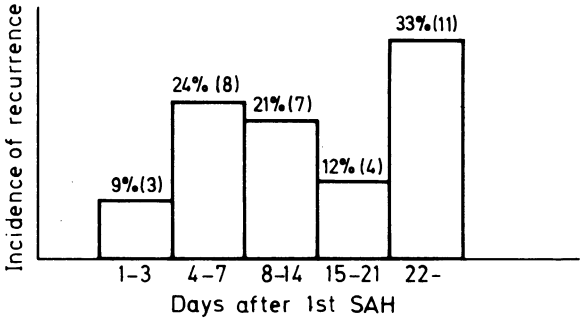

Fig. 2. Time distribution of recurrent hemorrhages after first SAH

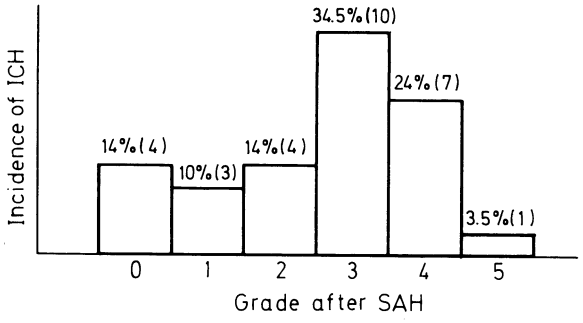

Fig. 3. Relationship between the presence of ICH after SAH and the initial clinical condition of the patient (classification of BOTTERELL)

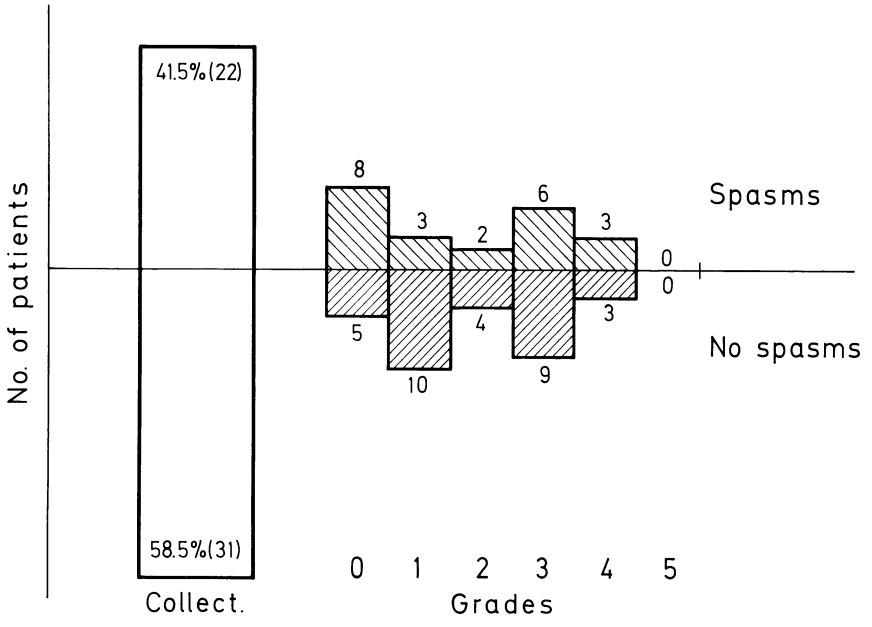

Fig. 4. Relationship between the presence of vasospasm and the initial clinical condition of the patient (grade classification of BOTTERELL)

Therapeutic Procedure in Aneurysms with Intracerebral Haematoma

P. GRUSS

Introduction

The extravasation of blood out of small sac-like aneurysms in the cerebral blood vessels, is usually into the subarachnoid space: the symptoms occasioned by such an event differ considerably, ranging from the characteristic attacks of severe headache to neurological clinical pictures accompanied by vegetative disturbances, and the manifestations of neurological deficits, and, in the extreme case, to sudden death in an apparently completely healthy individual. In contrast to subarachnoid bleeding alone, we are dealing with a cerebral space-occupying complication in the case of the intracerebral haematomas. This situation requires a special therapeutic orientation as our results and experience show.

Material and Approach

Over the last ten years 209 aneurysms have been treated at the Neurosurgical University Hospital at Würzburg. 28 of these were found to have an intracerebral haematoma. Some of these patients had been subjected to a lumbar puncture, and their cerebrospinal fluid was found to be more or less blood-stained. Four aneurysms were located on the carotid artery, 20 on the anterior cerebral artery or on the anterior communicating artery, 14 on the middle cerebral artery (Fig. 1). The findings were investigated on the basis of the medical records, the treatment measures recorded and critically evaluated (see Table 1 and 2).

Results

1. Carotid Artery Aneurysms

In the case of the carotid aneurysms giving rise to a haematoma, three patients presented with a so-called aneurysm of the carotid bifurcation. The thin-walled region surrounding the position of the anomaly, permitted the extravasation of blood into the basal parts of the frontal lobe. In the case of the bifurcation aneurysms, the haematomas were located not so far medially, but closer to the basal section of the fissure of SYLVIUS than was the case with the aneurysms of the anterior cerebral artery (Fig. 2a, b).

In one case, we observed a long extended supraclinoidal aneurysm of the carotid artery, whose posterior section extended to the basal parts of the brain, where an intracerebral hematoma developed.

Table 1

Aneurysm operation Age	Sex	Localization of aneurysm	Symptoms and grade	Day of treatment	Treatment	Follow-up
23	f	ICA	I-II, awake, hemi-paresis	1	Hematoma removed. Aneurysm clipped	Very good
55	f	ICA	II hemiparesis	1	Hematoma removed. Aneurysm clipped	Good, little paresis
33	m	ICA	III lethargic	1	Hematoma removed. Aneurysm clipped	+
35	f	IC	III-IV paresis mydriasis	1	Hematoma removed. Aneurysm clipped	+
37	f	ACA right	I awake	2	Hematoma removed. Aneurysm clipped	Very good
36	f	ACA left	II-III mydriasis	1	Hematoma removed. Aneurysm clipped	Very good
49	m	ACA left	II-III mydriasis	1	Hematoma removed. Aneurysm clipped	Very Good
49	m	ACA left	II	1	Hematoma removed. Aneurysm clipped	Good
25	f	ACA right	II hemiparesis	1	Hematoma removed. Aneurysm clipped	Good, little paresis
49	f	ACA + JCA	III hemiparesis	1	Hematoma removed.	+
49	f	ACA right	II hemiplegia	3	Hematoma removed. Aneurysm wrapped in muscle	+
41	m	ACA left	II lethargic	2	Hematoma removed. Aneurysm clipped	+
23	f	ACA left	IV mydriasis	1	Hematoma removed. Aneurysm clipped	+
72	m	ACA left	III-IV coma	1	Hematoma removed. Aneurysm clipped	+

Table 2

Aneurysm operation Age	Sex	Localization of aneurysm	Symptoms and grade	Day of treatment	Treatment	Follow-up
54	m	MCA right	Lethargic II	1	Hematoma removed. Aneurysm clipped	Very good
51	m	MCA left	Lethargic II	1	Hematoma removed. Aneurysm clipped	Very good
36	f	MCA right	Lethargic II	1	Hematoma removed. Aneurysm clipped	Very Good
58	m	MCA left	Lethargic II	1	Removal of hematoma. Aneurysm wrapped in muscle	Good
38	f	MCA right	Lethargic II	1	Hematoma removed. Aneurysm clipped	Good
37	m	MCA left	Semicoma III-IV	1	Hematoma removed. Aneurysm clipped	Paresis, dysphasia
40	f	MCA left	Lethargic III	1	Hematoma removed. Aneurysm clipped	+
50	m	MCA left	Lethargic III	1	Hematoma removed. Aneurysm clipped	+
37	f	MCA right	Semicoma III	1	Hematoma removed. Aneurysm clipped	+
30	m	MCA right	Semicoma III-IV	1	Hematoma removed. Aneurysm clipped	+
37	m	MCA right	Semicoma III-IV	1	Removal of hematoma. Aneurysm wrapped in muscle	+
38	m	MCA right	Semicoma III-IV	1	Hematoma removed. Aneurysm clipped	+
60	f	MCA right	Semicoma III-IV	1	Removal of hematoma. Aneurysm wrapped in muscle	+
55	f	MCA right	Coma IV-V	1	--------	

2. Aneurysms of the Anterior Cerebral Artery

The hematomas arising either from aneurysms of the anterior communicating artery or from the anterior cerebral artery itself, were located in the fronto-basal region, close to the mid-line. Some of these attained a considerable size, in particular in the posterior direction (Figs. 3, 4). The aneurysms located in the region of the anterior cerebral artery and accompanied by a hematoma, were all treated surgically via a sub-frontal approach.

3. Aneurysms of the Middle Cerebral Artery

Space-occupying hematomas originating from aneurysms of the middle cerebral artery were found in the region of the fissure of SYLVIUS and expanded into the temporal part of the brain, usually having the shape of an egg. As seen by the operating surgeon, the greater part of the hematoma was located over the aneurysm, which could then be approached after aspiration and removal of the coagulated blood. The temporal space-consuming processes were often discrete in the angiographic picture (lacking or slight shift of the anterior cerebral artery), but usually manifested a progressing clinical course. Fig. 5a shows a computerized tomogram with the typical localization of a temporal intracerebral hematoma, taking its origin in a small bean-sized aneurysm at the "trifurcation" of the left middle cerebral artery (Fig. 5b).

4. Vascular Spasm

In those patients in our case material (aneurysms with intracerebral hematoma) who were subjected to angiography, we observed vascular spasms in the region of the intracranial (intracerebral) parts of the carotid and the initial segments of the middle and anterior cerebral arteries in two cases of carotid artery aneurysm. Slight vascular spasms were seen in only two of the cases of anterior cerebral artery aneurysm. A marked vascular spasm was observed in a case of aneurysm of the middle cerebral artery and a very slight spasm in two of the aneurysms of the middle cerebral artery accompanied by an intracerebral hematoma.

Discussion

1. Remarks on the Surgical Procedure

a) Aneurysms of the Carotid Artery. The surgical approach to the carotid artery aneurysm, which only rarely gives rise to an intracerebral hematoma (see PIA, 1979, SANO, 1979 and SUZUKI, 1978), is quite naturally, from the anterior aspect, so that in contrast to the aneurysms of the middle and anterior cerebral artery, the anomaly itself is seen first, before the hematoma can be removed. Alternatively both the hematoma and the vascular anomaly present simultaneously (see Fig. 1). Thus, treatment of the source of the bleeding is carried out at the same time as the surgeon deals with the hematoma.

If an intracerebral hematoma has no clinically relevant space-occupying character, it may be sufficient to clip the "neck" of the anomaly, and to leave the hematoma untreated.

With respect to the evaluation as to whether and when space-occupying properties of a cerebral hematoma require therapeutic measures, continuous intracranial pressure measurement might also be an important requirement in addition to constant observation (GAAB et al., 1979).

b) Aneurysms of the Anterior Cerebral Artery. In our opinion, the sub-frontal approach to an aneurysm of the anterior cerebral artery accompanied by an intracerebral hematoma is to be preferred to the inter-hemispheric approach described by TÖNNIS and WALTER, 1966. As a rule, the hematoma is removed by a small fronto-basal cortical incision, somewhat anterior to the region of the gyrus rectus, that is somewhat lateral to the aneurysm itself, to avoid "awakening" it. Following the evacuation of the hematoma, the frontal lobe sinks inwards, so that the search for the vascular anomaly is made possible. The sub-frontal approach should always be performed from the hematoma side - the orientation with respect to its localization is more important than any consideration for the so-called dominant hemisphere. This also applies when it is possible to deal with the source of bleeding without removing the hematoma, as the case of a 50-year-old male patient showed us, in whom the carotid bifurcation, the course of the anterior cerebral artery and the neck of the aneurysm were exposed (aneurysm clipped) without the hematoma revealing any space-consuming character. The hematoma was obviously absorbed subsequently, since patient recovery was complete.

c) Aneurysms of the Middle Cerebral Artery. The aneurysms of the middle cerebral artery accompanied by a hematoma is approached from the temporal side, by dissecting the fissure of SYLVIUS, the incision being made directly beneath the vein. When the hematoma has been removed, the aneurysm generally becomes visible. In the case of rapid clinical development and a typical localization of a spontaneous temporal intracerebral hematoma, we would forego carotid angiography in view of this situation. This is how we actually proceeded in the case shown in Fig. 5a, b.

2. The Acute Situation

The severity of the clinical picture in cases of ruptured aneurysms is independent of whether the bleeding has occurred into the subarachnoid space, or into the brain substance (see BUSHE, 1973). The large majority of authors do not strictly separate their cases according to the type of hemorrhage (ANDREWS and SPIEGEL, 1979; HORI and SUZUKI, 1979; NORNES and WIKEBY, 1979; YOSHIMOTO et al., 1979). Other investigators refer to the special intracerebral form of hemorrhage and its therapeutic consequences, only en passent (TROUPP, 1976 and BRENNER and BÖCK, 1976).

Admittedly, SANO (1979) and PIA (1979) do differentiate their intracerebral hematomas. In the first instance, the aneurysm accompanied by an intracerebral hematoma, is to be considered as an acute case. Usually the cerebral local space-occupying character of the lesion is the most important clinical feature and urgently demands relief. Only rarely do conservative measures have the effect of slowing down the progressive course of the disease. The planning of the therapeutic measures to be taken should be effected immediately after the establishment of the diagnosis on the basis of neurosurgical considerations. Hopeless cases should be excluded from active therapeutic measures early (see also TROUPP, 1976).

3. The Question of Vascular Spasms

The tendency of aneurysms to bleed and give rise to a space-occupying lesion, to some extent depends on their localization with respect to the vascular and cerebrospinal fluid system. The more peripheral the location of the aneurysm, the greater is the tendency for cerebral hemorrhage to occur, since the cerebrospinal fluid spaces in the neighbourhood of the small vessels are correspondingly smaller. The location of the thin areas in the aneurysm wall must be closely related to the cerebrum so that a hematoma may develop within the substance of the brain. Our findings show that intracerebral extension of aneurysm bleeding is less likely to trigger a vascular spasm than typical bleeding into the subarachnoid space. In the case of the subarachnoid hemorrhage, the vasogenic effect of noxious substances is apparently distributed together with the blood within the cerebrospinal fluid. In the case of the intracerebral hematoma, these noxious substances are quite possibly, "bound up" within the hematoma, where they lose their effect. This is thought to happen in the case of intracerebral hematomas associated with aneurysms, where blood-stained cerebrospinal fluid is also usually found.

Conclusion

Of the total of 209 aneurysms of the cerebral blood vessels observed, the various types of hemorrhage are differentiated: 181 subarachnoid hemorrhages and/or oculomotor syndrome and 28 intracerebral hematomas. The last-mentioned type of bleeding is regarded as a space-occupying complication. Its particular pathological character is emphasized, since it requires a special therapeutic orientation. The aneurysm accompanied by an intracerebral hematoma, is to be considered an acute case in the majority of cases. A wait-and-see, conservative attitude to therapy is applicable only when such intracerebral hematomas do not manifest a clinical space-occupying character, which then require appropriate observation and therapeutic planning.

The various surgical approaches are discussed. If at all possible, the elimination of the source of bleeding and the removal of the hematoma is the objective. The apparently slight tendency of the cerebrovascular system to respond to the intracerebral type of aneurysmic bleeding with vascular spasm is emphasized and briefly discussed.

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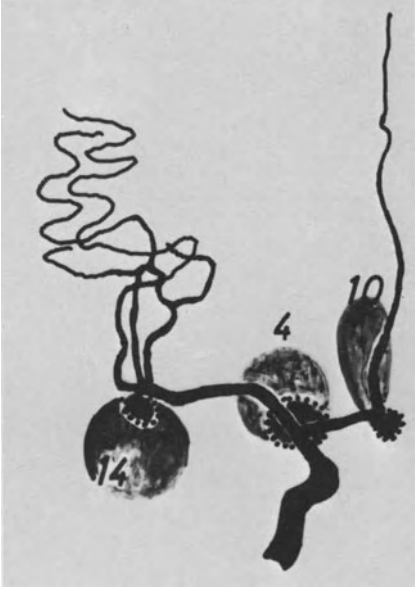

Fig. 1. Diagram of the localization of 28 aneurysms with intracerebral haematomas, as found in the case material consisting of 209 cerebral vessel aneurysms. These include four aneurysms in the carotid artery, of which only one was suparclinoidal, three so-called carotid-bifurcation aneurysms, ten in the region of the anterior cerebral artery or the anterior communicating artery and 14 at typical sites on the middle cerebral artery

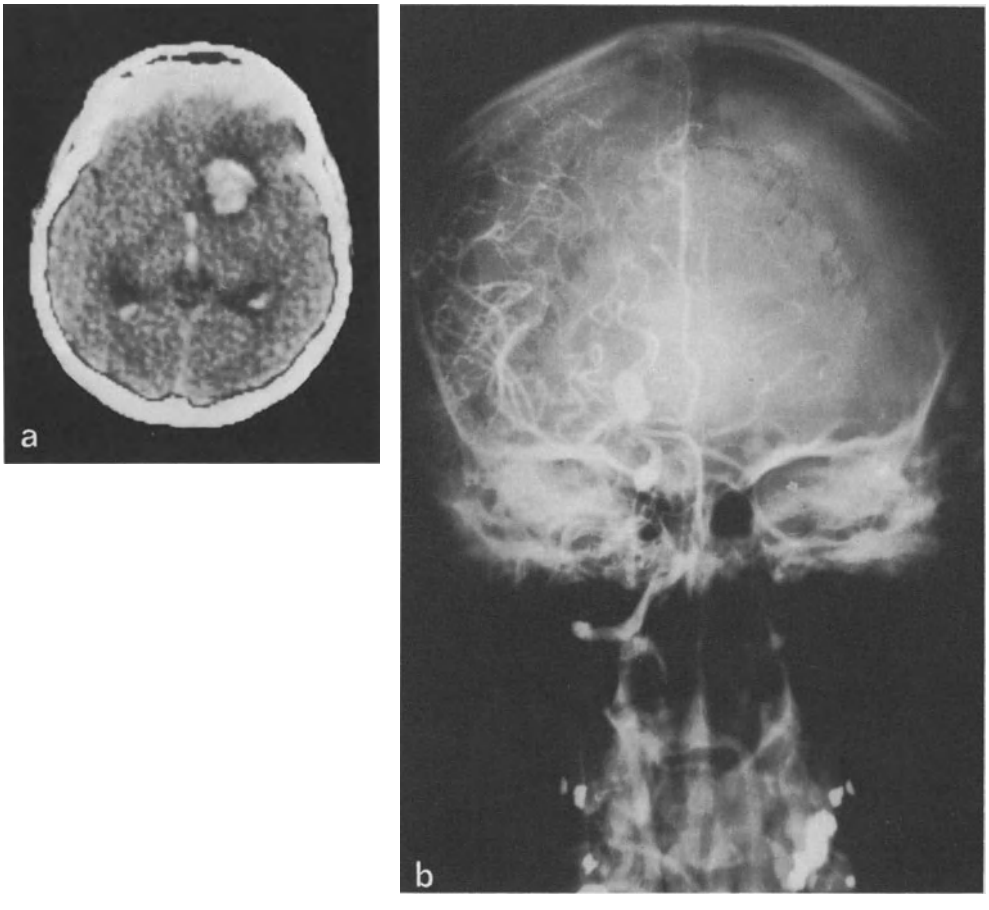

Fig. 2. a CT of an intracerebral haematoma originating from a carotid-bifurcation aneurysm. b The slight space-occupying character of the haematoma manifests in a discrete displacement of the basal parts of the anterior cerebral artery. The bean-sized aneurysm of the carotid bifurcation can be recognized

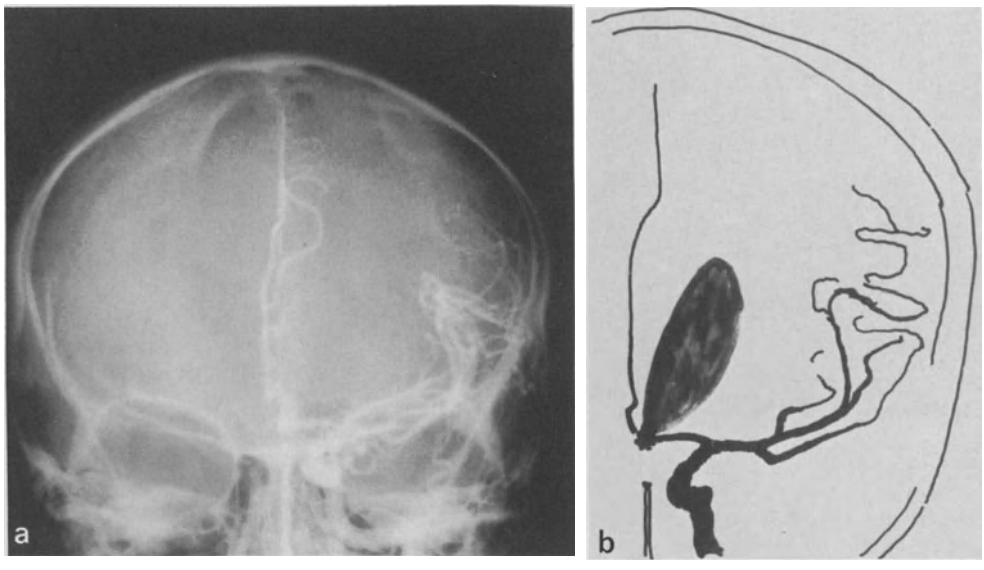

Fig. 3. a Anterior cerebral artery aneurysm accompanied by an intracerebral haematoma, whose space-occupying character is clearly manifest in the displacement of the blood vessel. b The schematic representation of the localization of the haematoma in the a.p. view, corresponding to Fig. 3a

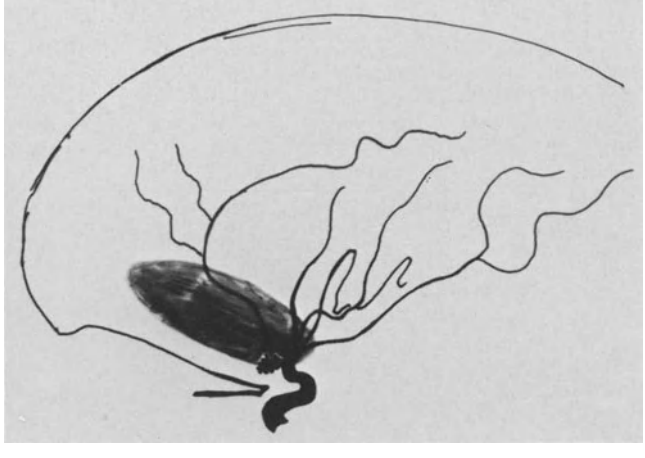

Fig. 4. The localization and extent of the haematoma seen in the lateral view. A striking observation in this case was the fact that no vascular spasm was demonstrable (see also Fig. 3a)

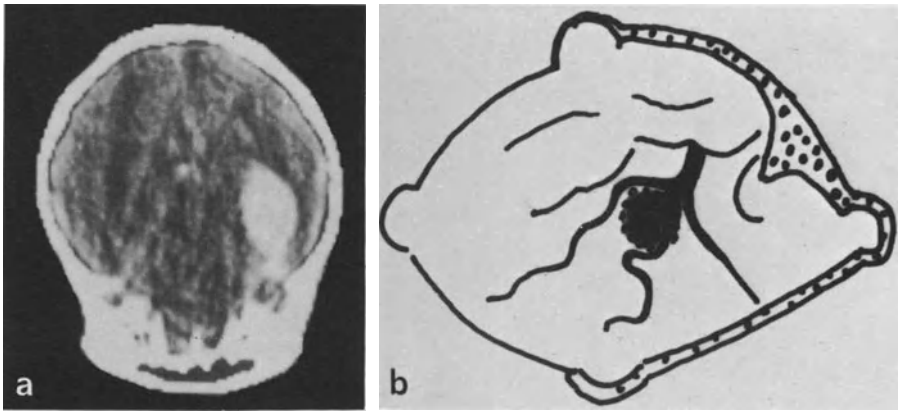

Fig. 5. a Haematoma in the left temporal region, spontaneous development from an aneurysm of the middle cerebral artery. b Schematic localization of the aneurysm at the "trifurcation" of the left middle cerebral artery. After removal of the haematoma, the aneurysm was dealt with by clipping

Prophylactic Extra-Intracranial Arterial Anastomosis in Cases of Large Aneurysms

J. BOCKHORN and K.-A. BUSHE

In contrast to aneurysms with subarachnoid hemorrhage or intracerebral hematomas, the timing of surgery in cases of large aneurysms is not primarily dependent on the rupture or the danger of recurrent bleeding. Giant aneurysms are defined as aneurysms with a diameter of more than 2.5 cm according to MORLEY (12). Normally these aneurysms do not attract attention because of a rupture but because they lead to signs of a space-occupying lesions and brain compression (9, 18).

Case Reports

In 1979 extra-intracranial arterial anastomoses were first performed as the initial step in the treatment of large intracranial aneurysms in four patients. In one patient a fusiform aneurysm close to the trifurcation of the middle cerebral artery was found. In another patient an aneurysm of the cavernous sinus region of the internal carotid artery was treated and in two cases large aneurysms of the intracranial carotid artery bifurcation were seen.

Technical details of the extra-intracranial arterial bypass procedure will not be discussed in this paper. The postoperative course after this operation and after the surgical procedure for the aneurysms itself seems more important.

In the first patient in whom a large aneurysm of the middle cerebral artery was detected, whose clinical symptoms indicated a space-occupying lesion and where computer tomography suggested a meningioma, the aneurysm was treated surgically several weeks after creating an extra-intracranial arterial bypass. At this time the aneurysm was found to be fusiform. It was treated by wrapping with dura and fibrine adhesive. Nevertheless the rupture of the aneurysm occurred some days later. After the rupture the aneurysm had to be excised completely. A slight postoperative hemiparesis improved over the following four weeks. Half a year after the removal of the aneurysm, there was almost no neurological deficit.

A similar uncomplicated course was observed in the patient with a large fusiform aneurysm of the internal carotid artery in the region of the cavernous sinus. Four weeks after the extra-intracranial anastomosis, the occlusion of the internal carotid artery in the neck was begun in this patient and completed two weeks later. Neurologic disturbances did not occur. The aneurysm was not visible at angiography four weeks later. The perfusion of large areas of the middle cerebral artery territory occurred by the surgically created anastomosis. In addition there was also collateral circulation from the opposite internal carotid artery from the anterior part of the circle of WILLIS.

Problems arose only in two patients with large aneurysms of the internal carotid bifurcation. In the first patient an ischemic lesion of the opposite middle cerebral artery, which was not protected by an additional extra-intracranial bypass, occurred after the complete occlusion of the ipsilateral internal carotid artery by a SALIBI clamp. In this case it must be assumed that an occlusion of the stem of the opposite middle cerebral artery occurred either by direct compression due to the thrombosed aneurysm or by progressive thrombosis from the right to the left side with thrombosis of the anterior communicating artery (11). Computer tomography revealed signs of ischemic lesions only in the fronto-temporal area (Fig. 1) perfused by the ipsilateral middle cerebral artery. Remarkable is the course in the fourth patient in whom a large aneurysm of the intracranial carotid bifurcation was found. After occlusion of the internal carotid artery in the neck over a period of two to three weeks, a progressing thrombosis of the aneurysm was found in the follow-up computer tomography, which began four weeks after creating the extra-intracranial anastomosis. But some four weeks later, a sudden deterioration of the neurological symptoms occurred with signs of an acute space-occupying lesion (headache and reduced level of consciousness). At computer tomography, there was still a filling of the aneurysm (Fig. 2) which surprisingly came from the bypass as was shown by angiography (Fig. 3). The large aneurysm was approached directly, and the blood-filled part was removed as well as the thrombosed areas. Although there was no connection between the perfusion area of the middle cerebral artery with the internal carotid artery of the same side or with the perfusion area of the opposite side, no deterioration of the neurological findings occurred.

Discussion

In large aneurysms especially in the region of the middle cerebral artery, the exact vascular relationship branching off the aneurysm from the parent vessel often cannot be visualized in spite of refined angiographic procedures. In some cases it is not possible to differentiate between a berry aneurysm and a fusiform aneurysm and it cannot be decided whether a berry aneurysm has a neck which may be occluded by an aneurysm clip. Furthermore it is sometimes difficult to decide whether there are important supply vessels close to the aneurysm which may possibly be occluded with a clip as well. The same problems exist in cases of large aneurysms in the region of the intracranial bifurcation of the carotid artery which often cannot be treated primarily by intracranial surgery. In this situation an occlusion of the extracranial internal carotid artery in the neck with subsequent thrombosis of the internal carotid artery and thus thrombosis of the aneurysm must be achieved. This is especially true for aneurysms close to the base of the skull, especially in the cavernous part of the internal carotid artery. These aneurysms are hardly accessible by direct surgical intervention. Here the stepwise ligation of the internal carotid artery in the neck is the only way of treatment (3).

The risk of the stepwise occlusion of the internal carotid artery by SELVERSTONE - or SALIBI - clamp are well known. Despite very slow and careful occlusion of the artery - in the sense of a vascular training, which should result in intracranial and intracerebral collaterals to the dependent perfusion area of the carotid artery, especially to the dependent middle cerebral vascular bed - ischemic lesions of the middle cerebral artery region with hemiparesis develop in certain cases, 24-36 hours after the complete occlusion of the internal carotid artery (10, 13, 14, 15).

Therefore it seems important to create a prophylactic extra-intracranial arterial bypass as the first step in the treatment of large aneurysms of intracranial vessels so that a time interval can elapse in which the anastomosis can establish itself. Then the operation of the aneurysm - either by stepwise occlusion of the internal artery or by a direct operative approach to the aneurysm may be performed. Even with faultless surgical technique and with adequate medical postoperative therapy, the risk of a thrombotic occlusion of the anastomosis in the region of the end-to-side suture line is 10 to 15% (2, 6, 16). The time of the highest risk of occlusion of the anastomosis is seen in the second and third week. After that time spontaneous recanalisation is possible.

A time interval of four to six weeks elapsed in our four patients between the anastomosing procedure and the surgery for the aneurysm. The anastomoses remained patent during this time although there was no real flow to the intracranial vascular territory. This was also the case in hypotonia which was achieved by medical therapy in the first patient.

Conclusion

The treatment plan of other authors (1, 4, 8, 17) who create the anastomosis and clip the aneurysm in one surgical procedure without the possibility of proving the patency of the anastomosis - those authors postulate a pressure gradient from the extra- to the intracranial vascular distribution for the patency of the anastomosis - harbours a larger risk of ischemic lesions than the two-stage procedure, particularly because of risk of rupture, which is dangerous in berry aneurysms, is very low in these large aneurysms.

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Fig. 2. CT-series with contrast enhancement (except lower left), aneurysm of the right intracranial carotid bifurcation
28.08.1979: STA-MAC anastomosis on the right side
28.09.1979: Carotid occlusion in the neck started
15.10.1979: Carotid occlusion in the neck completed
28.11.1979: Re-filling of the aneurysm in the frontal part (without and with contrast enhancement)
18.01.1980: Result 1 month after surgical exposure and partial removal of the aneurysm

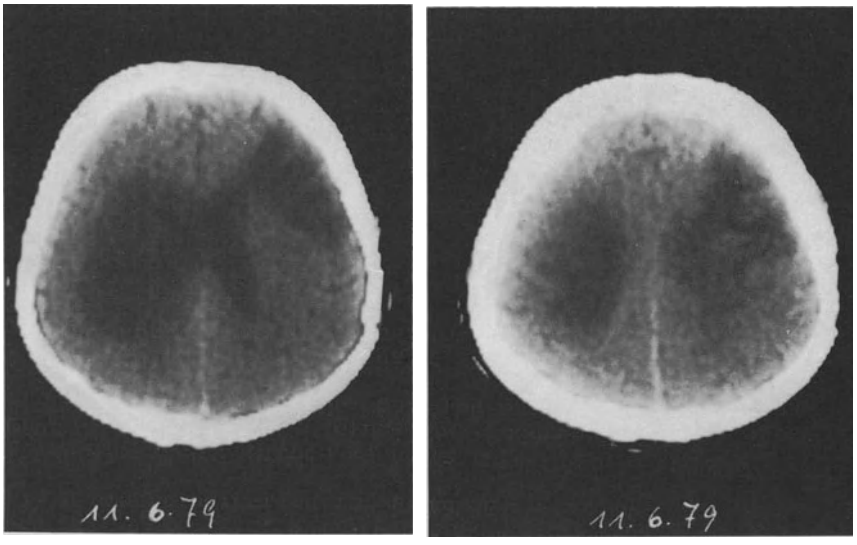
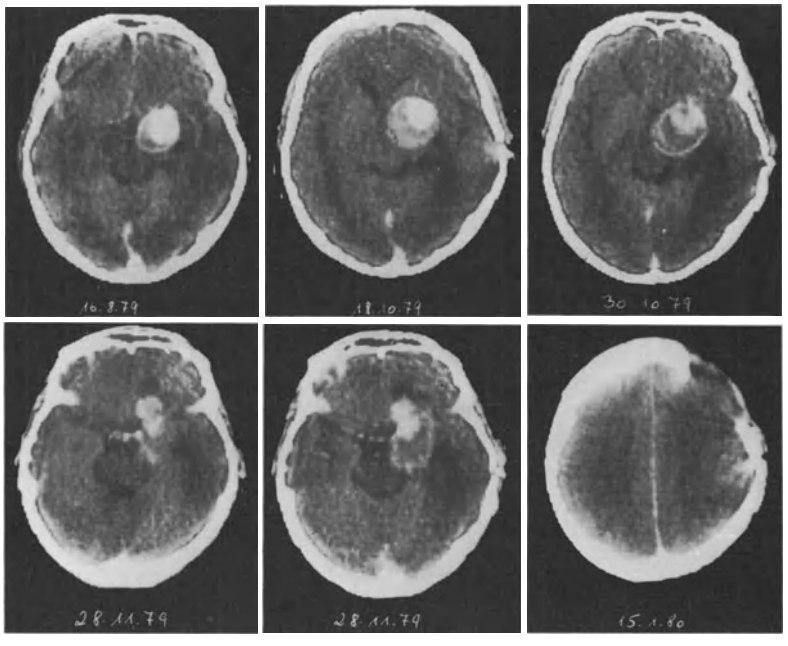


Fig. 1. Patient with large aneurysm of the right internal carotid artery bifurcation. 6 weeks after total occlusion of the right internal carotid artery in the neck, 3 months after STA-MCA (superior temporal artery - middle cerebral artery) anastomosis on the right side.
Hypodense areas on the left side corresponding to the middle cerebral artery region and in the right frontal-temporal area as signs of ischemic lesions



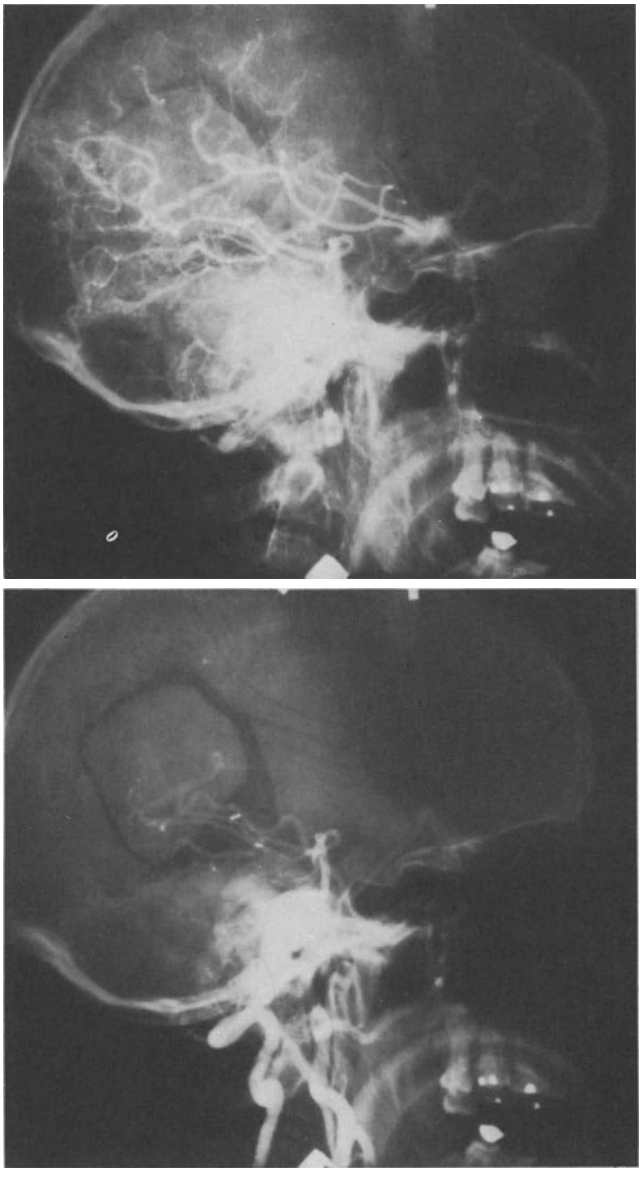


Fig. 3. Angiographic picture of re-filling of the aneurysm by means of the right STA-MCA anastomosis (corresponding to Fig. 2)

Timing Problems in the Diagnosis and Treatment of Subarachnoid Hemorrhage

Round Table Discussion

Under the Co-Ordination of Prof. MARGUTH

Prof. Marguth: I believe we should refer briefly to the symptomatology and discuss the necessary diagnostic measures. Obviously there are differences of opinion here. The subarachnoid hemorrhage in the clinical state grade one is often mistaken. In our patient material for example, these patients were thought to have neck-shoulder-syndrome, migraine, intoxication or botulism. We all know of cases where such a diagnostic error was fatal because of the subsequent recurrent hemorrhage. The question arises as to whether all these patients should have a lumbar puncture. Of course, the answer is no. However, I would say that such a procedure is indicated in all cases where acute headache is accompanied by vomiting. Furthermore the lumbar puncture should be drawn into consideration in all cases where a second attack occurs within several minutes or several hours, even if there is no loss of consciousness. Now I would like to ask Dr. BUSHE about the further procedure when the diagnosis of a subarachnoid hemorrhage is certain.

Prof. Bushe: In principle we should admit all subarachnoid hemorrhages in the clinical stage 1 and 2. The danger of a recurrent hemorrhage occurring during the transport is just as great in the time interval before angiography or operation. For the stages 3 and 4 there are no immediate operative consequences. Immediate referral is indicated in the case of patients with signs of beginning midbrain compression such as unilateral dilatation of a pupil.

Prof. Marguth: This would also mean immediate admission to our neurosurgical departments for patients, who have regained consciousness and for those, who have had no disturbance of consciousness, but definite proof of a subarachnoid hemorrhage. We would also have to admit patients with signs of a beginning midbrain compression as a result of a massive intracerebral hemorrhage. For these patients there is an absolute indication for operation, but there is no such indication for patients with bilateral dilated pupils. I have never seen a patient survive who has had no pupil reaction to light for a period of 40 min.
Now to the question of the right time for angiography, here too, I would like to hear your opinion, Dr. BUSHE.

Prof. Bushe: In the stages 1 and 2 there is a general tendency to operate within the first few days. Therefore angiography must necessarily be performed as soon as possible after admission. As Dr. KNEISSEL has pointed out, the danger of a recurrent hemorrhage during angiography is low. In the stages 3 and 4, angiography in the acute phase would have no therapeutic consequences, so that it seems reasonable to delay angiography in these cases.

Prof. Pia: One objection: Repeated angiographies are bad. If the angiograms are inadequate or technically of poor quality and angiographies

have to be repeated within the first days after subarachnoid hemorrhage, they have a gigantic morbidity and occasionally, mortality. Therefore we tell our colleagues in the peripheral hospital, "Don't do the angiograms yourselves, leave them for us". We perform the angiogram on the first or second day.

Prof. Marguth: The visualization of aneurysms demands experience and in the case of aneurysms of the anterior communicating artery, tangential views have to be shot in order to demonstrate the aneurysm. One question which we should perhaps ask Dr. FROWEIN: "What do you do when the aneurysm cannot be visualized at angiography, although there is definite proof of a subarachnoid hemorrhage?"

Prof. Frowein: I assume that a computer tomogram has been made which shows blood in the subarachnoid spaces; in that case angiography should be repeated after a suitable time interval. However, I would like to bring the factor of age into the discussion. I have shown that the age factor is of great significance and we must prevent a wave of subarachnoid hemorrhages which come from cerebrovascular lesions and not from aneurysms. Right from the start, it should be said "Admission up to the age of 50, in cases with good clinical condition up to 60 years of age, but above 60 a longer waiting period is always necessary".

Prof. Loew: I cannot quite agree that angiography should not be performed immediately on patients in stage 1 and 2. I am of the opinion that these patients should undergo angiography immediately and should then be operated on. If stage 1 and 2 have remained unchanged from the time of the subarachnoid hemorrhage up to the admission to hospital, then this is the most favorable point in time for the operative treatment, provided - and here comes our provided limitation which has nothing to do with the patient - we can manage this as far as the organisation and the capacity of our departments are concerned.
The operation of an aneurysm cannot be performed in an emergency operating room, there must be optimum technical conditions for this procedure. But the prerequisite for operating the patient at the earliest possible moment is the angiographic visualization. Therefore I recommend immediate angiography for those patients in whom immediate operation is possible as far as their clinical condition is concerned, not for the others.

Prof. Marguth: The reason for this is to avoid the recurrent hemorrhage which may have a fatal course in some cases.
There has been surprisingly little discussion on the antifibrinolytic therapy here. If the antifibrinolytic treatment would really guard the patient against one or more recurrent hemorrhages, then the decision when the operation should be performed would be considerably easier. I think we should hear something about the basic principles and the clinical results of the antifibrinolytic treatment and perhaps I could ask Dr. BECK to say a few words about this.

Dr. Beck: Although the good results of the antifibrinolytic treatment were more empiric at the beginning, the effect of this treatment has been proven by chemical laboratory results in the meantime. The principle of the antifibrinolytic therapy is to stabilize the thrombus which is formed at the perforation point of the aneurysm. This thrombus is stabilized from the inside by influencing the blood and from the outside by the arachnoid membrane. Two aspects are important:
1. The antifibrinolytic therapy must be begun immediately. Apparently there is no advantage if this antifibrinolytic therapy is begun 14 days or 3 weeks after the subarachnoid hemorrhage and 2. a certain blood level must be reached. These two conditions must be satisfied

and if you do that, then you will have good results. I always had an uncomfortable feeling today when I heard of the high recurrence rates. We have done this for many years and so have the other departments working with us, and we have a recurrence rate of 5% at the most. The antifibrinolytic treatment has a high level of effectiveness and therefore all risks of thrombus formation must be drawn into consideration. However, large statistics show that the amount of thrombus formation is not significantly higher than for other neurosurgical patients. Naturally antifibrinolytic treatment is stopped as soon as the aneurysm has been operated. I am not recommending the antifibrinolatic therapy for the treatment of aneurysms, it is only a prophylactic measure until the aneurysm can be clipped. In a series of 300 patients in grade I we have not had a single recurrent hemorrhage within the first week. The prerequisite is that the antifibrinolytic treatment is begun with the first 2 days after the subarachnoid hemorrhage.

Prof. Bushe: Yes, but there have been many reports on the many side effects and complications of this treatment. Dr. PENZHOLZ and I have just heard a great debate about the pro and contra of the antifibrinolytic treatment in the United States at the meeting of the Harvey Cushing Society. The poor results and the complications are apparently due to dehydrating measures and the failure to maintain the full blood volume. These two factors in addition to antifibrinolytic treatment lead to failure.

Dr. Beck: This is absolutely true and therefore we recommend ALDOCORTEN for our long-term patients rather than the dexamethasone or glucocorticoid treatment that is generally used today.

Prof. Pia: I would like to add a remark. When we used to admit our patients after the usual interval, we had the impression of a favorable effect of this treatment. Now that we get our patients immediately after the subarachnoid hemorrhage, they seem to get their recurrent hemorrhages in spite of this treatment. The problems of the effectiveness of this treatment are by no means as certain as your words would seem to indicate, Dr. BECK.

Dr. Hartmann: A careful survey of the literature has shown that complications can occur, I believe, and these complications must be drawn into consideration. Perhaps a better antifibrinolytic therapy can lower the complication rate, but one must always remember that complications can occur and as a neurologist, I want to ask the question: "If I have a patient with a subarachnoid hemorrhage in grade 1 or 2, should I delay the operation which I would recommend within the first 2 days in order to begin the antifibrinolytic treatment? I would think it is best to send the patient in grade 1 or 2 to the neurosurgeon as soon as possible and to reserve the antifibrinolytic treatment, which is still being discussed for the patients in stages 3 to 5, but not for the patient in stage 1 and 2.

Dr. Beck: An aneurysm is operated as soon as it is operable according to the criteria we have heard. However, we must be aware of the various situations we face. The patient can come at night. We do not obtain a blood group within the first hour or the patient has an unusual blood group. When everything has been prepared in an optimum way - up to this point in time and only till then should the antifibrinolytic therapy be given. The other point you have mentioned is that antifibrinolytic laboratory levels can be determined in many hospitals today and it seems reasonable therefore to adjust the dosage accordingly.

Prof. Yasargil: I would like to mention my views here briefly. This immediate treatment is impossible in our department in Zürich. We see less than 1% of our patients immediately after the subarachnoid hemorrhage and the others in whom we began with the treatment some time after the subarachnoid hemorrhage, we saw no effect, possibly disadvantages. My total impression is that you can initiate treatment, if you see the patient immediately after the hemorrhage. This is the case in less than 1% of the patients in the Kanton Zürich and the Kanton Zürich is a small Kanton compared to Bavaria. We have studied the autopsy reports and as you have seen, many patients died and we never really knew why. Generally a lumbar puncture is performed 2 or 3 weeks after a subarachnoid hemorrhage and then angiography is carried out and the report reaches us that the patient is in poor condition. Therefore we have no opportunity to make a decision on immediate antifibrinolytic therapy or not.

Prof. Marguth: We operate early of course. If the risk of a recurrent hemorrhage could be lowered markedly, then we would not be compelled to attempt the immediate operation.

Prof. Schürmann: May I ask Dr. BECK a question? If a peripheral hospital calls you about a subarachnoid hemorrhage, do you always say, "Please begin with the antifibrinolytic treatment" although perhaps you do not even know what type and what grade of hemorrhage the patient has? I recommend early angiography because one knows exactly what the patient has and is prepared to act when the time is right.

Dr. Beck: If the colleague in the peripheral hospital reports bloody CSF in the lumbar puncture and everything seems to speak for a subarachnoid hemorrhage, then we advise him to begin with the antifibrinolytic therapy as a matter of principle. We want the thrombosis of the aneurysm as soon as possible. I have never heard that venous thrombosis, for example in the pelvic veins, occurs in the first few hours after a subarachnoid hemorrhage due to this antifibrinolytic treatment.

Prof. Paal: As a neurologist in Munich, and on the basis of the cooperation with Prof. MARGUTH over the last 3 years, I can well support what Dr. BECK has been saying. However, I must add that we refer only a small percentage of these patients to him for operation. Therefore the results look somewhat different in our figures. In 3 years of antifibrinolytic therapy we have had only 2 complications in the first year. These were central venous thromboses. Since we have deep indwelling catheters we have never had any complications again. However, we do see recurrent hemorrhages. The number of these recurrent hemorrhages is no doubt lower than before the introduction of antifibrinolytic therapy, but we do see them. Those are the cases whose clinical condition is so poor that we do not refer them to the neurosurgeon. Therefore our results in view of the prognosis will be decidedly worse, because we do not refer patients in stage 4 or 5 as well as those of high age to the neurosurgeon.

Dr. Beck: We have compared a large collection of patients up to the antifibrinolytic era and after the antifibrinolytic era. Since we have not altered our criteria for the operation within the last 10 years, in other words we operate an aneurysm in good condition immediately and we delay the operation in patients in poor condition, therefore we can compare these two groups. We have found that the rate of recurrent hemorrhages has been reduced from 40% over a follow-up period of 6-8 weeks to 5%. The prerequisite is that the antifibrinolytic treatment is begun immediately, i.e. within the first 2 days, and

that an adequate blood level is maintained. There is little use in giving 1 g Ugurol and then nothing the whole subsequent night. If you do that, then you don't even have to begin with the treatment.

Prof. Marguth: Early diagnosis is particularly important, to be followed by angiographic confirmation of the diagnosis, especially in patients suitable for early operation. Angiography is delayed in patients, who are unconscious, particularly because we can always set the diagnosis by computer tomography as well.
One question has not been answered clearly as yet. All statistical data indicate that an aneurysm is not visualized in 20 to 30% of the cases with subarachnoid hemorrhage. In these patients the question arises, when should angiography be repeated? In a series of 1000 patients we were not able to demonstrate the aneurysm in 5 cases in the first angiogram. That is very little. We follow the policy of repeating angiography 6 weeks after the first angiogram if vascular spasm was evident the first time. In the other patients with a normal vasculature and adequate setting of the angiograms, a repeated angiogram is not necessary, of course on the condition that panangiography has been performed. That is definitely an absolute must even if the aneurysm was demonstrated in the first angiogram, a panangiography must be performed in order to exclude multiple aneurysms. Let me warn of angiography in the phase of vascular spasm. We have made it a rule to stop angiography if narrowed blood vessels are seen.

Prof. Pia: In children with subarachnoid hemorrhage and a normal angiogram, one should think of a cervical angioma. We have seen 3 such cases.

Prof. Schürmann: This is true for adults as well, for an arteriovenous malformation in the spinal canal can lead to a subarachnoid hemorrhage. If panangiography does not reveal an aneurysm, not even a supra- or infraclinoidal aneurysm, then one should think of an arteriovenous angioma.

Prof. Marguth: How great is our experience with immediate operation? Dr. LOEW, you championed the cause of the immediate operation before.

Prof. Loew: I do not have the figures here. We have altered our treatment plan in the course of the last year. Only 12 months ago it was fashionable in our department to wait 7 days and then to operate the patient on the 8th day after the hemorrhage and we had arranged this timing with the surrounding neurological hospitals as well. That worked well. Now we have changed the arrangement and the same hospitals send us patients in grade 1 and 2 immediately.

Prof. Marguth: Yes, stages 1 and 2, that brings us to the problem. Many years ago, we published a classification according to the level of consciousness. Subarachnoid hemorrhage grade 1 is without loss of consciousness, a subarachnoid hemorrhage grade 2 is characterized by a short period of unconsciousness or an undulating consciousness level over a period of hours or days, and in grade 3 the patients remained unconscious for hours or days. We fared quite well with this classification and patients, who are not unconscious, are the candidates for the early operation. If the patient has had a loss of consciousness for about 5 minutes then he is no longer in the group with the very favorable prognosis. A relatively high percentage of these cases are found to have an angiospasm which determines the subsequent clinical course. From large statistics we know that the spontaneous clinical course of patients with subarachnoid hemorrhages in grade 2 runs as follows: one-third a good clinical course, one-third very poor prognosis and one-third a protracted clinical course. This group which we have clas-

sified as subarachnoid hemorrhage grade 2 is the main problem in my opinion, not those in group 1 - we should operate the latter right away. But those in grade 2 - what other criteria do we use? I would say that computer tomography provides valuable information here. I believe that a patient who becomes conscious in the first few days after the hemorrhage, but who has a cistern tamponade in the computer tomogram is not a suitable candidate for an early operation. The same is certainly true for patients whose computer tomogram indicates diffuse cerebral edema. We operate these patients only after the 10th day.

Prof. Nadjmi: Because of computer tomography the diagnostic weight has shifted from the demonstration of the bleeding source to the sequelae of the hemorrhage. When a patient comes to us, we tend to advise the clinician to make the computer tomogram first, even before the lumbar puncture. If we see a hemorrhage and if we know whether the subarachnoid hemorrhage is combined with a hematoma or not, then we can choose the time for angiography much better and more directly, especially if there is a larger hematoma.

Prof. Marguth: Now I want to ask you whether you have noted factors influencing the prognosis, i.e. a relationship between prognosis and findings in the computer tomogram?

Prof. Nadjmi: Yes and this morning we have heard a series of discrepancies between angiospasm and the clinical picture: i.e. the correlation between vascular spasm and the clinical findings are 60%, while 40% do not correlate and I believe that computer tomography provides much better information about these 40%, especially about the fact whether there is actually vascular spasm present or not. If so, then this angiospasm must lead to morphological changes. When the new computer tomographs of the third and fourth generation come, then I think we will be able to determine not only the source of the hemorrhage but also to provide exact prognostic data on the further clinical development of the individual patient.

Prof. Marguth: You are absolutely right, Dr. NADJMI, for computer tomography shows you the exact morphological changes due to the angiospasm, while the angiogram reveals only the narrowed blood vessels, which do not necessarily have to lead to a pathological finding. In this respect computer tomography has a greater diagnostic weight. If the patient is found to have diffuse edema pervading the entire hemisphere or tamponade of the cisterns, then he is not suitable for the early operation.

Dozent Auer: We have analyzed our patient material for the computer-tomographic findings and we have found a very nice correlation between clinical grading and the CT findings. In one or two patients we have seen a slight hydrocephalus if they were in the clinical grading 1 and 2. But all the abnormal, pathological computer-tomographic findings were seen in grade 3 or higher and they are the patients which we do not operate early.

Prof. Marguth: If you have a patient who has obviously had a subarachnoid hemorrhage grade 2, and who has become conscious and whose CT does not show any diffuse brain edema, but does show blood in the cisterns. Would you advise operation here or not?

Prof. Pia: If the cisterns are filled with blood then the patient certainly is not grade 1. However, if there is only a little blood in the cisterns, then this does not bother us. However, one should begin to classify the computer findings better. That is a very important point you have mentioned here, that grade 2 is not grade 2,

and computer tomography offers us another diagnostic aid for determining the operation time better.
If I may say a word to the Japanese statistics, they really cannot be compared with us. A central hospital with 300 to 400 beds from which the cases are chosen, which Dr. Suziki or Dr. Sano operate, these are super-selected cases in grade 1 with a normal CT. With their large figures, they can achieve the results they publish, but our situation is entirely different.

Prof. Kazner: I would like to add the following comment. I have gained the impression that operative treatment is being recommended here for cases which are fully conscious, but whose CT demonstrates blood in the cistern. I think that is not good. We have seen spontaneous clinical courses with tamponade of the cistern where the patient regained full consciousness, but on the fourth to fifth day, the level of consciousness became worse. Had we operated on the third day then we would have operated into a beginning vasospasm and this would be a poor result of early operation. Your case, Dr. PIA, I would never operate and I believe that the recommended technique of rinsing blood out of the cistern is not possible. These patients may improve under conservative treatment and they may reach an operable state later. We have observed such cases.

Prof. Schürmann: Through the use of computer tomography, we have gained a great deal of additional information, such as whether there is blood in the cisterns or not, whether edema has developed, and whether an infarct is emerging or not. In all these cases, one should not operate in my experience.
I would like to enlarge on a point which Dr. BECK mentioned briefly. I have made the observation that patients who have had a subarachnoid hemorrhage and still have nuchal rigidity tend to recover less quickly from the operation than if one waits until a certain stabilization has occurred. Therefore I want to warn of performing an early operation in these cases. I believe early operation must be reserved for those cases who show little nuchal rigidity and are in a very good condition. Their computer tomogram indicate no blood in the cisterns and there are no other pathological signs in the CT. In these cases I could imagine achieving better results through early operation, but we get these patients far too little.

Prof. Koos: I think the danger lies in operating into a stage of instability. If a patient comes and his level of consciousness is stable, his circulation is stable and his vegetative nervous system is not disturbed - and this applies to most patients in stage 1 or a good stage 2 - then I have no objections to an early operation. But we also get the very poor cases. They come as a hematoma and those are the troublesome cases. One is forced to evacuate the hematoma in a stage where the kidney receivers are standing in line. Those are the cases we really would not want to operate.
I think we should get the patients early in order to carry out the diagnostic procedures ourselves.

Prof. Frowein: The desire to admit patients early is quite clear. But I am not certain whether one should really operate early. The papers held this morning presented a survey on 4000 to 5000 aneurysm operation. According to our present nomenclature 95% were operated late. Our actual experience with early operations - that was asked before - is limited to about 20 patients. Ladies and gentlemen, with data like that we cannot call for early operations. We can only express the wish that we want to do something in that direction and then sit down again together in 2 years and report what we have seen on the positive as well as on the negative side.

Dr. Marx: I would like to ask a question about the treatment of vascular spasms, because I believe this topic is relevant at the moment. At the International CWF Congress in Tokyo, I had a long talk with Dr. HASHI, one of the prominent Japanese aneurysm surgeons and he told me that he operates immediately. Not the early operation, the immediate operation. He goes to the hospital immediately and operates, even patients in grade 2 and 3. And his reason for doing so is that he says there is only method of treating vascular spasm and that is induced arterial hypertension. He showed me statistics which were very surprising. As chance would have it, he had admitted a patient with an aneurysm of the anterior communicating artery to the intensive care unit on the previous day, and he had been operated immediately. Six hours later the level of consciousness became disturbed and a paresis of the leg set in. The blood pressure was raised to 200 mm Hg systolic pressure and the next morning the patient was fully awake and had only minimal leg lowering when he lifted it. I would like to know if such a treatment has been carried out here and if we have experience with this method of treatment? It was a single case, but I must say that the mortality with this procedure was 10%-12%.

Prof. Schmidt: There are very marked forms of vascular spasm and here a blood pressure increase of 30-40 mm Hg - one cannot go higher - is not enough to achieve sufficient perfusion so that the neurological deficits improve. I think this will work only in selected cases. Our experience is not great, we have treated half a dozen patients in this way. This treatment is not without danger, as it is difficult to steer and requires exact surveillance.
If you say that you have had not recurrent hemorrhages under the treatment with epsilon-aminocapronic-acid, we do that too, then surely we can await a more suitable time. Operative risk is higher in the first days as the statistics have shown us.

Prof. Penzholz: I would like to comment on the remarks of Dr. SCHMIDT. Several years ago we operated very early, on the third, fourth or eighth days. We observed a somewhat higher operative mortality. Because of our knowledge about vascular spasm which Dr. HAMER showed so well this morning, and because these spasms reach a peak on the seventh day, we have become more conservative again. Of course we had to accept the possibility of recurrent hemorrhages. But when we regard our total mortality we see that it has not become lower than at the time when we operated earlier. I think this observation will encourage us to become more courageous in setting the indication for operation. One should not operate between the fourth and the eighth day. But perhaps there are possibilities of admitting patients earlier.

Prof. Grote: Perhaps the coordinator of our round-table discussion could say a final word on the treatment plan in cases of multiple aneurysms, that have been demonstrated by angiography?

Prof. Marguth: I have operated several patients in whom the aneurysm was an incidental finding. As far as multiple aneurysms are concerned, we operate in one session if the aneurysms are on one side, otherwise in 2 sessions.
Ladies and gentlemen, let me attempt to summarize what we have discussed. Despite our uncertainty there is a trend to earlier operations in order to prevent the fatal recurrent hemorrhage. Which cases are these? They are the subarachnoid hemorrhages grade 1. These patients have not had a loss of consciousness, they are fully awake, their computer tomogram shows no sign of a tamponade of the cisterns and no signs of angiospasm. There is a certain insecurity about the time of operation for patients who have regained consciousness, but whose level of conscious-

ness was disturbed initially and whose computer tomogram indicates signs of bleeding (grade 2). I think these patients should be handled with caution. We have operated these patients on the 10th day until now and we should stick to that. Patients of the first grade should have an early operation but the question is still on which day to operate. We generally operate these patients one week after the hemorrhage. I did not have the impression that other tendencies were expressed in the papers.

Free Topics

Brain Metabolism Following Experimental Vascular Suture

E. WINTERMANTEL, W. DRIESEN, M. HAPPE, W. HELLER, and P. Oldenkott

Introduction

Experiments with Sprague-Dawley rats of the Wistar strain were performed in order to analyze brain and liver metabolism following microvascular end-to-end anastomosis of the right carotid artery of the rat. The purpose of these experiments was to determine how much a temporary interruption of the bilateral blood supply of the brain during the procedure would interfere with the normal carbohydrate metabolism of the brain, an organ supplied by the clipped artery, and of the liver, an organ farther away from the field of blood supply of this artery.

Material and Methods

In order to standardize the clamping-time of each artery the right carotid arteries of 140 rats were ligated for 30 min in an additional experiment. General anaesthesia of all animals was achieved with pentobarbitone. Blood flow was restored by removing the ligature after 30 min and the wound was closed.

Six groups of animals were formed in order to determine biochemical parameters 1 day, 10 days and 30 days postoperative and in order to find out whether the sequence of removal of brain and liver tissue would by itself influence the examined parameters. In one group the brain was removed before the liver, in another the liver was removed first.

The metabolism of the removed organs was stopped immediately by freezing the tissue in liquid nitrogen. Adenosine triphosphate (ATP) and lactate were the parameters submitted to biochemical analysis.

Results

The results of the groups surviving for 1 day and for 10 days postoperative are shown in Figs. 1-4.

Even 30 days after the operation highly significant changes of the ATP level were found in brain tissue of the group of which the liver had been removed first. The lactate and ATP levels in the liver tissue showed the same changes.

Conclusion

The results show an alteration of the carbohydrate metabolism in liver and brain tissue following an interruption of the blood supply of the brain through one carotid artery.

Further experiments are planned in order to establish whether these results indicate hypoxia or whether a more complicated mechanism, controlled by enzymes, can be detected in both organs.

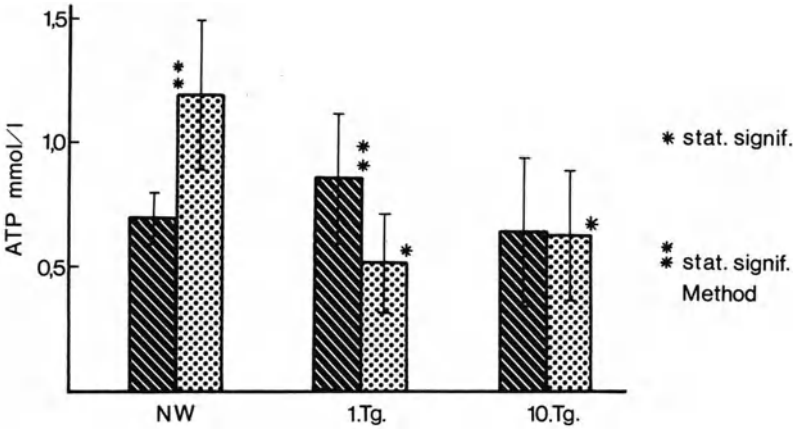


Fig. 1. Three groups of columns representing ATP levels in brains of animals without ligature of a carotid artery (NW) as compared to a 30-minutes ligature 1 day (1 Tg.) and 10 days (10. Tg.) postoperative. Stars indicate statistical significance in relation to the NW-group (*) or to the sequence of removal of the organs (**): The first column always represents the group with brain removal first ▨, the second stands for liver removal first ⁘ . ATP is statistically lowered 1 day and 10 days after operation in the group in which the liver was removed first. The two different methods of organ removal resulted in significant differences in the ATP levels of the NW - and the 1.-Tg.-group

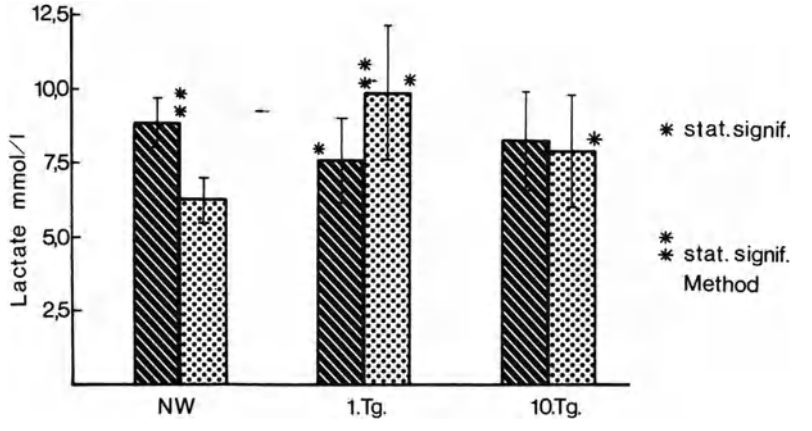


Fig. 2. Lactate levels in the brain. In the group in which the brain was removed first the lactate level is lowered on the first post-operative day, whereas in the group in which the liver was removed first this level is higher, thus indicating the different results depending on the method used

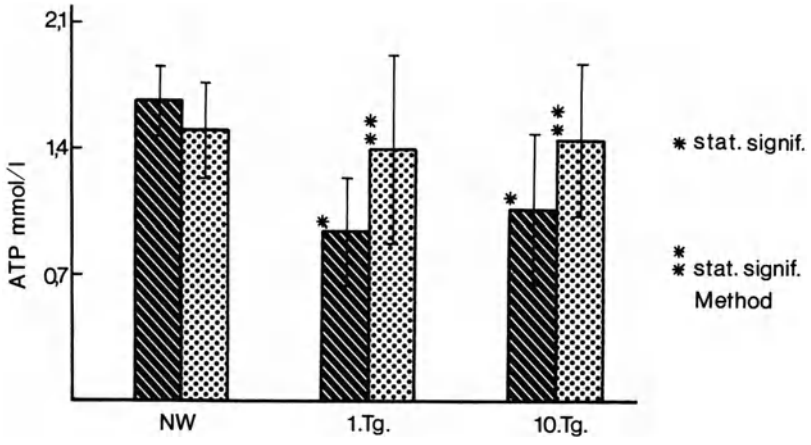


Fig. 3. ATP levels in liver tissue. In the group with brain removal first, lowered levels were found in the first and tenth postoperative days

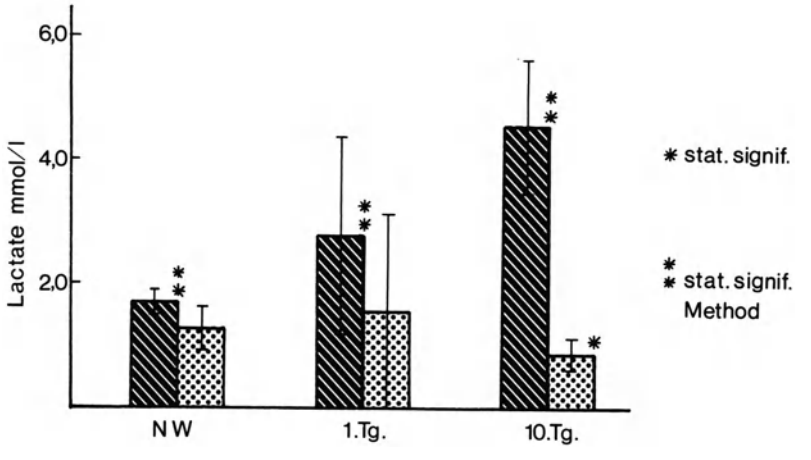


Fig. 4. Increase of lactate levels in liver 1 day and 10 days postoperative when the brain was removed first

Selective Endoscopic Coagulation of the Choroid Plexus Using Nd-Laser Techniques. A new Approach to the Treatment of Hydrocephalus?[1]

O. J. BECK, K. BISE, W. GORISCH, L. RUPRECHT, and G. KÜBLER

Introduction

Despite considerable progress in neurosurgical techniques during recent years, the management of patients with hydrocephalus still remains a major problem. This is particularly true in view of the increasing incidence of communicating hydrocephalus occurring following neurological procedures. This is, at least in part also, due to the fact dynamics of cerebrospinal fluid (CSF) production and absorption is only partly understood in this situation (6).

As early as 1955, BERING (1) pointed out that the choroid plexus not only produces CSF but also transmits the arterial pulsation which leads to the enlargement of the ventricle (BERING effect). DANDY (3) and BERING (2) have investigated CSF production and dynamics, respectively. Occlusion of the two foraminae of Monroi and resection of the plexus of one ventricle (DANDY) lead to its collapse, whereas the other ventricle dilates (Monroi-block). If both foraminae of Monroi remained open (BERING), resection of the plexus of one side resulted in a decrease of the ventricular lumen, or at least in no dilation. PLETS (8) observed syymetric decrease of both ventricles after bilateral plexectomy in dogs, but did not observe its reduction to normal size. Further observation revealed ischemic areas within the postero-lateral part of the thalamus leading to atrophy and necrosis.

Our goal, therefore, was to reduce the plexus tissue producing CSF and to prevent nutritive deficiencies within the postero-lateral thalamus through preservation of the respective vessels.

Open extirpation of the plexus has led to a high mortality rate during surgery. The brain often collapses post-operatively and CSF fistulae most often led to death. In order to reduce the risks of open surgery, DANDY (4) tried to coagulate the plexus endoscopically using a cystoscope connected to special mirror. PUTNAM and SCARFF further improved endoscopic instrumentation. IIZUKA (5) combined the endoscope with stereotactic guiding equipment.

Materials and Methods

Seven pigs of the race "Deutsches veredeltes Landschwein" were chosen for our experiments. In order to induce hydrocephalus, 4 ml kaolin suspension (1 g kaolin, 7 ml saline and 2 ml contrast medium (Dimer X) was injected into the cisterna cerebello-medullaris (SOP) in 10 week old animals (approx. 25 kg body weight) during short term anesthesia (Metomidat-HCl, Azaperon). Afterwards, most animals showed motor dis-

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turbances, irritability and spastic signs. Their general condition and appetite was reduced. These clinical symptoms were thought to be due to chemical meningitis. Meningitis within the outer CSF spaces caused hydrocephalus and symmetric enlargement of the ventricles as demonstrated by computerized tomography.

During transition from the acute to the chronic form of meningitis, a slight improvement in the condition of the animals was noted. Usually, CT revealed a constant size of the ventricles, which led us to operate on 6 animals approximately 6 weeks after SOP. One animal was operated on 10 days after kaolin injection and died from an anesthesia overdose. For endoscopic coagulation, anesthesia was performed as described before. Additional pentobarbital sodium was given when necessary. A hole was drilled either into the right or left or into both parietal bones and enlarged to a diameter of approximately 1.5 cm with rongeur.

After incising the dura mater, the cortical vessels were coagulated with bipolar current and the endoscope was introduced. After penetrating about 27 mm (average) into the brain tissue the endoscope reached the lateral ventricle. Our endoscope was developed in cooperation with the WOLF company (16 charriere, 110 mm length) and included vision optics, open angle of 60^{o}, illumination and a biopsy channel for the laser light guide. Manually activated valves allowed for saline irrigation. The Nd:Yag laser light was transmitted through a 2 meter long flexible fused quartz monofiber of 0.6 mm core diameter. Outer diameter including ladding was 1.1 mm. The fiber output open angle (in air) was 10^{o} which results in an approximately 2 mm spot at 1 cm distance. The tip of the fiber could be moved forward and backward so that its distance from the tissue surface (normally 2-4 mm) could be varied.

The pars centralis of the plexus was primarily exposed to a series of single pulses of 25 Watt, 0.5 seconds up to a total dose of 1000 Ws. If possible, arteries were coagulated selectively and veins saved. Selective plexus coagulation was performed in 6 animals; 3 times on one side and 3 times on both sides. The animals were sacrificed and examined 6-8 weeks postoperatively.

Results

The postoperative condition of most of the animals was good. Unilateral coagulation led to collapse of the involved ventricle; with one exception the contralateral ventricle was enlarged.

Histologic evaluation confirmed the impression that the area of laser-induced effect is certainly localizable and is identical with the documented operative site (Fig. 1). Tissue reactions were only observed in small areas and to a minor extent within the irradiated plexus tissue.

Occasional CSF examination shoed an increase of cells (up to 1000/3 per mm^3) and high total protein content (up to 2000 mg per dl); kaolin crystals were abundant. Damage to the basal ganglia or the ventricle walls was not observed.

Discussion

Seven pigs with kaolin induced meningitis developed marked hydrocephalus. Distinction should be made clinically between an acute course of

2-3 weeks and a relatively silent chronic one. The operative technique was quick and simple and all procedures could be done without intubation anesthesia. Irreversible respiratory disorder occurred only once probably due to anesthesia overdose. After unilateral selective plexus coagulation, homolateral ventricular collapse was found (Fig. 2,3). However, during the initial phase (CT control!), the ventricle could even show a temporary increase in size. With one exception, the contralateral ventricle remained enlarged.

Bilateral plexus coagulation was performed as two-stage procedure, with a time interval of 1-2 weeks. All animals had a moderate hydrocephalus as demonstrated on post-mortem studies. The decrease in ventricular size was more marked on the side on which choroid plexus destruction was more intensive. The observation time between kaolin injection and animal sacrifice was approximately 3 months.

Summary

Selective plexus coagulation using laser ventriculoscopy is possible and influences ventricular size. It appears possible that aimed thermal damage of parts of the plexus tissue results in reduction of its CSF producing potential. At the same time, thalamic blood flow can be preserved.

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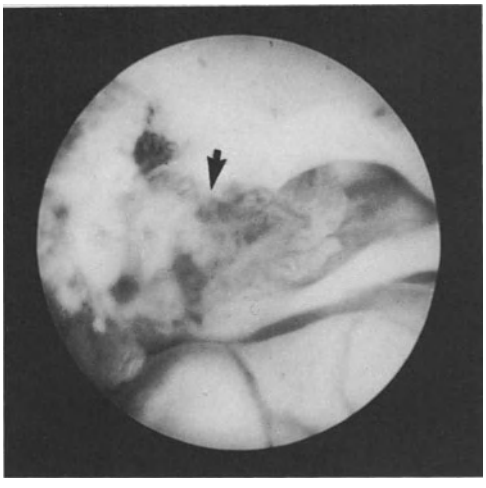

Fig. 1. Choroid plexus at the foramen of Monroi. Coagulated tissue *(arrow)* is sharply demarcated from normal plexus

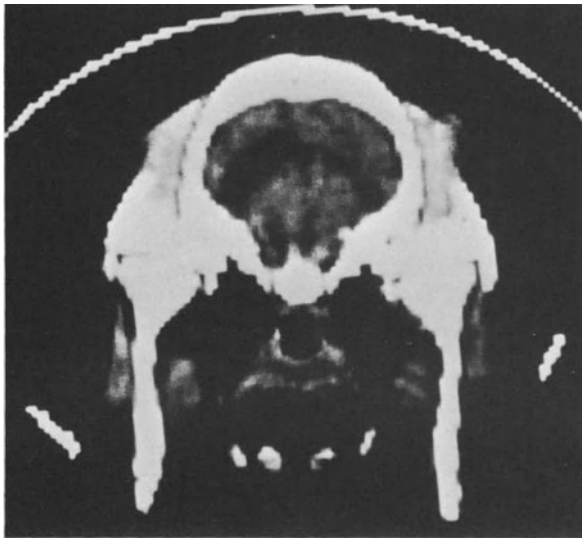

Fig. 2. Selective endoscopic coagulation of the choroid plexus. Decreased size of right lateral ventricle

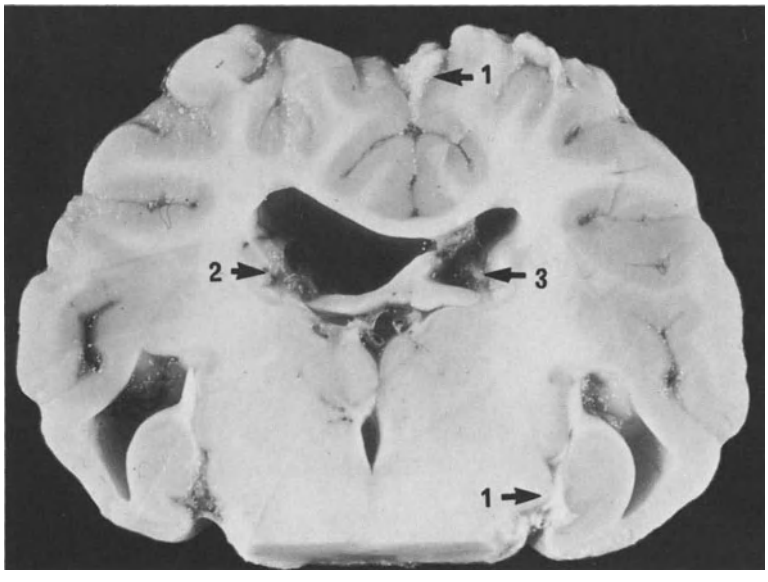

Fig. 3. Frontal section at the level of the foramen of Monroi: 1 = persistent kaolin-meningitis, 2 = hydrocephalus internus with intact choroid plexus, 3 = postoperative reduction in size of the lateral ventricle containing a small rest of scarred choroid plexus

Histologic and Autoradiographic Studies of the Development of Experimentally Induced Gliomas in the Rat Brain

F. ALBERT, H. WALDBAUR, and H. SCHMIDT

Experimental neurooncology has developed several methods to produce an appropriate tumor model for investigations on the pathogenesis of brain tumors, and for the development of new procedures for the diagnosis and management of these neoplasms. Most successful has been the selective induction of neurogenic tumors in experimental animals by resorbable chemical carcinogens. Here, *transplacental* administration of N-ethyl-N-nitrosourea (ENU) in pregnant rats has revealed a special effectiveness in respect to high incidence and specific neurogenic origin of the tumors induced in the offspring (2, 3, 6-8, 13, 15, 16). Moreover, this method is very reliable, requiring little effort and having a relatively low cost. The neoplasms induced nearly always occur at multiple sites (15, 16). Their histologic features are often comparable to the neurogenic tumors in man (6, 17).

Until present, there are few experimental investigations on the *long-term development* of transplacentally induced brain tumors (9, 10, 12, 14). Furthermore, they are almost exclusively confined to the early lifetime of the animals studied (9, 10, 12).

The purpose of our studies was to obtain further insight into the long-term development of experimental gliomas in the rat, extending the period of observation to older animals as well.

Three pregnant BD II-rats were given a single intravenous injection of 25 mg ENU per kg body-weight on the 15th and 17th day of gestation respectively. The offspring (28 animals) were killed gradually from 4-25 months of age and the brains cut into serial sections (at intervals of 60 and 120 µm) for histological investigation by light microscopy. In addition, 8 brains were examined autoradiographically utilizing Tritium-labeled thymidine in order to investigate the proliferative activity and the origin of the gliogenic neoplasms. Microscopic investigation of serial brain sections improved the accuracy of identification even of the smallest neoplastic proliferations.

The incidence of transplacentally induced neurogenic tumors was 93%; *intracerebral* neoplastic proliferations were found in 89%, most of them (92%) mutliple (Fig. 1), with a mean tumor frequency of 4.3 per brain. Altogether there were 108 intracerebral neoplasms. Additionally, we found 5 gliomas of the spinal cord, 5 malignant neurinomas of the trigeminal nerve, and 2 neurosarcomas of peripheral nerve plexus. According to biological criteria of tumor growth (size of the tumor, cyto- and histo-architecture), about 2/3 of the brain neoplasms were classified as *"Early stages"*. It was also remarkable that the oldest rats still showed early neoplastic proliferations - after prenatal exposition to the carcinogenic agent! About half of the blastomatous proliferations were oligodendrogliomas, mixed oligo-astrocytic gliomas, and some tumors with the histological patterns of "malignant gliomas".

The others (especially the early stages) did not admit an exact classification because of their *low graded differentiation*.

In 3 cases the propagation of *metastases* via the CSF-pathways was observed (Fig. 2). There were some *preferential sites* of tumour growth, the hippocampal region and the anterior horns of the lateral ventricles amounting to 62% of the neoplasms (Table 1 and Fig. 3). By examining the rat brains after different life-spans, a long-term observation of the tumor development was possible to some extent. From these studies we drew the following conclusions:

1. Experimental gliomas in the rat seem to go through *different developmental stages:* early neoplastic proliferations with only a few isomorphic cells (Fig. 4); microtumors with abundant cells, mitotic activity, but without signs of malignancy; polymorphic, perhaps space-occupying tumors with the histological signs of "malignant gliomas". The neoplasms also reveal a tendency to form mixed gliomas.

2. The *confluence* of several neoplastic foci to a multicentric blastomatous area seems to be an important factor in the growth of experimental gliomas (Figs. 4 and 5).

Table 1. Localization of 108 ENU-induced intracerebral neoplasms

Hippocampal region	39,8% (n = 43)
Adjacent subcortical white matter	26,0% (n = 28)
Hippocampus	8,3% (n = 9)
Adjacent cortex	5,5% (n = 6)
Region of the anterior horns of the lateral ventricles	22,2% (n = 24)
Subependymal region	9,3% (n = 10)
Angle between corpus callosum and caudate nucleus	7,4% (n = 8)
Adjacent corpus callosum	5,5% (n = 6)
Basal ganglia	13,0% (n = 14)
Pons, cerebral peduncles	8,3% (n = 9)
Medulla oblongata	8,3% (n = 9)
Cortex	6,6% (n = 7)
Subcortical white matter	0,9% (n = 1)
Optic chiasm	0,9% (n = 1)
	100,0% (n =108)

By using ^{3}H-thymidine *autoradiography*, we were able to demonstrate an increased mitotic activity in the subependymal cell plate of the outer walls of the lateral ventricles. Solitary, mitotically active neuroglia cells could also be identified in regions corresponding to the sites of predominant tumor development mentioned above (corpus callosum, subcortical white matter adjacent to the hippocampus). This phenomenon was also observed in a control animal not exposed to the carcinogenic agent. The appearance of dividing glia cells in specific cerebral regions also under normal conditions might, perhaps, account for the predominance of certain sites of neoplastic growth, since mitotic activity represents an important prerequisite for carcinogenesis

(5, 11). In this context, the special role of the *subependymal cell plate* must be pointed out, a presumptive source of *stem cells* of gliomatous tumors that underwent cancerogenic transformation (1, 4, 9, 12).

Our results might be related to the pathogenesis of *human* brain tumors as follows:

1. Is the *transplacental* induction of neurogenic tumors also relevant to man? Is there an increased sensitivity of the human fetal nervous system to cancerogenic substances, responsible for the frequency of neurogenic neoplasms during childhood? Can the gliomas occuring in adult life also be considered the result of intrauterine exposure to a carcinogen, presuming an inverse relation between latency period and dose of the carcinogen?

2. Which role do the *subependymal plate cells* play in the genesis of human gliomas? Might the phenomenon of *preferential tumor localizations* be determined by these stem cells of gliogenesis, particularly susceptible to carcinogenic agents (4, 9, 12) and occurring in defined cerebral regions (subependymal plate, corpus callosum, subcortical white matter adjacent to the hippocampus) (1, 9)?

3. The confluence of several neoplastic foci to a *multicentric* preformed tumor seems to be an important factor in the growth of experimental gliomas. Perhaps the high postoperative recurrence rate of gliomas could also be determined by the presence of several neighbouring tumor nodules, some of which are not large enough to be diagnosed preoperatively or recognized and removed during the surgical intervention. K.J. ZÜLCH (18) pointed out that human gliomas not rarely develop within multiple growth centres interconnected to each other by thin layers of tumor cells.

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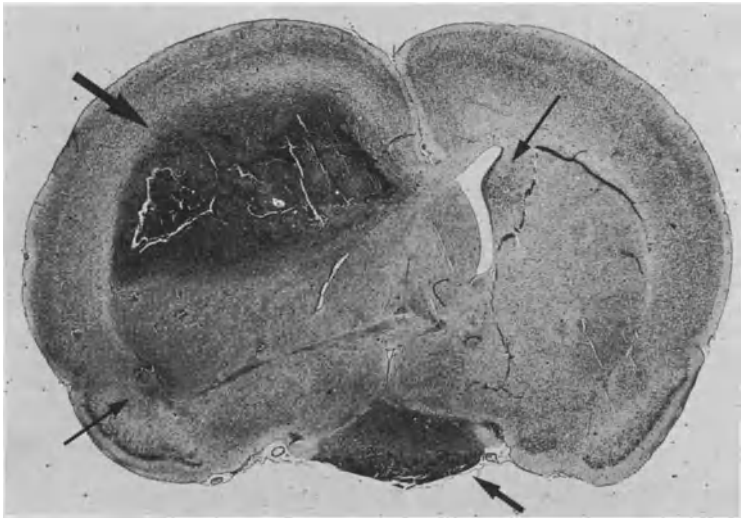

Fig. 1. Multiple growth of transplacentally induced brain tumors (arrows) following a single intravenous injection of ENU (25 mg/kg) in a pregnant rat on the 17th day of gestation. Cresylviolet. x 9

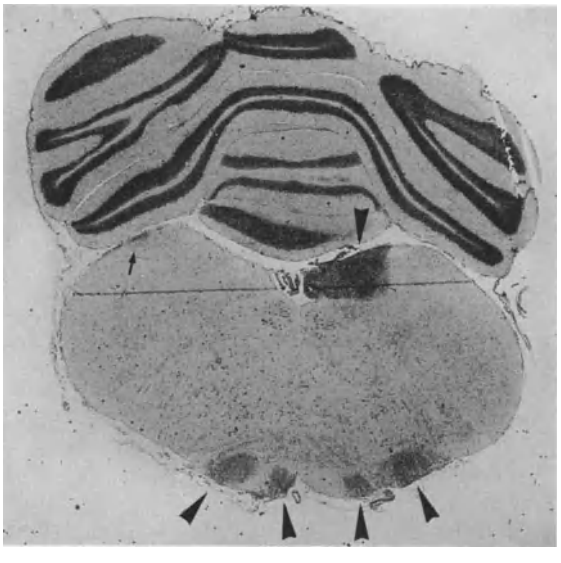

Fig. 2. Intracranial metastases (arrows) of a primary malignant glioma of the spinal cord. Spreading of the metastases along the CSF pathway can be assumed. Cresylviolet. x 8.5

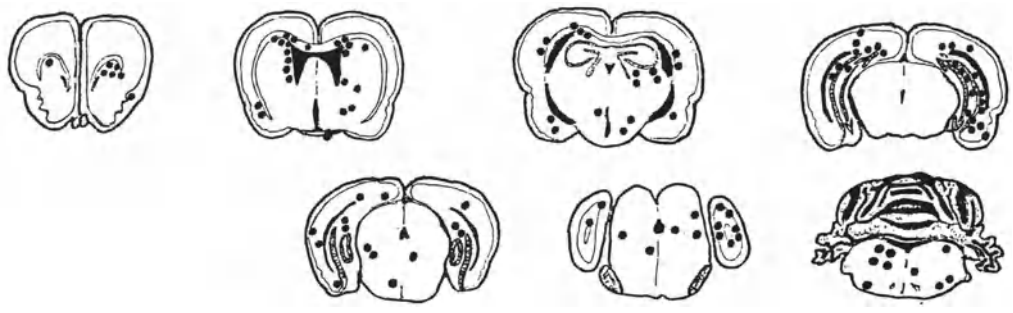

Fig. 3. Topography of ENU-induced tumors of rat brain

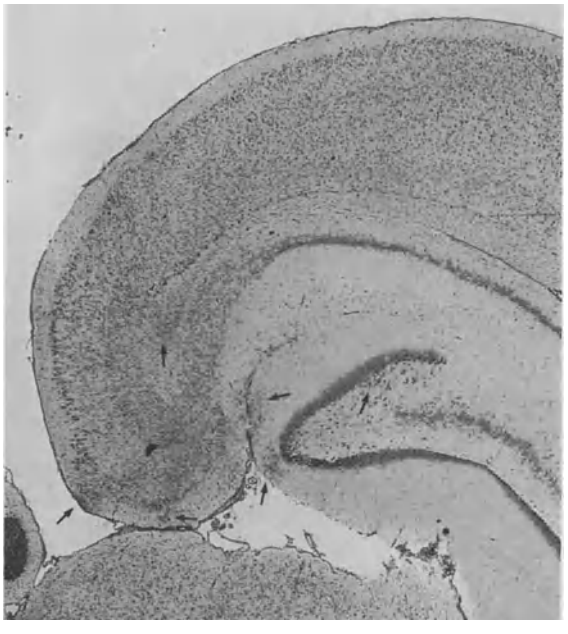

Fig. 4. Area of six early neoplastic proliferations (arrows) in the hippocampal region. The minute blastomatous foci are still separated, suggesting a subsequent confluence (see also Fig. 5). Cresylviolet. x 21

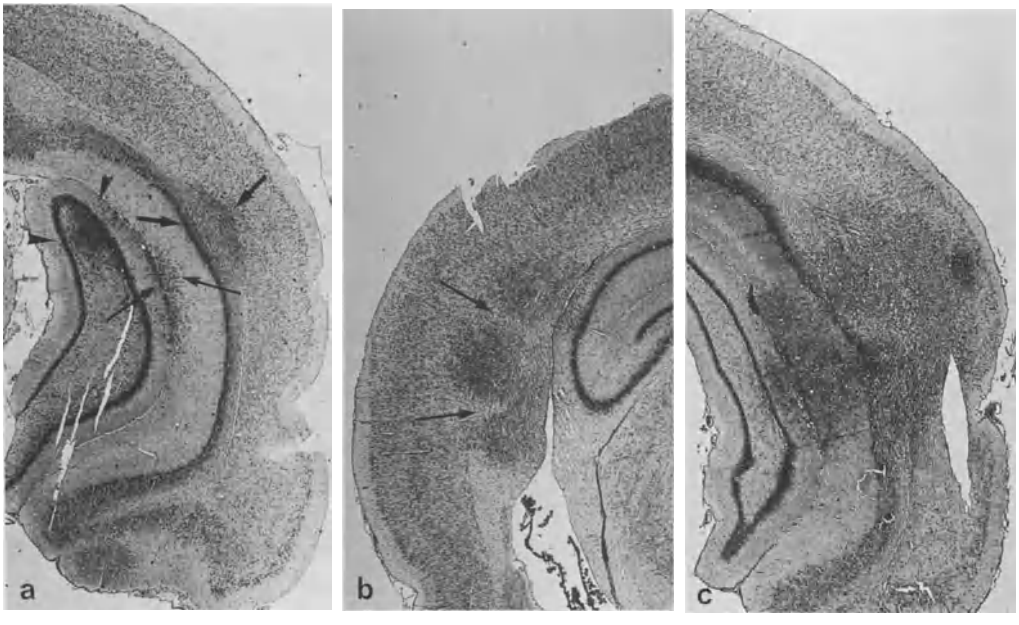

Fig. 5 a-c. Different stages of confluence of experimentally induced rat gliomas. The samples clearly reveal the primordial growth centres. Cresylviolet. x 19

Ultrastructural Studies on the Selective Elimination of Pain Fibers by Thermocoagulation in Trigeminal Neuralgia

M. BRANDT and D. DORSIC

Introduction

Nowadays selective elimination of pain fibres with preservation of touch fibers is the declared aim in trigeminal surgery (3, 6, 7, 10, 14, 24). By preserving the tactile sensibility, the risk of keratitis and anaesthesia dolorosa is reduced, since these two complications originate from decreased sensibility (5, 13).

SWEET (22) hypothetized that nonmyelinated pain fibers (C-fibers) are more sensitive to heat than myelinated touch fibers (A-beta fibers), and that for this reason a selective elimination of pain fibers by thermocoagulation is possible. This hypothesis was supported by corresponding clinical experience (Table 1) and electrophysiological experiments (4, 8). However, morphological studies on this problem have not been reported yet (18, 19).

We raised the question of whether selective elimination of non-myelinated nerve fibers occurs after thermocoagulation, and what conditions of coagulation would be the most suitable in order to achieve this aim. In literature different coagulation-temperatures (47-90° C) and coagulation-times (10-120 sec) are recommended for the thermocoagulation of the Gasserian ganglion (Table 2).

Material and Methods

The ganglion inferius nervi vagi (ganglion nodosum) was exposed by microtechnique in 25 rabbits. Being a sensitive ganglion of a mixed nerve, it is anatomically comparable to the Gasserian ganglion (16, 21). The ganglion nodosum was exposed 1 cm caudal to the base of the skull. Thermocoagulation was carried out under visual control by the use of the Owl universal radiofrequency generator, which is also used for the Gasserian ganglion.

The thermistor was introduced into the ganglion following previous puncture with a double-sharpened cannula. Coagulation current was conducted to the thermoprobe via a crocodile clip. Thus, the thermoprobe was used as coagulation electrode simultaneously. The indifferent electrode was placed under the forehead skin of the rabbit. This coagulation technique reduced the mechanical lesion to a minimum.

Thermocoagulation was performed between 50° C/30 sec and 90° C/60 sec. Immediately after coagulation the vagus and its coagulated ganglion were removed with the aid of micro-scissors over a length of 2 cm and immersed in 2.5% glutaric acid dialdehyde for electron microscopy. Methylene blue sections for light microscopy and ultrathin sections for electron microscopy were made from the center of the coagulated

Table 1. Clinical results following thermocoagulation of the Gasserian ganglion

Authors	No. of patients	Re-currency	Letha-lity	Neuro-logical failure rate	Keratitis (%)	Anesthesia dolorosa (%)	Par-esthesia (%)
BROGGI, 1975	46	10,9	0	0	2,0	0	22,0
ONOFRIO, 1979	359	28,6	0	1	2,2	1,6	9,4
PERTUISET et al., 1977	100	13,0	0	0	0	0	4,0
SENGUPTA and STUNDEN, 1977	39	10,0	0	0	5,0	0	8,0
SIEGFRIED, 1977	500	4,3	0	1	1,4	0,8	1,8
SWEET, 1975	484	28,0	0	1	5,7	1,2	25,0
TEW and MAYFIELD, 1973	60	10,0	0	2	4,0	0	15,0

Table 2. Thermocoagulation of the Gasserian ganglion

Authors	Temperature (°C)	Time of coagulation (sec)
ASCHER and SCHRÖTTNER, 1976	60 - 90	Not mentioned
BROGGI, 1975	56 - 95	10 - 60
MARTINS and UMBACH, 1975	62	20 - 25
MÜKE and SCHMIDT, 1979	55 - 80	60
ONOFRIO, 1975	80	30
PENZHOLZ, 1976	70	60
PERTUISET et al., 1977	60 - 75	60
SENGUPTA and STUNDEN, 1977	60	120
SIEGFRIED, 1977	65	60
SINDOU and KERAVEL, 1976	60 - 80	60
SWEET and WEPSIC, 1974	47 -65	60
TEW and MAYFIELD, 1973	65	60

region (about 2 x 2 mm). Samples were taken from 3 rabbits without thermocoagulation, used as normal controls (Fig. 1).

Results

Thermocoagulation at *50° C/30 sec* led to signs of disintegration of the fine structures in the axoplasm of the non-myelinated nerve fibers: neurofilaments, microtubuli, mitochondria, agranular endoplasmatic reticulum and vesicles. The myelinated nerve fibers remained intact.

Thermocoagulation at *50° C/60 sec* caused complete axolysis of most non-myelinated fibers (Table 3). However, at this low temperature, the axons of the myelinated nerve fibers were regular. Only the myelin sheath was slightly deformed. Frequently, myelinated fibers with intact ultrastructure were observed in close proximity to completely destroyed non-myelinated fibers (Fig. 2). Thus, a selective elimination of non-myelinated fibers was seen with thermocoagulation at this low-temperature. Selective thermolesion of the non-myelinated fibers was also present, although less pronounced, when coagulation was made at a temperature 10° higher but for a period only half as long (30 sec).

With thermocoagulation at *60° C/60 sec*, a selective destruction of the non-myelinated nerve fibers also prevailed (Fig. 3), but in this stage individual myelinated axons also showed signs of disintegration. The lamellar structure of the myelin sheaths was destroyed in a portion of the myelinated fibers.

With thermocoagulation at *70° C/60 sec* all non-myelinated fibers were destroyed and the axolemma was ruptured. However, most of the myelinated fibers were also destroyed, with lysis of the fine axonal structures and destruction of myelin sheaths.

Thermocoagulation at *80° C/60 sec* and higher temperatures resulted in the complete destruction of both myelinated and non-myelinated fibers. In place of the non-myelinated fibers nothing but necrotic fluid poodles were discernible (Fig. 4). The myelin sheath of the myelinated fibers was dissolved and the fine axonal structure of the myelinated fibers was destroyed. Selective thermolesion of non-myelinated fibers was no longer found to occur under these conditions.

In the ganglion-cells and Schwann's cells we found disintegration of the cell-organelles at 50° C/30 sec, rupture of the cell-membrane at 70° C/60 sec and destruction of the nuclei (karyolysis) at 80° C/60 sec.

Conclusions

These first ultrastructural studies of the effect of thermocoagulation on a ganglion (ganglion inferius nervi vagi) akin to the Gasserian ganglion have shown that selective pain fiber elimination can only be expected from thermocoagulation at temperatures not higher than 50° C/60 sec or 60° C/60 sec.

Even if the results of these animal experiments can only be applied to clinical practice by analogy, it appears that one can recommend to start thermocoagulation in trigeminal neuralgia at low temperatures (50° C/60 sec or 60° C/60 sec) and to increase it in steps of 5-10°, if necessary, after checking the sensitivity to pain.

Table 3. Ultrastructural changes after thermocoagulation of the ganglion inferius nervi vagi (ganglion nodosum) in 25 rabbits. Coagulation time 60 sec

Ganglion cells and Schwann cells	Disintegration of cell organelles		Rupture of the cell membrane	Karyolysis
Myelinated nerve fibres	No axolysis	Axolysis of single fibres	Axolysis of several fibres	Axolysis of all fibres
	Myelin sheath deformed			Myelin sheath destroyed
Non-myelinated nerve fibres	Axolysis	Axolysis	Axolysis with rupture of the axolemma	Axolysis with total necrosis
Temperature of coagulation (^{o}C)	50	60	70	80

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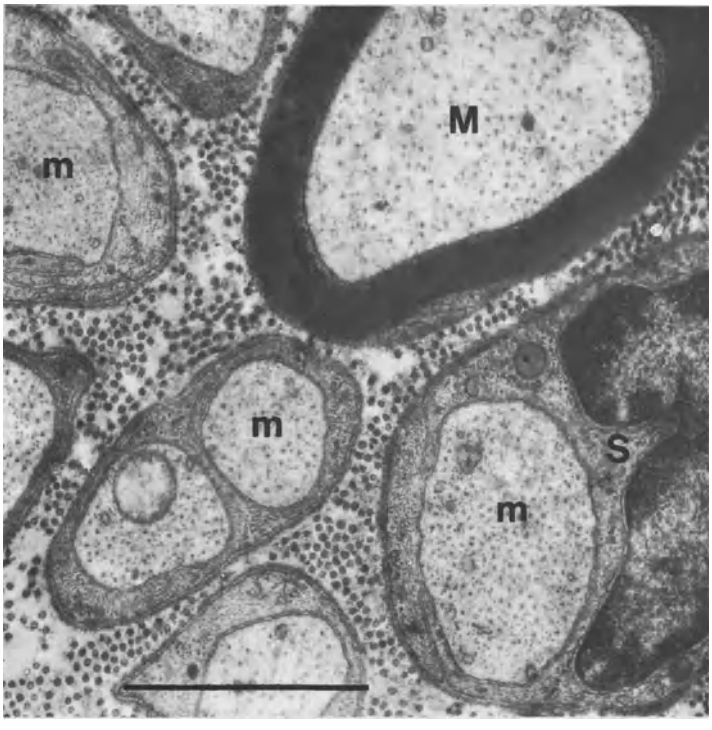

Fig. 1. Electron micrograph of myelinated and non-myelinated nerve fibers. *Normal finding* without thermocoagulation. Transverse section of the ganglion inferius nervi vagi of the rabbit. Myelinated fiber (M), non-myelinated fiber (m), Schwann's cell with nucleus (S). The black line corresponds to 1 µm

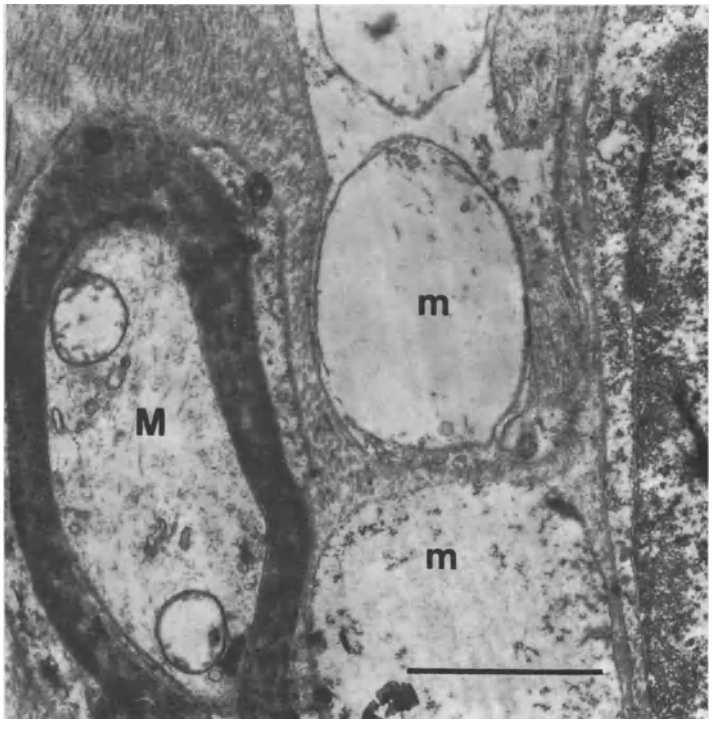

Fig. 2. Thermocoagulation of the ganglion inferius nervi vagi of the rabbit at *50° C/60 sec*. The fine structures of the axoplasm of the non-myelinated nerve fibers (m) are destroyed (axolysis). The adjacent myelinated nerve fiber (M) is largely intact. The fine structures of the axoplasm are discernible. The myelin sheath is intact. The black line corresponds to 1 µm

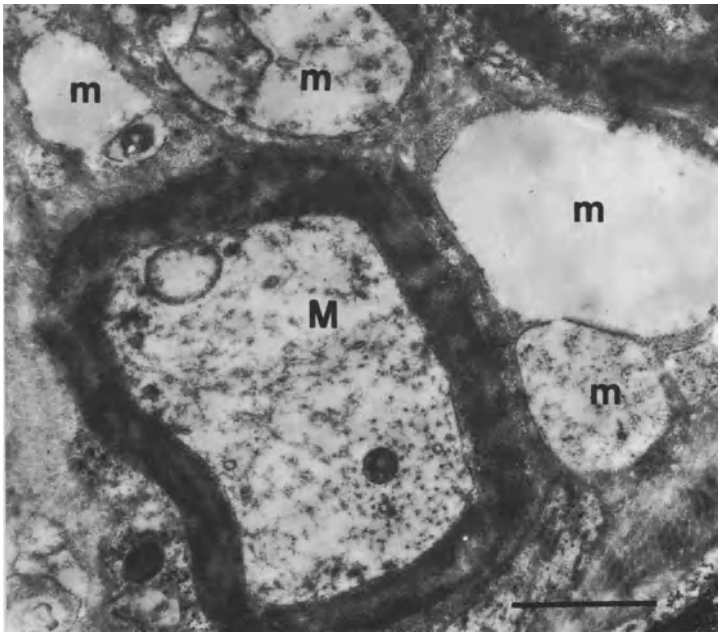

Fig. 3. Thermocoagulation of the ganglion inferius nervi vagi of the rabbit at *60° C/60 sec*. The myelinated nerve fiber (M) shows almost intact fine structures such as neurofilaments and microtubuli. The lamellar structure of the myelin sheath is preserved. Complete axolysis of the juxta-positioned non-myelinated nerve fibers (m). Axolysis, partly with rupture of the axolemma. The black line corresponds to 1 µm

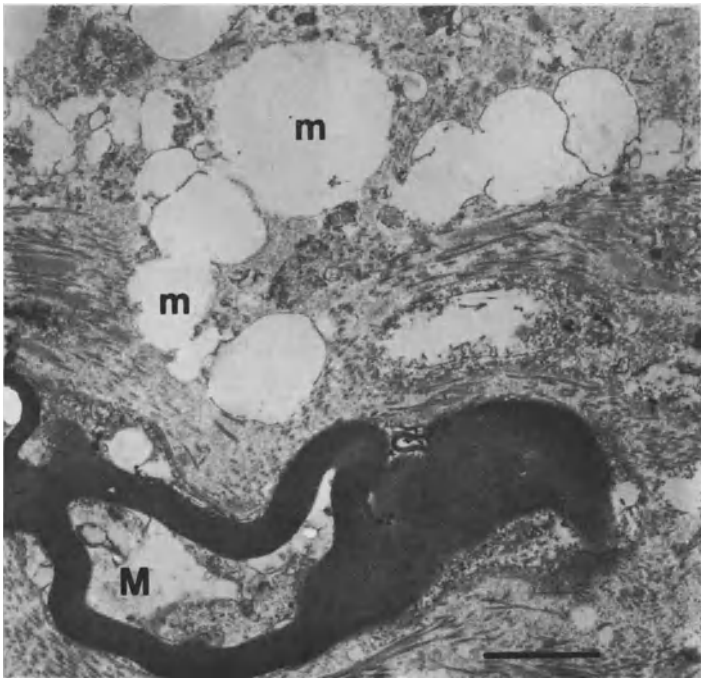

Fig. 4. Thermocoagulation of the ganglion inferius nervi vagi of the rabbit at *80° C/60 sec*. Both the myelinated (M) and non-myelinated (m) nerve fibers are completely destroyed. The non-myelinated nerve fibers appear as homogeneous necrotic fluid puddles. The myelin sheath is completely melted as a result of the heat. Under these coagulation conditions, a selective elimination of the non-myelinated nerve fibers is no longer identifiable. The black line corresponds to 1 µm

Experimental Observations on the Effect of Controlled Hypotension with Trinitroglycerine (TNG) on Intracranial Pressure

F. OPPEL, V. W. A. PICKERODT, and M. Bilan

Summary

It is known that hypotension induced by halothane or sodium nitroprusside (SNP) increases intracranial pressure (ICP). In order to investigate, if hypotension induced by trinitroglycerine (TNG), has the same effect on ICP, TNG was infused in anesthetized cats. During hypotension ICP rose by 4 mm Hg (average) under normoventilation and by 2 mm Hg (average) under hyperventilation. This compares favourably with the ICP-increase known for SNP. However, we observed a marked tachyphylaxis to the use of TNG.

Introduction

Controlled hypotension is a procedure used to prevent greater blood losses, to facilitate surgery by providing a "dry" field (as already reported by CUSHING in 1917 (6)) and to reduce the operative risk, especially in cases of surgery of vascular malformations. The following procedures of controlled hypotension have been used: (1) high spinal or epidural anesthesia, (2) hemorrhagic hypotension, (3) application of ganglion blockers, (4) deep halothane anesthesia, (5) sodium nitroprusside (SNP) and (6) trinitroglycerine (TNG) (1, 2, 4, 7-11, 13-16, 18, 19, 21-23, 28). The most commonly used technique at present is the administration of sodium nitroprusside, which acts directly on the vascular smooth muscle and is easy to regulate. This substance, however, has three disadvantages: (1) impairment of cerebral autoregulation in the posthypotensive phase (17), (2) formation of toxic metabolites (cyanide) (20, 24, 26, 27) and (3) increase of intracranial pressure during hypotension (14, 25). These disadvantages lead CHESTNUT et al. (3) to apply trinitroglycerine (TNG), known from cardiology, as an alternative for controlled hypotension in neurosurgery. In a series of experiments in cats, we have tested the behavior of intracranial pressure during controlled hypotension with TNG.

Material and Methods

Seventeen cats of both sexes, anesthetized with pentobarbital, relaxed with suxamethonium and alcuronium and intubated, were maintained under general anesthesia with 66% nitrous oxide in oxygen and artificially ventilated with a Starling-pump. A 6-chanel-recorder and electronic pressure transducers (Statham P 23 db) were used to record arterial and central venous pressures (by way of centrally positioned catheters) and intracranial pressure (ICP) via a 23 G needle in the cisterna magna. In addition, the ECG was continuously recorded, the body temperature continuously measured and regular blood-gas analyses (ABL 2, Radiometer, Kopenhagen) performed. The TNG-dose necessary for hypo-

tension varied between 0.2 and 2.5 mg/min. Twenty-three hypotensions were carried out under normoventilation and twenty-four under hyperventilation ot an arterial PCO_2 of 2 to 3 kPa (1 kPa = 7.5 mm Hg).

Results

Analysis of the 24 hypotensions under hyperventilation 1 min after onset of the TNG-infusion shows an average reduction of mean arterial pressure to 72.1% of the initial value. In the same experimental animals, ICP increased by 2 mm Hg on average with decreasing mean arterial pressure. The maximal ICP-increase in this experimental group was 3 mm Hg (Table 1). During the period of infusion, mean arterial pressure was maintained between 72 and 79% of the initial value. Fig.1 shows the typical behavior of arterial and intracranial pressures during administration of TNG. After 1 min of infusion mean arterial pressure dropped to 61.8% of the control value, while the mean ICP increased by 3 mm Hg.

In normoventilated cats, mean arterial pressure decreased to 71.2% of the initial pressure within 1 min, and ICP increased by 4 mm Hg in average (Table 1). Figure 2 shows mean values of ICP-changes in the presence of decreasing and increasing mean arterial pressure, and demonstrates that the ICP-increase is greater in normoventilated than in hyperventilated animals. Considerable tachyphylaxis was observed following repeated TNG-administration.

Table 1. Effect of trinitroglycerine (TNG)-hypotension in hyperventilated cats. Mean values ($\bar{x}$) and standard errors of the mean (sem) for mean arterial pressure (MAP) one minute after the beginning of TNG-infusion (percent of control value) and maximal increase of intracranial pressure (ICP). In the bottom line, the maximal ICP-increases observed in individual experiments are given

		Hyperventilation	Normoventilation
n		24	23
Mean arterial pressure (MAP) at 1 min (%)	$\bar{x}$	72.12	71.23
	sem	2.74	3.47
Intracranial pressure (ICP) Increase (mm Hg)	$\bar{x}$	1.97	4.00
	sem	0.19	0.82
Maximal ICP increase (mm Hg)		3.00	6.40

Discussion

The report of CHESTNUT et al. (3) contains no data on the behavior of ICP during TNG-hypotension. Until present there has been no systematic investigation on the effect of TNG-hypotension on ICP. GAGNON et al. (12) and COTRELL (5) observed increases of the ICP under TNG-administration in humans. The average increases of the ICP of 2 and 4 mm Hg, observed in our experiments, can be regarded as clinically irrelevant, even though constant. Influence of the pentobarbital anesthesia on the

ICP-changes under TNG-hypotension cannot be ruled out. Similar conditions probably exist, however, during a neuroleptanalgesia in humans.

If one discussed the substance trinitroglycerine in view of the disadvantages of sodium nitroprusside mentioned in the literature (e.g. 25), the results obtained show a markedly smaller increase in ICP during the hypotensive phase. Regarding toxicity, it has been pointed out by various study groups that trinitroglycerine is a substance without known toxicity. No valid statement can be made on the impairment of autoregulation. However, changes in ICP were studied in 8 animals to which 0.005% noradrenalin was infused in the posthypotensive phase. As shown in Fig. 3, no significant ICP-increase occurred during arterial hypotension, probably indicating intact autoregulation. During comparable investigations under halothane or sodium nitroprusside hypotension, KEANEY et al. (17) observed a disturbance of autoregulation.

In conclusion, trinitroglycerine is suited for controlled hypotension in the animal experiment. No significant ICP-increases could be detected in any of the experimental groups. Although our results cannot clarify all unanswered questions related to controlled hypotension for neurosurgical procedures, and particularly their applicability to humans requires further investigations, they do support previous findings. A way seems to be opening up which permits avoiding the use of the potentially toxic sodium nitroprusside with its known side effects.

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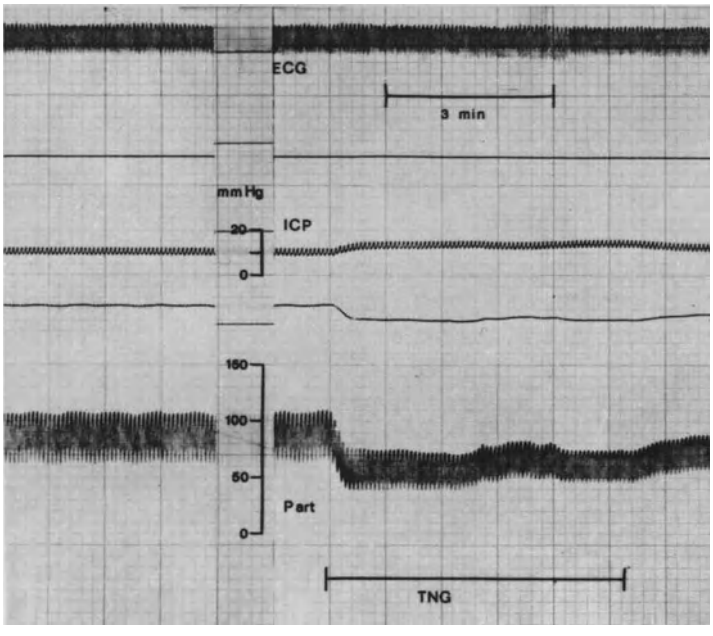

Fig. 1. Effect of hypotension induced with trinitroglycerine (TNG) on ECG, intracranial pressure (ICP) and arterial pressure (P art) in a hyperventilated cat. Original recording

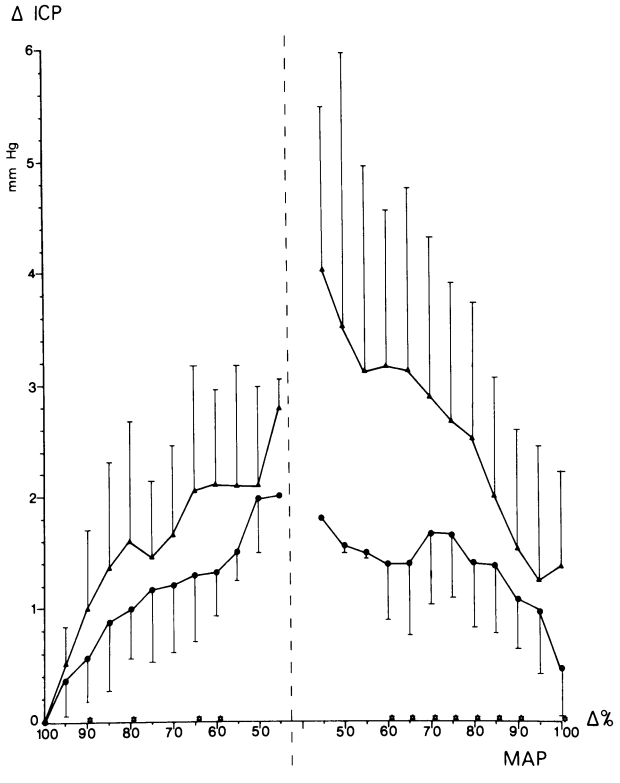

Fig. 2. Effect of hypotension induced with trinitroglycerine: Mean changes of intracranial pressure (Δ ICP) (± s.d.) in the presence of decreasing and increasing mean arterial pressure (MAP), expressed as percent of control value on the abscissa, in hyperventilated (●—●) and normoventilated (▲—▲) cats. Asterisks above the bottom line represent significant differences on the 5.0% level

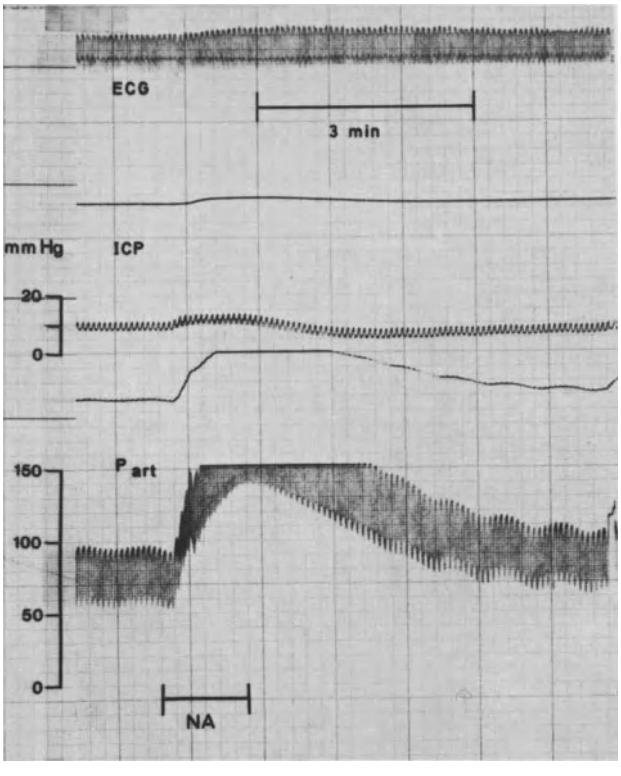

Fig. 3. Effect of noradrenaline (NA) infusion on ECG, intracranial pressure (ICP) and arterial blood pressure (P art) in the posthypotensive phase. Original recording

Membrane Stability Changes of Subcellular Organelles After Barbiturate Treatment

D. STOLKE and H. DIETZ

Barbiturates are lipid-soluble sedative and anesthetic drugs.

In the early seventies another effect of barbiturates came into discussion. NILSON, 1971 (21) and MICHENFELDER et al., 1973 (19) found barbiturate anesthesia to have a protective effect during brain ischemia and hypoxia. In the years to come there were many reports on the beneficial effects of barbiturates on local (13, 14, 27) and global brain ischemia (2, 3, 26, 30). All authors reported clear improvements and less neurological deficits when the animals were treated with barbiturates during brain ischemia. MARSHALL et al. (16, 17, 18) were able to decrease ICP of severely brain injured patients by means of barbiturate therapy and, thus, to improve outcome and reduce mortality rate.

HOFFMANN et al. (15) reported on a seven year old girl coming to admission because of a posterior fossa tumor. She suffered a circulatory arrest of six minutes during anesthesia introduction. She was treated with a high dosis of thiopental according to SAFAR's proposal (23) to avoid or ameliorate postischemic brain damage. Eleven hours after resuscitation she woke up without further neurological deficits.

The experimentally well documented protective effect of barbiturate anesthesia in cerebral ischemia has been assumed to be primarily a consequence of the reduction in cerebral metabolic rate (4, 19, 21). In their studies NORDSTRÖM et al. (22) demonstrated that the protective effect of barbiturates, observed following complete cerebral ischemia, did not seem to be the consequence of reduced energy requirements.

NEMOTO et al. (20) explain the efficacy of barbiturates in ameliorating ischemic brain damage by the improvement and normalisation of CBF, improved brain glucose availability and utilisation, suppression of anaerobic glucose utilisation and improved oxygen utilisation coefficient. As compared to untreated animals, cAMP and lactate are reduced by barbiturate therapy.

ASTRUP et al. (1) state that the specific effect of barbiturates is to prevent progressive increase in the rate of rise of extracellular potassium during ischemia. It is suggested that this indicates a membrane sealing-effect of barbiturates in the cerebral cortex.

FLAMM et al. (10) suggest an additional pathologic molecular mechanism for the process set in motion by ischemia, namely free-radical destruction of membrane lipids. A radical is defined as a substance with a lone electron which confers unusual chemical reactivity. They studied the abrupt loss of oxygen in cerebral tissue at the end of the electron transport chains in mitochondria, leaving a number of occurring

radicals uncontrolled, such as Flavin Adenine Dinucleotide (FAD) and Coenzyme Q. Uncontrolled, they may initiate pathological radical reactions among membrane lipids.

Treating the animals with methohexital during MCA occlusion, the results suggest that this lipid-soluble barbiturate may produce protection of the CNS from ischemia by controlling these abnormal radical reactions.

Lysosomes are small subcellular particles or vesicles found in all animal cells (6, 7).

They are identified by a surrounding lipoprotein membrane and by containing a large collection of acid hydrolytic enzymes. In most cell types lysosomes are sites of intracellular digestion.

Lysosomes released from their membranes may catalyze destructive damage throughout the surrounding tissue by their hydrolytic activity on cellular components. Lysosomal membranes are known to be stabilized by steroids (6, 25, 29). Our own studies (28) confirm these results and underline the suggestion that steroids are incorporated into the membrane itself.

This study aims at answering the following questions:

- Is there any effect of barbiturates on lysosomal membranes?
- Do the results of this study offer an explanation about the site of effectiveness barbiturate?

The long-acting barbiturate pentobarbital as well as the short-acting thiopental were studied.

The lysosomal enzyme β-glucuronidase was assayed. It participates in the degradation of mucopolysaccharides.

De DUVE (6, 7) defined the grade of stability of the lysosomal membranes as the relation of the share of free activity (solved in the cytoplasm) to total activity of the lysosomal enzymes after destruction of the membranes by polyethylene-glycol-mono-ether (Triton x-100). I.e., a decrease of the share of free activity means an increase in lysosomal membrane stability.

Material and Methods

Three groups of 8 adult cats each (2-4 kg) underwent the following procedures:

The first group served as control and was sacrificed under pentobarbital anesthesia (60 mg/kg body weight intraperitoneal) after a 24 hours fasting.

The second group was pretreated with 40 mg/kg body weight of pentobarbital i.p. and was sacrificed 24 hours later in the same way as the first group.

The third group was pretreated with 60 mg/kg body weight thiopental i.p. and was sacrificed 2 hours later in the same way as the other groups.

The brain tissue was separated into white and gray matter, weighted and homogenized in a POTTER-ELVEHJEM all-glass homogenizer. Homogenates were prepared in a 0.25 mol sucrose medium.

Cell nucleus and cell membrane particles were centrifuged at 1.280 g for 10 minutes and the supernatant was decanted. A 10% homogenate was used for assaying the activity of the lysosomal enzyme β-glucuronidase (E.C.3.2.1.31) according to FURTH and ROBINSON (11).

Free activity was measured first, thereafter total activity was assayed after destruction of the lysosomal membranes by poly-ethyleneglycol-mono-ether (Triton x-100). Free or released activity was expressed in percentage of total activity. According to the studies of De DUVE et al. (6, 7) a decrease of free activity means an increase of lysosomal membrane stability.

Results

Table 1 and Fig. 1 show the behavior of the lysosomal enzyme β-glucuronidase after pretreatment with pentobarbital as compared to the control group. In the control group the share free activity of β-glucuronidase in the gray matter is 61,4% (mv = mean value), 51,8%-70,9% (ci = confidence interval). There is no significant decrease as compared to the group with barbiturate pretreatment, 57,8% (mv), 53,8 - 61,8% (ci). In the white matter, however, there is a significant decrease of the share of free activity after pentobarbital pretreatment ($p \leq 0,05$), 37,7% mv, 31,9%-43,6% ci, as compared to the control group 46,4% mv, 39,1%-53,6% ci.

Table 2 and Fig. 1 show the results of the same assay after pretreatment with thiopental. The share of free activity of β-glucuronidase in the gray matter is 55,5% mv, 51,9-58,9% ci. There is a significant decrease of the share of free activity of the lysosomal enzyme β-glucuronidase after thiopental pretreatment ($p < 0,05$) as compared to the control group.

The corresponding values in the white matter, 41,5% mv, 30,8-56,3% do not show a significant change after thiopental pretreatment as compared to the control group.

Table 1. Comparison of the control group with the group of animals pretreated with pentobarbital (β-glucuronidase)

	Gray matter	White matter	
Control	61,38	46,37	mv
	51,85 - 70,91	39,14 - 53,60	95% ci
	5,54	5,17	Ta U/g x 100
Pentobarbital	57,83	37,73	mv
	53,84 - 61,83	31,91 - 43,55	95% ci
	5,93	4,73	Ta U/g x 100
p <	---	0.05	sign.

mv, mean value; ci, confidence interval; TA U/g x 100, total activity in units per gram x 100; sign., degree of significance

Table 2. Comparison between control and thiopental (pretreatment) groups (ß-glucuronidase)

	Gray matter	White matter	
	61,38	46,37	mv
Control	51,85 - 70,91	39,14 - 53,60	95% ci
	5,54	5,17	Ta U/g x 100
	55,45	41,54	mv
Thiopental	51,97 - 58,93	30,82 - 52,26	95% ci
	4,88	4,21	TA U/g x 100
p <	0,05	-	sign.

Discussion

Many lipid-soluble drugs in low concentrations protect cell membranes and subcellular membranes (26). The term "membrane stabilization" was introduced by GUTTMANN, 1940 (12) who found that Ca^{++} or Mg^{++} prevented or stabilized the resting potential of the nerve membrane from depolarisation by potassium.

Lysosomal membranes are known to be stabilized by steroids (6, 7, 25, 28, 29), by fat-soluble vitamins, by tranquilizers and local anesthetics (6, 7, 25, 29). Other drugs or different concentrations of the above mentioned drugs may labilize these subcellular membranes.

In the present study we tried to answer the following questions: Is there any effect of the barbiturates beyond the well-known influences on cerebral blood flow, on oxygen consumption (9), on increased ICP after severe head injury (5, 16, 17, 18) and on cerebral metabolic rate (4, 19, 21).

The question, then, arises as to the site of barbiturate effectiveness in the cell and its organelles.

This study indicates that barbiturates are able to stabilize lysosomal membranes. According to de DUVE et al. (6, 7), the relation of free activity (solved in the cytoplasm) to total activity of lysosomal enzymes in tissue extracts after destruction of the lysosomal membranes by Triton x-100 is a measure of membrane stability.

This is significantly so in the white matter after pentobarbital and in the gray matter after thiopental treatment. The different lysosomal population might explain the different behavior of lysosomal enzymes in gray and white matter (24) On the other hand, 2 hours might be too short to demonstrate this protective effect of barbiturates in the white matter because of its reduced rCBF as compared to gray matter. We conclude from our results that the protective effect of barbiturates takes place in the membrane itself. Barbiturates as lipid-soluble drugs might be incorporated into the liposomes of the membrane itself.

These results agree with those of WEISSMANN (29) who found that steroids cause compaction or stabilization by condensing or restricting the fluidity of the phospholipid acyl chains and rendering them less mobile and, therefore, more stable. We suggest that barbiturates might act likewise and regulate enzyme activity, i.e., increase membrane stability after preincorporation into the bilayer walls of the lysosomal membrane.

FLAMM et al. (10) and DEMOPOULOS et al. (8) suggest that barbiturates control free radicals of Coenzyme Q and FAD and by this control retard or even prevent the pathological radical reactions among the phospholipids of the membranes. Our results do not show whether barbiturates are incorporated into the membranes and stabilize them by restricting fluidity of the phospholipid acyl chains (29) or if uncontrolled pathological radical reactions are inhibited by barbiturate treatment (8, 10). Both hypotheses lead to a stabilization of the lysosomal membranes. In other words, the beneficial effect brought about by barbiturate treatment is an increase in lysosomal membrane stability. By preventing the release of acid lysosomal enzymes into the cytoplasm and into the surrounding tissue, greater damage and more severe neurological deficits are inhibited which would be followed by a chain-spreading autolysis after destruction of the lysosomal membranes.

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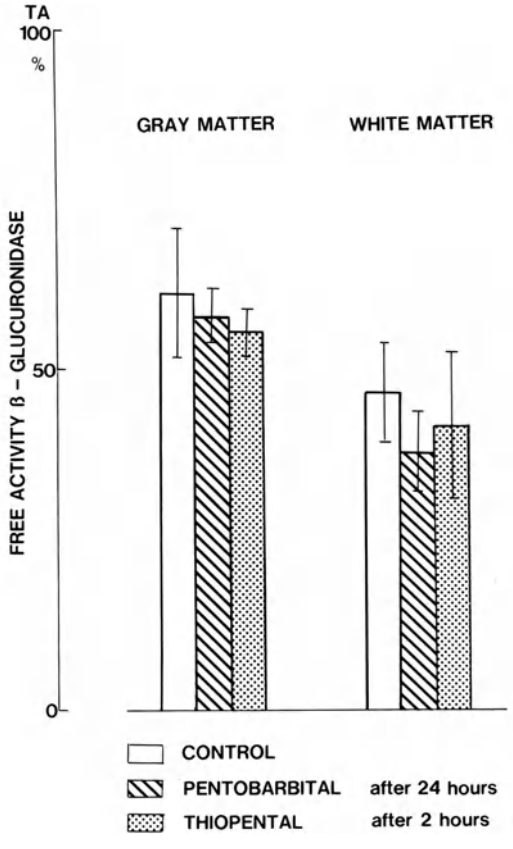

Fig. 1. Graphic display of the results contained in Tables 1 and 2. Control-Pentobarbital-Thiopental

Further Evidence for Glutamate and the Kallikrein-Kinin-System as Brain Edema Factors[1]

A. BAETHMANN, O. KEMPSKI, A. UNTERBERG, K. MAIER-HAUFF, and R. GEIGER[2]

Introduction

Damage to structural elements of the blood-brain barrier in arteriolar, capillary and venous segments by mechanical, ischemic or other insults, causes leakage of plasma-like, i.e. vasogenic, edema into the extracellular space of the cerebral parenchyma. Influx of edema into cerebral tissue raises the question as to its significance. Is it the mere addition of volume to a confined intracranial compartment, which alone determines the further course, or is it the initiation of secondary pathological processes, e.g. enhancing influx and spread of edema and, hence, magnifying the cerebral tissue damage? Taking a traumatic, or ischemic focal insult of brain tissue as an example, it is obvious that the primary lesion is more than just an area of increased blood-brain barrier permeability. A focus of traumatic or ischemic nature consists of many necrotic glia-, nerve- and endothelial cell elements, occluded vessels and perhaps of petechial hemorrhage. Flooding of the extracellular space by a protein-rich plasma filtrate entering the parenchyma through a focus of cell necrosis, and thrombosed vessels can be considered the basis leading almost inevitably to the concept of an involvement of chemical mediator compounds in the ensuing pathophysiological process. A great number of potential brain edema factors is conceivable. However, we found the aminoacid glutamate and the components of the kallikrein-kinin system particularly attractive candidates. An increase of the extracellular glutamate concentration, which is normally very low, was shown to induce swelling of nerve- and glia cells by an extra- to intracellular fluid shift secondary to raising Na^+-permeability of the cell membranes (1, 5).

The presence of glutamate in brain tissue, albeit strictly intracellularly, in high concentrations and its potent neuropharmacological properties render this compound an excellent edema factor which conceivably mediates secondary cytotoxic edema. Massive leakage of glutamate into the surrounding extracellular space can be surmized to happen in tissue damage with cell necrosis. Activation of the kallikrein-kinin system may be considered, if in vasogenic edema a plasma filtrate containing kininogen as the precursor of kinins enters the cerebral extracellular space. Kininogen is a natural component of the α_2-globuline fraction of plasma. Formation of bradykinin in brain tissue may interfere with microcirculatory control, thus enhancing edema influx, but may lead to cytotoxic damage as weel. In former studies we have shown that direct exposure of brain tissue by ventriculo-cisternal perfusion, so as to bypass the blood-brain barrier, to either glutamate,

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or plasma, causes formation of brain edema as concluded from an increase in brain water content. Moreover, formation of kinins during ventriculo-cisternal perfusion was demonstrated by a marked decrease of the kininogen concentration in the plasma perfusate following passage through the ventricles (3). Now we report on further studies conducted to characterize the nature of brain edema induced by either glutamate or plasma perfusion of the cerebral ventricles. We included recent results on ventricle perfusion with bradykinin, performed to obtain direct evidence for the potential edema forming properties of this peptide.

Material and Methods

1. Glutamate

The experiments were conducted in male Sprage Dawly rats of 200-350 g body weight in chloralehydrate anesthesia (360 mg/kg). Two different methods were used to expose brain tissue to glutamate: Superfusion of the cerebral cortex after removal of the overlying dura mater, or ventriculo-cisternal perfusion. Exposure of the brain to glutamate was always preceded by a control period using mock CSF. Electrical conductivity was calculated as the reciprocal value of the specific electrical resistance of the brain tissue (impedance) to an alternating current of 1000 Hz. The voltage was 13 mV. Impedance was measured by a balanced resistance-capacitance bridge. In experiments with superfusion, two Ag/AgCl surface electrodes were placed on the cerebral cortex. Impedance was measured only after exposure, since the superfusate shortened the electrodes. In experiments with ventriculo-cisternal perfusion, impedance was measured during perfusion, using the infusion cannula as an electrode and impaling another needle electrode in adjacent brain tissue. Duration of ventriculo-cisternal perfusion was 150 min. Following ventricle perfusion the animals were exsanguinated from the aorta and vena cava to induce complete cerebral ischemia. This was to determine the ischemic conductivity change as a measure of the fluid volume which remained in the extracellular compartment after exposure to glutamate. Subsequently, the brain was removed to analyze the cerebral water- and electrolyte content.

2. Kallikrein-Kinin System

The experiments were conducted on male mongrel dogs of 10-12 kg body weight under pentobarbital anesthesia (25 mg/kg body weight) and under mechanical ventilation. Both lateral ventricles were cannulated for ventricle perfusion, and an additional tube was introduced into the cisterna magna after incision of the atlanto-occipital membrane. The ventricle perfusion pressure was continuously monitored. Prior to perfusion with (a) plasma, or (b) bradykinin in mock CSF, the ventricular system was perfused with artificial cerebrospinal fluid for 30 min. Perfusion with either plasma or bradykinin was performed over 180 min. The animals were subsequently sacrificed with KCl i.v. Both cerebral hemispheres were removed and brain tissue samples were taken from cortex, the basal ganglia and white matter. Gross damage of brain tissue due to ventricular cannulation was recognized by uptake of Evan's blue, administered 1 to 2 hours prior to sacrifice.

Results and Discussion

1. Glutamate

The response of the electrical conductivity of the cerebral cortex of a single experimental animal to superfision with Ringer's solution, or glutamate (70 mM in isotonic solution) is shown in Fig. 1. As seen, superfusion with Ringer's solution for 5 min led to a small drop in conductivity with immediate recovery after removal. Superfusion with 70 mM glutamate for 5 min was found to induce a marked fall in conductivity which, however, had an obvious tendency to recover after removal of the aminoacid. Subsequent exposure for 60 min led to further reduction in conductivity which, then, was followed by a period of sluggish and incomplete recovery (Fig. 1). In addition, ischemic conductivity change was markedly reduced when compared to control animals. Table 1 demonstrates the electrical conductivity changes of rat brain tissue to ventriculo-cisternal perfusion with different solutions. The data are given in % of the conductivity value at the beginning of perfusion. In these studies, impedance was continuously measured in the tissue, using the perfusion cannula as an electrode, while the other electrode was impaled into adjacent brain tissue. Ventricular perfusion with mock CSF did not change conductivity when compared to sham-operated control animals (Table 1). On the other hand, perfusion with 20 mM glutamate led to a gradual and statistically significant decline in conductivity over the observation period of 150 min. Induction of cerebral circulatory arrest by exsanguination caused in controls a reduction in conductivity of 45-48% of the pre-ischemic value which is in perfect agreement with earlier observations (4, 5). Reduction of electrical conductivity secondary to cerebral circulatory arrest most likely results from disappearance of the extracellular fluid into the intracellular compartment, due to the breakdown of the intra-extracellular Donnan-distribution (4, 5). As a result, the extracellular fluid space shrinks, thus impeding the electrical current which mainly flows through the extracellular channels of the tissue.

Table 1. Changes in electrical conductivity, in percent of conductivity at the onset of perfusion, in controls and during perfusion with different isotonic and buffered glutamate solutions. Indicates the statistical significance level at $p < 0.05$, or less. Six animals were studied per group

Perfusiontime (min)	30	60	90	120	150	Ischemic conductivity change (% of pre-ischemic value)
Sham-operation	98,9 ±0,8	101,1 ± 0,6	101,4 ± 0,8	101,4 ± 0,8	100,9 ± 0,8	48,3 ± 1,4
Mock CSF	99,9 ±0,6	101,1 ± 0,9	101,0 ± 1,5	100,9 ± 1,4	99,5 ± 1,5	44,8 ± 1,7
Glu 20 mM	98,6 ±0,7	97,4^{+} ± 1,4	92,6 ± 1,3	94,9 ± 2,4	94,3^{+} ± 2,1	34,8 ± 2,5^{+}
Glu 20 mM no Ca^{++}	98,9 ±0,7	98,4^{+} ± 1,0	99,1 ± 1,4	98,2 ± 2,0	96,1 ± 1,9	39,0 ± 2,3
Glu 20 mM no Mg^{++}	98,2 ±0,8	96,4^{+} ± 0,6	95,4^{+} ± 0,9	92,6^{+} ± 1,3	90,8^{+} ± 1,5	35,9 ± 2,0

This impedance to the electrical current is reflected by the decrease in conductivity. As shown in Table 1, the ischemic change in conductivity is significantly smaller in experimental animals previously perfused with glutamate (Glu 20 mM). The reduction of the ischemic conductivity response in glutamate animals can be explained by the previous shrinking of the extracellular space, already reduced by ventricular perfusion with the aminoacid. Thus, less extracellular fluid was available thereafter for the extra- to intracellular shift upon induction of ischemia. In these experiments we also studied modifications of the Ca^{++} and Mg^{++} concentrations in the glutamate perfusion fluid. This was to find out whether the effect of glutamate observed in brain tissue was influenced by varying the electrolyte composition of the perfusate. As seen, removal of Ca^{++} ions from the perfusate caused a tendency to attenuate the cerebral conductivity response to glutamate, while removal of Mg^{++} ions had the opposite effect.

Lowering of electrical conductivity was most pronounced if the glutamate perfusate was devoid of Mg^{++}. In this group (Table 1), conductivity fell to the lowest value after 150 min of perfusion as compared to the other experimental groups. These results indicate that Mg^{++} ions attenuate, while Ca^{++} ions enhance the effects of glutamate on brain tissue.

2. Kallikrein-Kinin-System

Tissue water content of samples of cerebral cortex, caudate nucleus, and white matter of dobs are given in Table 2. As shown, ventriculocisternal perfusion with homologous heparinized plasma for 180 min caused edema formation only in the periventricular white matter, but not in caudate nucleus or cerebral cortex. Moreover, in these studies, a decrease in clearance capacity of brain tissue for the excess K^+ ions contained in the plasma perfusion fluid with continuing perfusion (2). This would suggest that cellular uptake mechanisms in periventricular tissue were damaged by the exposure to plasma. Impairment of brain tissue to control extracellular K^+ may reflect a cytotoxic type of injury.

Table 2. Cerebral water content, in ml/100 g of fresh weight, after 3 hours of ventriculo-cisternal perfusion with mock CSF, homologous plasma, or bradykinin in mock CSF

	Cortex	Nc. caudatus	White matter
Plasma	80,95 (12) ±0,75	80,26 (12) ±0,69	68,51 (9) ±1,51
	n.s.	n.s.	$p < 0.05$
Mock CSF	80,94 (7) ±0,58	80,29 (6) ±0,84	66,17 (6) ±1,04
	$p < 0,02$	$p < 0,001$	$p < 0,05$
Bradykinin	81,63 (8) ±0,35	81,89 (8) ±0,40	68,01 (8) ±1,70

Another series of experiments was conducted to obtain further evidence for a role of the kallikrein-kinin system as brain edema factor. Although in these and earlier investigations the brain-water content increased to ventriculo-cisternal perfusion with plasma, and kinins were formed during perfusion, the evidence for a kinin-specific edema mechanism must be considered circumstantial at best, because plasma is an undefined mixture of many compounds. Therefore, ventriculo-cisternal perfusion was performed again in dogs, this time employing pure bradykinin dissolved in isotonic and buffered mock CSF.

The tissue water content of different brain areas was again measured after a perfusion period of 3 h. The data are shown in Table 2, where it is seen that bradykinin perfusion of the cerebral ventricules increased the water content not only in white matter, but also in cerebral cortex and caudate nucleus. To our knowledge, this is the first time such an observation has been made. Table 3 demonstrates the concentration profiles in percent of either plasma-kininogen (A), or bradykinin (B) of the perfusate after passage through the ventricle. The decrease in kininogen-concentration during perfusion in dogs, and, hence, formation of kinins, appears to be smaller than what was observed in earlier studies in rats (3). This may result from the markedly higher perfusion rate employed in dogs, which was 1 ml/min, as compared to rats, in which it was only 0.04-0.06 ml/min. Table 3 shows that during ventricular passage, bradykinin concentration fell to 45-23% of the entering concentration. Potential dilution due to endogenous formation of CSF was corrected for using inulin as volume marker. These data make obvious the enourmos capacity of the brain to clear, or inactivate bradykinin suggesting that brain tissue disposes of powerful protection against the formation of kinins.

Summary and Conclusions

This report presents experimental findings which provide further evidence that glutamate and the kallikrein-kinin system may have a role as mediators of secondary processes in brain edema. Measurements of the electrical conductivity of brain tissue during, or after exposure to glutamate by superfusion of the cerebral cortex, or ventriculo-cisternal perfusion demonstrate an intracellular localization, i.e. a cytotoxic nature of the glutamate edema. This conclusion finds further

Table 3. Kininogen- or bradykinin concentration profiles in perfusate after ventricular passage. Kininogen concentration in plasma perfusate was indirectly determined as kinin-activity using a biological assay system. Thus, decrease of kininogen concentration after ventricular perfusion indicates proportionate formation of kinins. The decrease in bradykinin concentration during perfusion (group B) is significant at $p < 0.005$-0.001

	Inflow-concentration (%)	Outflow-concentration (% of inflow) 30'	60'	90'	120'	150'	180'
(A) Plasma	100 (=2686±270 ng/ml Bradykinin activity)	94,5 ±8,9 (9)	105,5 ± 7,9 (9)	88,7 ±7,4 (9)	95,3 ±8,5 (9)	92,6 ±8,1 (9)	94,1 ±8,1 (9)
(B) Bradykinin	100 (=2476±322 ng/ml Bradykinin	43,1 ±10,1 (9)	45,1 ± 9,7 (9)	36,7 ±6,5 (9)	22,9 ±7,0 (9)	31,0 ±9,0 (9)	30,1 ±8,0 (9)

confirmation in studies of the electrical conductivity change performed during acute cerebral ischemia. Previous exposure to glutamate was found to reduce significantly the ischemic conductivity change measured thereafter, again indicating a glutamate-dependent expansion of the intracellular compartment at the expense of the extracellular space.

Ventriculo-cisternal perfusion with bradykinin resulted in a significant increase of water content of the cerebral cortex, white matter and caudate nucleus. The latter experiments were conducted to obtain further evidence as to whether formation of kinins during cerebral exposure to plasma observed in earlier studies may in fact cause cerebral edema. Determination of the bradykinin concentration prior to and after ventricle passage revealed an enormous kinin-clearance capacity of the brain, indicating that this organ disposes of powerful protection mechanisms against an activation of the kallikrein-kinin system. Taken together, the evidence so far obtained provides further support for our concept (a) that glutamate release from damaged nerve and glia cells in focal areas mediates secondary cytotoxic edema, and (b) that activation of the kallikrein-kinin system upon penetration of plasma proteins into cerebral parenchyma would enhance the edema process.

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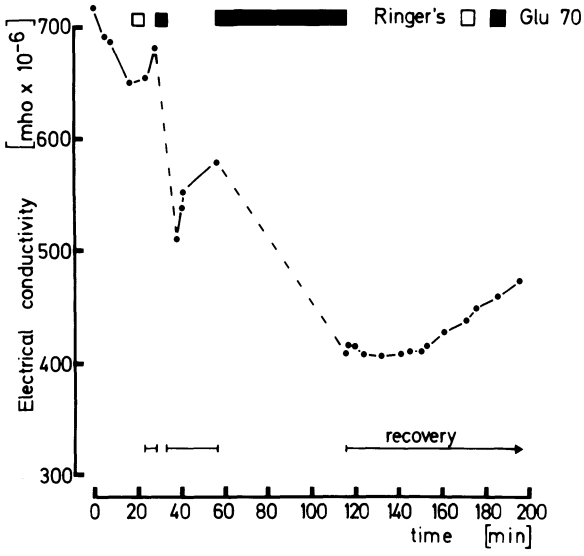

Fig. 1. Electrical conductivity of the cerebral cortex of an experimental animal after superfusion with Ringer's, or isotonic solution containing 70 mM glutamate. For measurement, the superfusates were exchanged against paraffin to avoid shortening of the impedance electrodes placed few millimeters apart on the cortical surface. As seen, a fall in conductivity and a delay in recovery were the more pronounced the longer the exposure to glutamate

Experimental Acute Brain Swelling

Z. CZERNICKI, T. GENNARELLI, and U. WALD

In cases of head injury with untreatable intracranial hypertension some authors recommend a wide decompressive craniectomy (1). Although good results may be achieved with this method, one should be aware of a severe increase in brain volume after this procedure.

Studies of epidural brain compression have shown that a sudden deflation of the balloon causes a rapid increase in intracranial pressure (ICP) (3, 4). In addition to edema as a result of the intracranial hypertension caused by the epidural balloon, it has been found, using the window technique, that vasodilatation related to vasoparalysis develops after balloon deflation (8).

The aim of this study was to determine the respective contributions of these two mechanisms, brain edema and vasodilatation, to the increase in brain volume observed after sudden decompression in cases with severe head trauma.

Material and Method

This study was performed on 13 Maccaca monkeys weighing from 3700-8600 g. The high acceleration head injury model was used. The head was rotated by 60^{o} in the sagittal plane. The radius of rotation ranged from 8-13 cm, the duration was 12 msec and the average angular acceleration 10.1×10^{4} rad/sec^{2}. The following parameters were recorded: blood pressure, respiration, end-tidal CO_2, ECG, heart rate, central venous pressure, ICP, EEG, rectal temperature. In addition, the following measurements and studies were made: cerebral blood flow using intravenous Xenon 133 technic (6), arterio-venous oxygen difference, cerebral metabolic rate of oxygen, pH, $PaCO_2$, PaO_2, morphology, alterations in blood-brain barrier, brain tissue water content, autoradiography using C^{14} sucrose (2) and ultrastructure using an electron microscope.

The animals were anaesthetised and connected to the monitoring devices. One hour prior to the impact anaesthesia was discontinued, the animals woke-up and monitoring of control values was started. At the same time, the neurological status of the animals was evaluated. Next, the animals were subjected to the impact using a selected value of acceleration.

In 10 cases (non-surviving group) the impact resulted in a very severe injury with progressive deterioration of all recorded parameters and subsequent death. In 3 cases (surviving group) corneal reflex was absent for more than 30 sec but the animals gradually recovered.

To study the effects of decompression, craniectomy was performed in the left fronto-temporo-parietal region 10-16 min after the impact. The diameter of the craniectomy was 1.5 cm, the dura was widely opened. In the non-surviving group a rapid increase in brain volume with the subsequent formation of a fungus was observed within 3-5 min. In the surviving group the increase in brain volume was less pronounced, the brain protruding only slightly above the bone level.

The animals were sacrificed 30-40 min after craniectomy. The brain was removed, cut through the fungus in the frontal plane and frozen. The frontal part was used for water content measurements and the posterior part for autoradiographic studies. The water content determinations were made both in the cortex and the white matter employing the wet-dry matter weight difference technique. In one animal of the non-surviving group an electron microscope examination was performed.

Results

The changes observed in physiological parameters, cerebral blood flow, cerebral metabolic rate of oxygen and arterio-venous difference of oxygen are discussed elsewhere.

A cross selection of the brain of a monkey from the non-surviving group is shown in Fig. 1.

As can be seen, the structures of the basal nuclei are displaced into the fungus. Only trace amounts of Evans blue are visible around hemorrhagic foci in the fungus, but the dye is not present in amounts indicative of blood-brain barrier disturbances. The average volume of the fungi was 1.4 cm^3. There was a strong dependence of fungus volume from blood pressure. When blood pressure was rapidly increased, for example by epinephrine administration, breaks appeared in the fungus surface causing vessel ruptures. After the animals had been sacrificed the volume of the fungus was reduced to one fifth.

The results of water content measurements are presented in Table 1.

Statistical analysis did not reveal significant differences in water content in the fungus and the contralateral hemisphere in both the grey and the white matter.

Figure 2 shows autoradiographs from the brain of monkey C-123 from the non-surviving group.

Table 1. Tissue water content in non-surviving monkeys in %

	Grey matter		White matter	
	Control	Fungus	Control	Fungus
C 121	79,1	76,1	65,7	64,2
C 122	78,9	82,5	68,5	69,0
C 123	77,5	75,6	65,9	68,1
C 124	79,2	76,6	69,8	67,7
C 125	79,3	77,3	68,3	68,0

No characteristic fungoid shape is seen in these pictures. This is due to the fact that after sacrificing the animal the fungus collapsed. There are no signs of sucrose accumulation in places other than those surrounding hemorrhagic foci.

The zone of sucrose evidence coincides with that of Evans blue accumulation. The dark spots visible in the picture are dilated vessels.

The electron microscopic study was performed on samples taken from a living monkey and fixed with glutaraldehyde.

Interpretation of the obtained pictures was limited by the relatively large amount of artefacts caused by the fixation technique employed. It was only possible to evaluate the vessel wall and the extracellular space; there was no sign of destruction of the vessel wall and the extracellular space in the white matter was not distended.

Discussion

In explaining the observed increase in brain volume after decompressive craniectomy the authors considered two possible mechanisms: brain edema and vasodilatation.

The aim of the Evans blue study was to determine if there was any increase in blood brain barrier permeability, typical of vasogenic edema. Evans blue was found to be present only in a narrow zone surrounding hemorrhagic foci, no appreciable amount of the dye being visible in the interior of the fungus. In order to determine whether blood brain barrier permeability was altered for compounds with low molecular weight, C^{14} sucrose studies were performed. Also here there was no evidence of increased blood brain barrier permeability. Taken together with the non-significant increase in water content in the grey and white matters, and the results of the electron microscopic study, this proves that vasogenic edema is not responsible for the formation of the fungus. Therefore, vasodilatation seems to be responsible for the observed increase in brain volume.

In previous works on the effects of sudden decompression, an increase in cerebral blood flow following balloon deflation has been observed (5). Likewise, in other studies involving observations of the cortex through the transparent calvarium, dilatation of the cortical vessels has been reported (8). In the above mentioned works, decompression was performed after the blood vessels had already been damaged by ischemia produced by intracranial hypertension. In this study the vasomotor disturbances were caused by the impact.

It is possible to calculate the capacity of the vascular bed from the anatomical data given by HUNZIKER et al. (7). They determined that the total capillary length per mm^3 of the cortex is about 200 cm. Therefore, vasoparalysis is likely to produce a considerable increase in tissue volume.

Conclusion

The results of this study show that sudden decompression of a severely injured brain causes a rapid increase in brain volume. Since there is no evidence of edema in regions other than the zone surrounding hemorrhagic foci, it can be concluded that this increase in brain volume is caused by vasodilatation. Thus, it seems that vasoparalysis should be

added to brain tissue damage and mass lesions (haematomas) as the main prognostic factor following severe head trauma.

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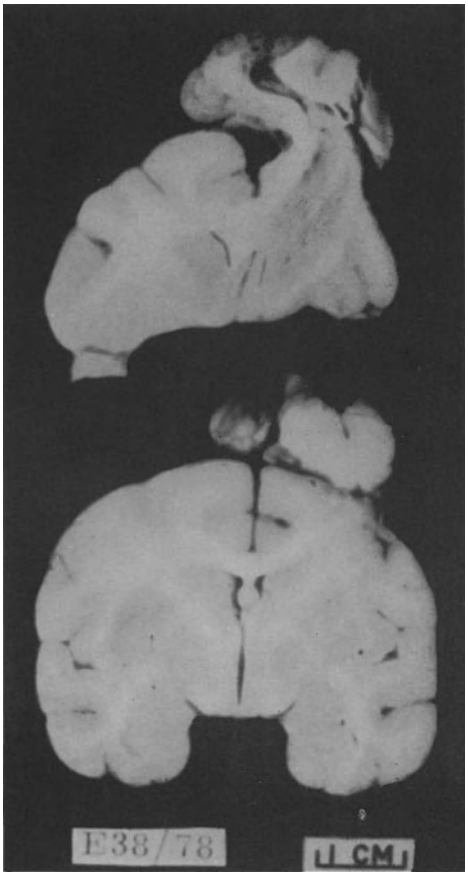

Fig. 1. Fungus formed after decompressive craniectomy performed in monkey E-38 from the non-surviving group

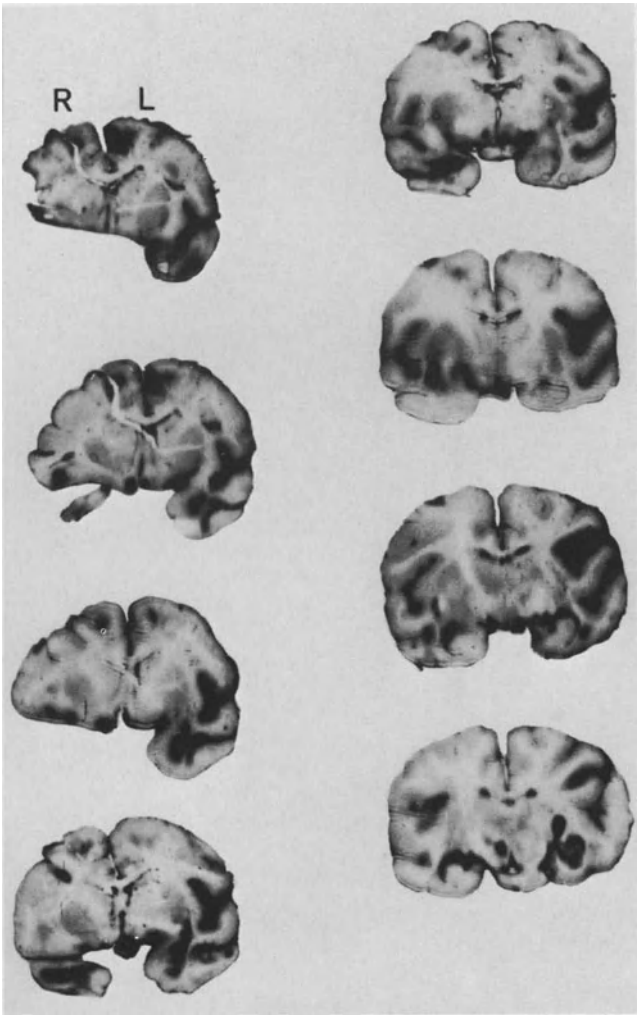

Fig. 2. Autoradiographs obtained using C^{14} sucrose in monkey C-122

Compression of the Terminal Bridging Vein Segments – the Cause of Intracranial Pressure Plateau Waves

H. ARNOLD and R. LAAS

The phenomenon "plateau wave", since first described by LUNDBERG in 1960 (6), has been a challenge to neurosurgeons, neurologists, and neurophysiologists. Despite skillful experimental work, it eluded satisfactory explanation. Precapillary autoregulatory mechanisms, or cerebral venous drainage impairment were supposed to be causative of plateau-waves (PW).

From experiments on the rat and simulation by means of a physical model, PW proved to be caused by bridging-vein compression. Methods and special results of experimental work are reported elsewhere (1, 5). In consideration of previous investigations, performed by others, which dealt with PW, intravascular and intracranial pressure (ICP) relations, cerebral blood flow (CBF) during raised ICP, and cerebrospinal fluid (CSF) dynamics, we propose an explanation of the whole course of PW (Fig. 1).

As a rule, PW develop from an ICP level increased to about 30-40 mm Hg. Occasionally, however, they arise from an ICP close to normal, especially in hydrocephalics. To elicit PW in such cases, a triggering-like coughing or abdominal compression is required in most cases.

An absolute prerequisite for compression of the terminal bridging vein segments (TBVS) is a distinct reduction of intracranial compliance. Otherwise an additional intracranial volume sufficient for TBVS compression can be rapidly compensated for. Two pressure gradients act on TBVS. From outside the vessel it is the gradient ICP/venous sinus pressure (VSP), from inside the gradient venous pressure (VP)/VSP. The gradient ICP/VSP hampers venous outflow to the sinus thus preventing collapse of the leptomeningeal veins. Consequently, VP must surmount ICP. In dogs the difference between VP and ICP has been demonstrated to vary from 5-25 cm H_2O over a wide range of ICP (8, 11). A steep drop in VP was observed at about 2 mm proximal to the venous junction to the sagittal sinus (8). This is the point, where increasing ICP compresses the veins. Due to their slitlike shape, TBVS are particularly prone to compression. They act like throttle valves. This has been shown not only in animal experiments, but angiographically in humans too (3). It is evident that VP will increase, if ICP increases.

Normally, there are two resistances to CBF. The arterioles represent the first resistance, the TBVS the second one. If intracranial compliance and ICP are in a normal range, the second resistance will be insignificant. Concurring to rising ICP the venous flow resistance increases. Obviously, the additional flow resistance of the venous compartment is initially compensated for by dilation of the precapillary vasculature (12). The precapillary flow resistance decreases. The main flow resistance changes from the arteriolar-capillary level to

the entrance of the cerebral veins into the venous sinuses (2). In case of generalized brain edema the main flow resistance is located in the capillaries; consequently PW cannot develop.

Concerning flow, it is to be considered that the displacement of the main flow resistance from the arteriolar-capillary level to the venous outlets corresponds to a diminution of venous conductance, whereas arterial conductance increases. Thus, if main cerebral flow resistance shifts to TBVS, a state will be reached, at which compression of TBVS then results in that the pressure of the arterial compartment acts directly upon the veins. Provided compliance is poor and TBVS are severely compressed, a steep ICP rise will happen. Under normal conditions ICP determines VP. From the moment, at which TBVS are sufficiently compressed to produce a congestion of the cerebral vasculature, VP determines ICP. ICP equalizes VP. Simultaneously with the intravascular pressure ICP rises steeply. Temporarily, due to the lacking difference between VP and ICP, a re-opening of the venous junctions to the sinuses is hampered.

A reduction of CBF coincides with the pressure rise of PW (6a). Simultaneously the cerebral blood volume begins to augment (9). The cerebral oxygen availability decreases (7). In experiments on dogs VSP was found to drop with the beginning of PW (4). CBF does not totally cease. As could be observed in our physical model, too, a residual flow is maintained. The amount of residual flow determines the difference between plateau pressure and mean arterial pressure (MAP), since the residual venous drainage represents a pressure loss of VP (= ICP) compared to MAP. The greater the residual flow is, the lower is the plateau pressure.

During the plateau phase high ICP improves CSF absorption. Thus, space is gained. Cerebral vasculature expands, flow slowly improves, and the plateau decreases slightly. Finally, the re-opening of TBVS causes sudden normalisation of cerebral venous drainage. ICP drops abruptly. The duration of the plateau phase depends upon to what extent CSF absorption can be enhanced by the plateau pressure. During the plateau phase CSF has been absorbed to an extent as great as needed for giving space to the dilated vasculature and for complete distension of the cerebral veins. Therefore, owing to re-established cerebral venous drainage, the pressure stops to below the pre-wave level at the end of PW.

PW, which develop from an ICP level, only slightly elevated, are thought to be elicited in the following way: provided intracranial compliance is distinctly diminished, a rapid increase of VSP (coughing, defecation) induces a congestion of draining veins accompanied by a sudden simultaneous elevation of VP and ICP. At the moment, when VSP is abruptly reset to normal, TBVS are rapidly emptied due to the high gradient ICP/VSP, whereas the proximal venous segments remain distended. ICP equalizes VP. As a result, TBVS flow resistance remains high.

To elicit PW from an elevated ICP level, minimal trigger-mechanisms may suffice. An irregularity of heart-beat or an undulation of cardiac output may be enough to disturb the balance between arterial influx and venous drainage if the main resistance to CBF has shifted to TBVS.

After the phase of pressure-fall, cerebral blood volume (CBV) still remains somewhat increased (9). In contrast to the plateau phase, however, CBF is enhanced (6). These findings are to be interpreted as compensatory hyperemia following CSF reduction during the plateau phase.

Summary

Plateau waves are caused by terminal bridging vein compression. The most important prerequisite for PW development is a reduction of intracranial compliance. During ICP increase the main resistance to CBF shifts from the arterioles to the terminal bridging vein segments, except in brain edema. The shifting of flow resistance to the venous outlets is the second prerequisite for PW. In generalized brain edema PW cannot develop. PW resolution is brought about by improved CSF absorption - and possibly brain shifting - due to the very high ICP during the pressure plateau phase. Thereby space is gained for re-distension of the terminal bridging vein segments. The pressure drop of PW indicates the restoration of sufficient cerebral venous drainage.

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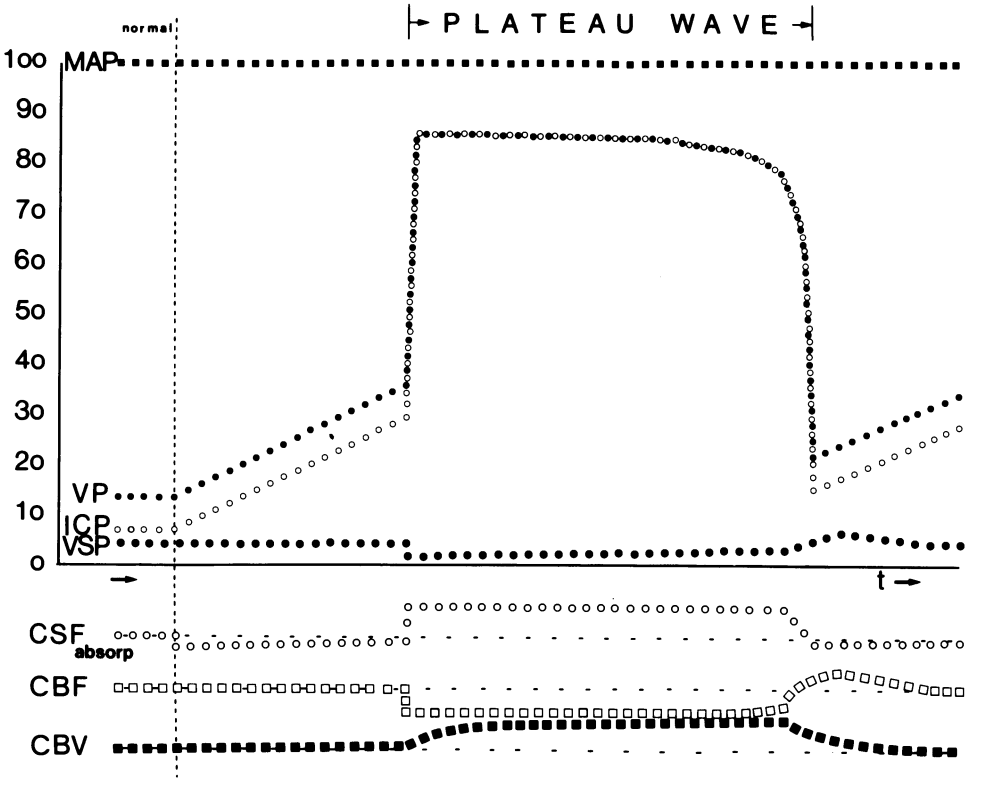

Fig. 1. Time-course of mean arterial pressure (MAP), cerebral venous pressure (VP), intracranial pressure (ICP), venous sinus pressure (VSP), cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebro spinal fluid absorption (CSF_{absorp}) during a plateau wave. Normal values or proportions are inscribed for comparison. CSF_{absorp} = CSF absorption in relation to CSF production (dotted line)

Intracranial Pressure Gradients in the Presence of Various Intracranial Space-Occupying Lesions[1]

A. BRAWANSKI and M. R. GAAB[2]

Introduction

While the clinical value of intracranial pressure recordings is not questioned, the possibilities of errors within the available methods are still under discussion. ZIERSKI (10) reported considerable differences between epidural and ventricular measurements. However, it is not certain whether these differences were due to methodological errors, or represent true intracranial pressure gradients. Therefore we investigated the intracranial pressure distribution in the presence of various space occupying processes, both in animal experiments and clinically.

Methods

Animal Experiments

In 48 cats, different intracranial space-occupying processes were caused. As a model of *general volume increase*, infusion of CSF either into the lumbar region or into the lateral ventricle was used, as well as the induction of generalized convulsions (5). Filling of a subdural balloon over one hemisphere and unilateral cold lesion (5) were used as *localized space occupying processes*. Epidural pressures over both hemispheres (rEP, LEP), and over the posterior fossa (pEP), ventricular pressure (VP), cisternal pressure (CP), lumbar pressure (LP), and sagittal sinus pressure (SP), were recorded in all animals.

Clinical Studies

As a model of *generalized space-occupying* process, we studied patients with communicating hydrocephalus. As an example of *local volume increase*, we investigated 40 patients with disturbances in CSF circulation and with local contusions, tumors, hematomas or abscesses.

Depending on the clinical indication (the position of the space-occupying process), epidural pressure was measured over both hemispheres (lEP, rEP) and the posterior fossa (pEP). Additionally we recorded the ventricular pressure (VP), and the pressure of the subdural (SP) and lumbar space (LP). Measurement of the CSF-pressure was carried out via catheters, epidural and subdural measurements being performed with a miniature pressure transducer (2).

1 This work was supported in part by grants of the VW Foundation.
2 We gratefully acknowledge the competent technical assistance of Mrs. Y. WAGNER.

Evaluation

All the measured values were evaluated in a computer (HP 9845) using our own programmes, as time-shortened course representation. The correlation between the pressures was calculated.

Results

Animal Experiments

During *lumbar infusion of fluid* (Fig. 1a), no significant differences in pressure were seen. In contrast, with *infusion into the lateral ventricle*, differences in pressures can be recognized at the points of measurement, varying with the infusion-rate. The pressures over the hemispheres are nearly parallel, but, at higher rates of infusion, a marked cranio-caudal gradient occurs (Fig. 1b, c). During *generalized convulsions* the pressures over the hemispheres increase identically, but clearly recognizable pressure gradients exist from supra- to infratentorial (Fig. 1d).

Unilateral filling of a subdural balloon also causes an unequivocal pressure-gradient between the hemispheres as well as a gradient from cranial to caudal (Fig. 2a). The most impressive pressure gradients are seen in *local cold injury*. Here, both considerable pressure differences between the hemispheres and between supratentorial and infratentorial regions exist (Fig. 2c). All measured pressures are correlated with one another in a *linear* manner (Fig. 2b, d).

Clinical Measurements

No pressure gradients were found in patients with *communicating hydrocephalus* (Fig. 3a). Taking into account the hydrostatic levels, all measurements revealed an identical course. In contrast, considerable pressure differences are sometimes seen between the individual compartments in presence of *disturbances of cerebrospinal fluid circulation* (Fig. 3b). Pressure increases in the compartment "cut-off" by a passage block of CSF, are transmitted either not at all, or only to a slight degree to other compartments. In presence of *local space-occupying processes*, marked pressure differences can be observed, related to the spreading rate of the lesion. Over the traumatized hemisphere in presence of acute hemorrhage or of tumors, the pressure is higher than over the uninvolved hemisphere (Fig. 3c). In addition, *supratentorial* pressures are clearly increased in comparison to the *infratentorial* values. While in the case of supratentorial space-occupying processes a considerable cranio-caudal pressure gradient may be obtained, it can be *reversed* when the processes are localized in the posterior fossa (Fig. 3d). Generally the pressure differences between the individual compartments are correlated linearly, although not as significantly as under experimental conditions. But no correlation between the pressures can be seen, if the CSF pathways are completely blocked.

Discussion

Animal Experiments

The measurements during *CSF-infusion* revealed a simultaneous increase in all pressure values. Apparently the various reserve volumes of the

individual (3) compartments have no influence here. According to LANGFITT (7) the pressures are transmitted uniformly in the subarachnoid space. Only slight, constant differences are observed (9). In our study the difference amounts only up to 5 mm Hg, which represents the limit of measuring accuracy. This in this case, by means of lumbar pressure measurements, a general information about the pressure status can be obtained. But during measurement the body-position must be taken into account (8).

In the case of CSF-infusion in one ventricle, however, the pressure above the site of infusion is increased in comparison to the other hemisphere and the posterior fossa, the difference depending on the rate of infusion. These gradients are caused by the *hydrodynamic resistance* of the internal CSF pathways. Namely the differences across the low resistance of the foramen Monroi are less marked than those across the high resistance of the narrow Sylvian aqueduct. Since the resistance (2) of these "bottle-necks" remains constant, the pressure-gradient (P) must grow with increasing flow (F) according to the general perfusion-equation $P = F \times R$.

In the case of *generalized convulsions* a craniocaudal pressure-gradient also occurs. Here, according to previous investigations (6), the supratentorial blood-volume is increased. Apparently this increase is transmitted through the incisura tentorii only incompletely.

The *subdural balloon inflation* and the *local cold injury* also lead to caudal. These gradients are, however, more marked in the case of local cold injury. With the filling of the subdural balloon the hydrodynamic transmission of pressure in the persisting subarachnoid space is possible. Following a lesion in the brain-tissue itself, however, the contusional swelling of the hemisphere squeezes out the subarachnoid and ventricular spaces. In addition with the increasing mass-shift a cingular and tentorial herniation occurs (Fig. 4b) andccuts off the hydrostatic pressure conduction. In the contrary, the stresses are inhomogeneously transmitted through the visco-elastic tissue caused by the elastic resistance as well as by the force-consuming viscous deformation.

Clinical Measurements

The results in patients with *communicating hydrocephalus* are similar to those obtained in the experiments with slow injection of CSF: No pressure gradients occur. In patients with *non-communicating hydrocephalus*, however, pressure gradients are observed, depending on the degree of CSF blockage. The patients with *local space-consuming processes* showed marked differences in the pressures between the hemispheres and between the supra- and infratentorial spaces. The direction of this gradient is determined by the site of the lesion (infra-, supratentorial).

Conclusions

In the cranio spinal cavity considerable differences in pressure may occur, either when the involved forces are transmitted only incompletely by the visco-elastic brain-tissue, or when the hydrodynamic pressure transmission is impaired by a blockage of the CSF-circulation. In the case of *disturbed CSF-circulation*, the pressure gradients may be explained by an increased flow resistance in a *hydrodynamic model* (Fig. 4a). Primarily, this may be caused by stenosis of Monro's fora-

men or of the Sylvian aqueduct. Secondarily this can follow a mass shift with cingular and tentorial herniation. In the presence of a *local brain swelling* the stresses are inhomogeneously transmitted through the *elastic viscous brain tissue*, which diminishes the vectors by its elastic resistance and viscous deformation (Fig. 4b). These differences may be varied by changes in the properties of tissue (edema, tumors, hemorrhage). For this reason in ICP monitoring the pressure should be measured in the vicinity of the lesion (CT) or even at several sites (supra-, infratentorial). For this purpose, miniature pressure transducers for epidural implantation (4) should be prefered, since here no artifacts due to imperfectly positioned membranes (tilted position) or varying non reproducable depth of penetration of the transducer occur.

Summary

The distribution of ICP in the presence of various intracranial space-occupying processes was investigated by experiment and clinical study. Generally the experimental results were confirmed by the clinical measurements: In *communicating hydrocephalus* no pressure differences could be detected. In the case of *disturbance of CSF-circulation* or of *local space-occupying lesions*, however, considerable *pressure gradients* occur, which depend on the site of the lesion and its rate of expansion. Therefore differences could be observed, either between the hemispheres or between supra- and infratentorial. The experimental and clinical findings are explained by two models according to the hydrodynamic resistance and the visco-elastic properties of brain tissue. The results suggest in the presence of localized expanding processes, that the ICP should be measured either in the vicinity of the lesion or over several sites.

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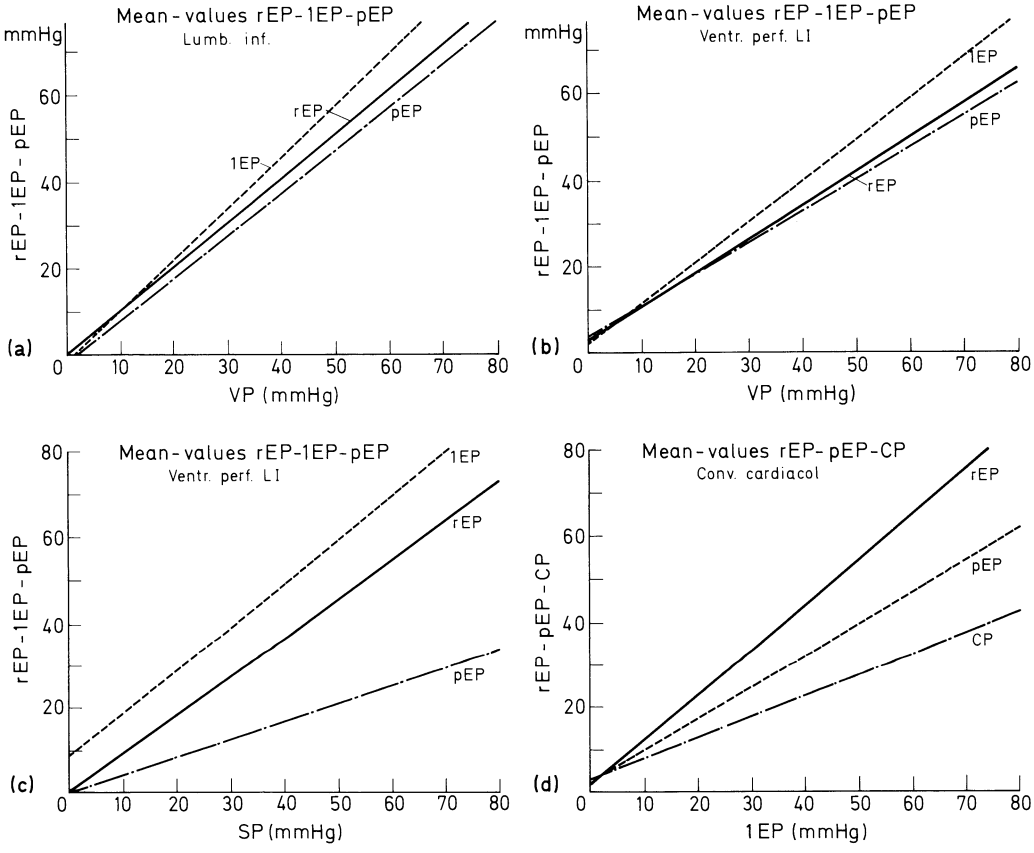

Fig. 1 a-d. *Correlation* among different craniospinal pressures during lumbar insufion (a n=12), ventricular perfusion (b 0,48 ml/min, n=5; c 2,33 ml/min, n=7) and artificial epileptic seizure (d n=12). During lumbar infusion, no pressure gradients are seen, whereas with ventricular perfusion at high flow rates, marked gradients occur, especially from supra- to infratentorial. Similar cranio-caudal differences are measured in epileptic seizure. lEP, rEP, pEP, epidural pressures over left/right hemisphere and over the posterior fossa; VP, ventricular pressure; SP, pressure within the superior sagittal sinus

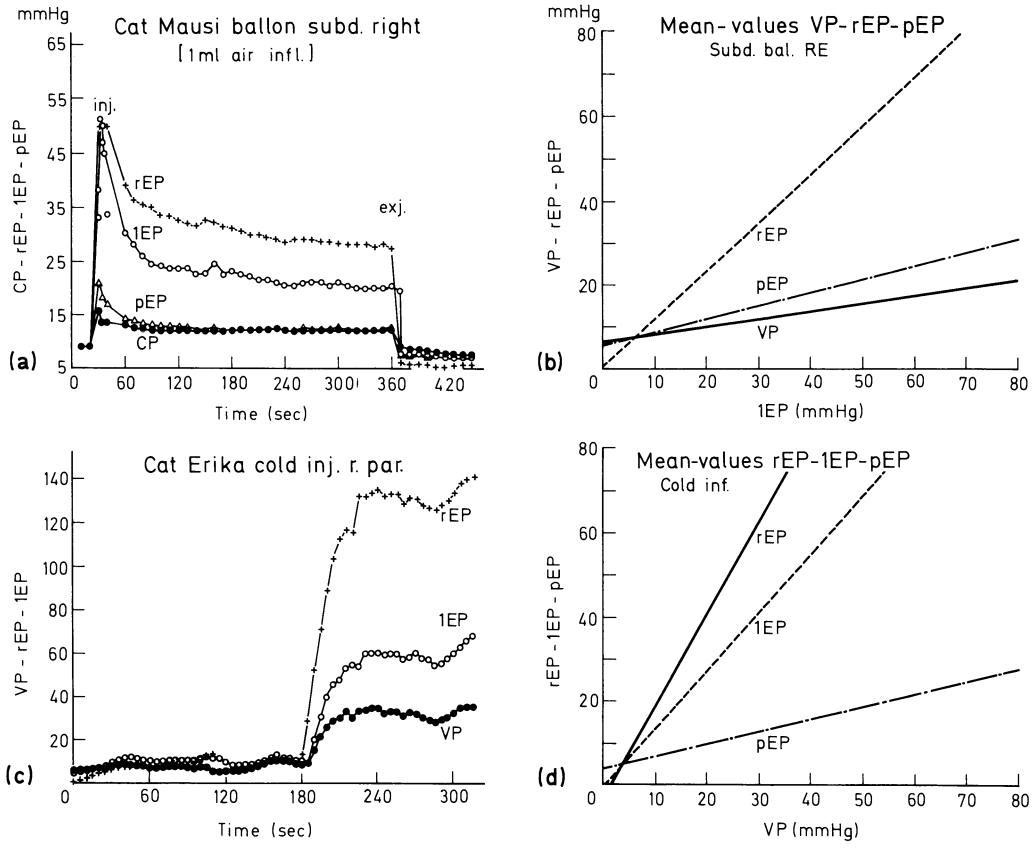

Fig. 2 a-d. *Pressure gradients* in supratentorial *balloon inflation* (a time plot; b correlation, n=12) and *cold brain injury* (c time plot; d correlation, n=12). Here, marked pressure gradients between the hemispheres and from supra- to infratentorial space exist, being more pronounced in cold injury

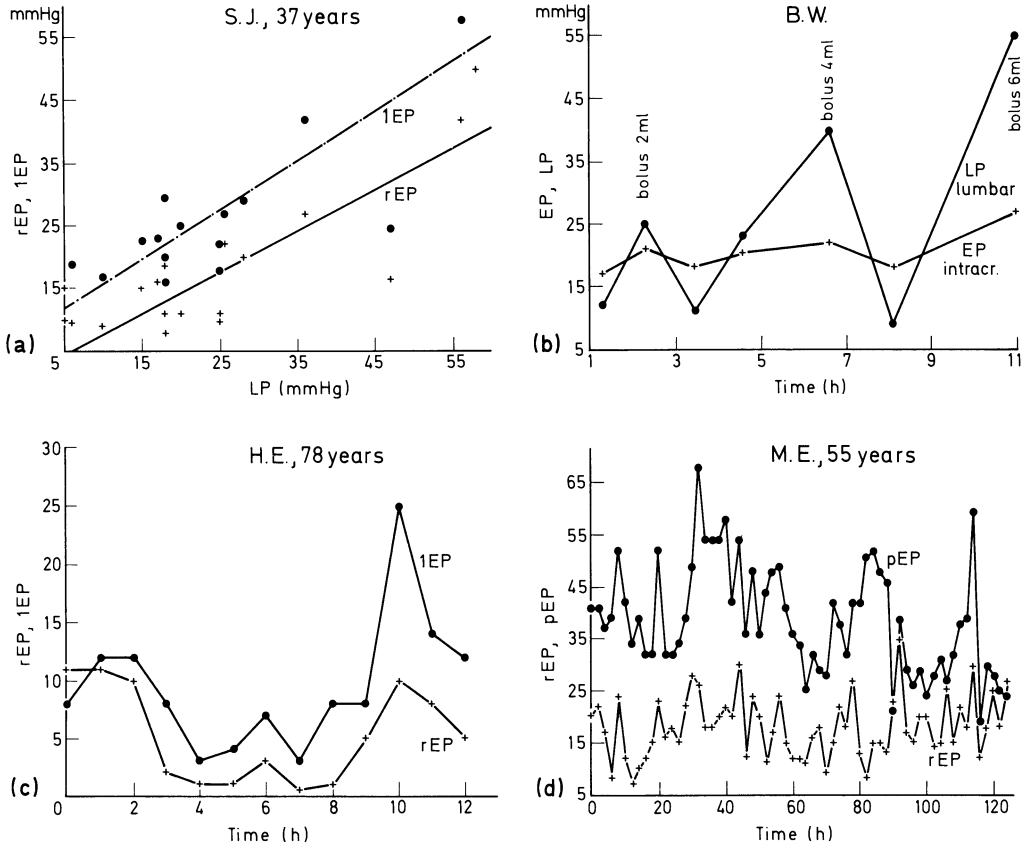

Fig. 3 a-d. *Pressure distribution measured in patients.* In *communicating hydrocephalus* (a), no pressure gradients are seen. However, in *aqueduct stenosis*, lumbar bolus injection (b) gives rise only to increases in lumbar pressure, with no transmission to the supratentorial space. Marked pressure gradients are observed between the hemispheres in left frontal *hematoma* (c), and from infra- to supratentorial space in *cerebellar abscess* (d)

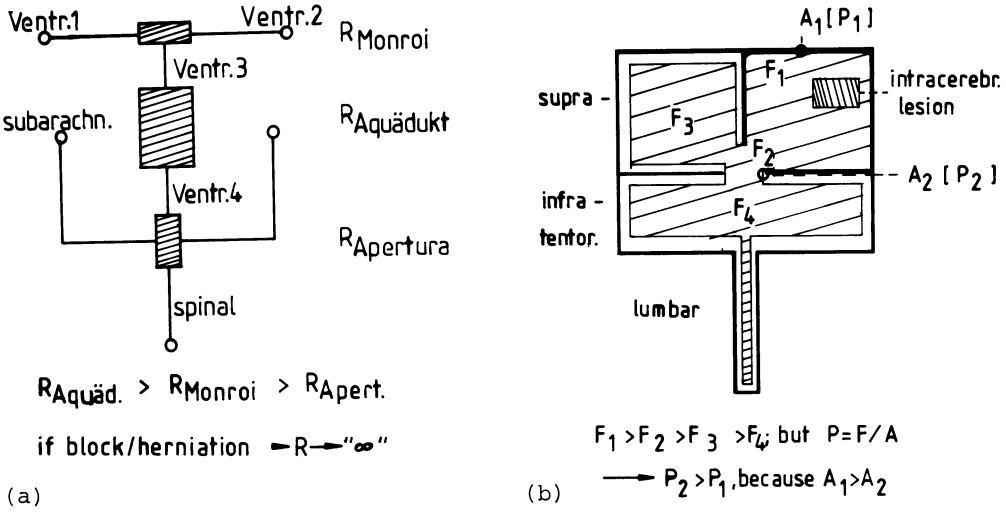

Fig. 4 a,b. *Explanation of pressure gradients* in disturbance of CSF circulation (a), and local intracerebral increase in volume (b). In disturbance of CSF passage, the pressure gradients are based on the increased flow resistances in a hydrodynamic model (R in a); in local volume increase, the stress is unequally distributed due to the visco-elastic properties of brain tissue (b) Additionally, the hydrodynamic pressure distribution is eliminated after compression of the CSF spaces

Infection Rate of Continuous Monitoring of Ventricular Fluid Pressure with and Without Open Cerebrospinal Fluid Drainage

W. PÖLL, W. v. WALDTHAUSEN, and M. BROCK

Introduction

The main advantage of continuous monitoring of ventricular fluid pressure (VFP), as compared to other methods of intracranial pressure (ICP) recording, is the possibility of performing cerebrospinal fluid (CSF) drainage for diagnostic and therapeutic purposes. A great disadvantage, however, is the risk of intracranial infection. In clinical practice the infection rate of VFP measurements is of importance in order to evaluate the risk of VFP monitoring for each patient.

Material and Approach

During the period of December 1., 1978 to March 31., 1980 100 continuous recording of VFP were performed in 94 patients at the Neurosurgical Department of the Klinikum Steglitz Berlin. The tip of a small polyethylene catheter was introduced into the frontal horn of the non-dominant hemisphere under strict aseptic conditions in the operating theatre. The ventricular catheter was connected to a pressure transducer (Statham P 23 ID) and to a commercial CSF drainage bag under aspetic conditions at the patients bedside. The system was calibrated daily. CSF was sampled for cultures, cell count, and cytological differentiation[1]

1. on the day of ventricular catheterisation,
2. on the following day,
3. twice a week, and
4. at the time of removal of the catheter.

Criteria of infection were:

a) clinical symptoms of meningeal irritation (e.g. headaches, meningism, and fever)
b) more than 100/3 cells per mm^3 in the CSF,
c) a positive CSF culture.

According to the literature (4), only the fulfillment of all three criteria were considered indicative of *definite infection*. In the presence of pathological cell-counts associated with clinical signs but with a negative CSF culture we speak of *suspect infection*.

No antibiotics were given prophylactically. Patients with positive CSF cultures, however, were treated with antibiotics.

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1 We are indebt to PD Dr. G. EBHARDT, Institute of Neuropathology, Klinikum Steglitz (Head: Prof. Dr. J. CERVOS-NAVARRO).

Results and Discussion

Fifty-three patients were male, forty-one female. Age ranged from 6 months to 80 years (mean: 42.2 years). The mean period of CSF pressure monitoring was 10.0 days, ranging from 1 to 122 days. Diagnoses are seen in Table 1.

Table 1. Patients studied

Diagnosis	
Closed head injury	23
Intracranial hematoma	17
Hydrocephalus	35
Supratentorial tumor	5
Posterior fossa tumor	14
Total	94

Definite infection (4) was found in two patients (2%). This is in good agreement with data reported in the literature (1, 2, 3, 5). CSF cultures showed Staphylococcus aureus in one case and Streptococcus viridans in the other.

Suspect infection (4) occurred in 14 recordings (14%) In 9 cases only a pathological cell-count without any clinical symptom was seen (9%) (Fig. 1).

Alltogether, a pathological cell-count occurred in 25 recordings (and/or drainage) periods (25%). In this group of patients with more than 100/3 cells per mm^3, the occurrence of clinical signs was associated with an increase of leucocytes in CSF (average: 67,5%), whereas in symptom-free patients monocytes predominated (average: 56%) (Table 2).

Table 2. Differential CSF cell-count in 25 patients with more than 100/3 cells per mm^3

Pathological cell count	Granulocytes (%)	Monocytes (%)	Other cells (%)
+ Clinical infection + Positive CSF culture	68	20	12
+ Clinical infection Negative CSF culture	67	22	11
No Clinical Infection Negative CSF culture	33	56	11

CSF drainage was primarily required in 44 cases, because ICP exceeded 30 mm Hg (= 4 kPa)[2]. In 6 cases secondary drainage was necessary. Fifty cases had ICP values of less than 30 mm Hg (= 4 kPa). Ventricular drainage per se, or its duration did not influence the rate of infection in this series (Fig. 2).

2 (7.5 mm Hg = 1 Kilopascal - kPa -).

Conclusion

Definite infection as defined occurred in 2 out of 100 VFP monitorings (recording and/or drainage) (2%), suspect infection in 14 (14%). Pathological cell-counts without any clinical sign of infection were observed in nine cases in which the differential CSF count showed a monocytosis. The rate of infection does not seem to be influenced by CSF drainage.

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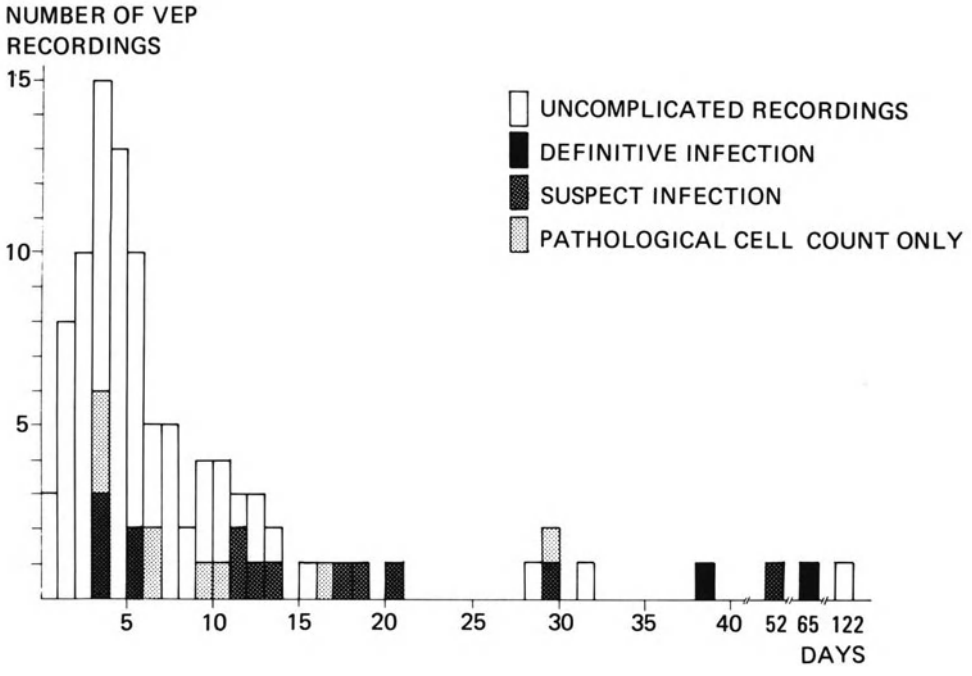

Fig. 1. Number (vertical axis) related to duration (horizontal axis) of every recording and/or drainage period

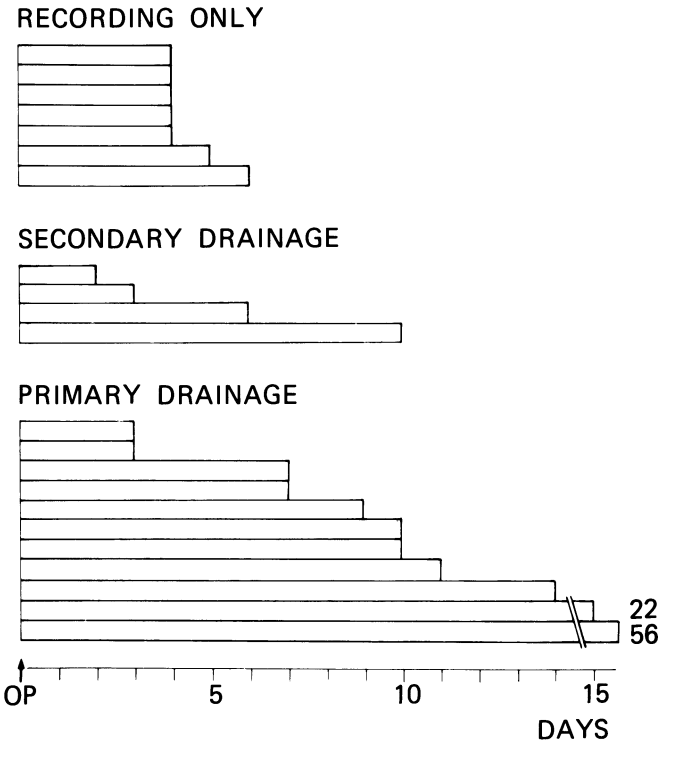

Fig. 2. Time span between ventricular catheterisation (OP) and onset of infection (i.e. first clinical symptoms and/or first pathological cell-count). Each column represents one patient

Critical Evaluation of ICP-Measurement Using Transducers Screwed into the Cranial Bone

H.-J. SCHMITZ

Introduction

Intracranial pressure rises are believed to contribute to the pathogenesis of neurological and neurosurgical diseases. Based on clinical signs of the so-called "brain pressure" dehydration therapy by osmotic agents and diuretics has often been instituted, sometimes causing renal damage, while having only temporary beneficial effects or none.

Measurement of ICP by GAELTEC ICT/b (3) showed that about 40% of neurosurgical patients had no ICP rises (ICP < 20 mm Hg), about 40% had moderate pressure rises from 20-50 mm Hg, and only 20% showed pressure rises about 50 mm Hg. Therefore, a uniform, schematic therapy seems questionable. By pressure measurement with a ventricular cannula and a subcutaneously implanted RICKHAM reservoir (1) even lower pressures were reported. Only 33% of the patients with closed head injury were found to have ICP above 20 mm Hg (2). In general, epidural techniques of measuring ICP are favored, because of the lower incidence of infections or other complications, which may amount to an infection rate of 10% and a mortality of 2.5% for CSF pressure measuring technics (2). Epidural ICP measurement, however, is difficult because of the impossibility of calibrating and zeroing in vivo most available devices. Further, baseline drift has to be considered. Additionally, particular problems seemed to be attached to ICP measurement by transducers held by a screw directly inserted into the cranial bone and placed on the dura. For example, measurement with STATHAM P 50 transducers plus screw, SIEMENS monitoring systems, or PHILIPS ICP transducers not always yielded correct values.

This study was designed to elucidate the factors influencing recording of ICP by these techniques, to eliminate possible faults and to develop it to a degree reliable for routine application.

Material and Approach

In a special calibration chamber, which closely simulates membrane loading conditions of the cranial cavity according to MAJORS (4), "epidural" pressure was measured through a membrane and compared to the internal chamber pressure ("ventricular" pressure). Pressures from 1-150 mm Hg were applied by a GAUER manometer. The resulting "epidural" pressure curves were plotted against the "ventricular" pressures for a range of various insertion depths, using STATHAM P 50 pressure transducers, held in an original screw (transducer surpassing the screw by about 1 mm, Fig. 1, 2) and in screws modified so as to permit coplanar application (screw precisely as long as transducer, Fig. 1, 3).

The screw was inserted via a 11 mm burr hole after having cut a tread by means of a special tool. Insertion depth was checked by measurement with a small gauge. After application of pressure to the inner chamber, P_i(ventr.), the pressures at the outside of the membrane were recorded various insertion depths, P_a(epi). Depth of insertion ranged from the thickness of the cranial bone, (= $\pm$ 0), and -0.5 mm up to + 1.6 mm.

The insertion depth which yielded the best correlation between outer ("epi") and inner ("ventr.") pressures in these experiments was adopted, and the method transferred to patients suspected of having increased ICP, or in whom ICP rises had to be ruled out.

Patients subjected to ICP measurement included cases with tumor of the posterior fossa, closed head injury with and without brain contusion, posttraumatic communicating hydrocephalus, unilateral hemispheric swelling following contusion or hypoxia. Space occupying intracranial lesions had been ruled out priorly by CT or angiography. The pressure transducer was implanted as described above for the model and correctness of epidural pressure measurement was checked for by lumbar cerebrospinal fluid (CSF) pressure measurement.

Results

It was found that by using the original screw (Fig. 1, right), outer pressure values, P_a (epi), clearly depended of the positioning of the transducer and of the insertion depth. Changes of $\pm$ 0.5 mm in insertion depth yielded transmembrane pressure values which were either 50% too high or 50% too low in the 100 mm Hg pressure-range. In the low, physiologically more important pressure range, the possible error turned out to be even more pronounced, since too little insertion produced artifactually too high values. Excessive penetration yielded zero values up to nearly 50 mm Hg (Fig. 2).

Because the precise measurement of implantation depth necessary in vivo is difficult and, in most cases, impossible, measurement with the transducer held in the original screw becomes useless, especially for decisions concerning therapy.

By modification of the screw which holds the transducer (Fig. 1, left), the epidural values were essentially less affected by variations of insertion depth. Although the characteristic behaviour of epidural versus ventricular curves remained the same (Fig. 3). If implantation was more superficial than the thickness of the cranial bone, values tended to be too large and even higher than "ventricular" values. If penetration-depth was excessive, however, "epidural" values were too small, at least in the low, physiological pressure range.

It was found that careful insertion up to the thickness of the cranial bone plus 3/8 turns (= 0.6 mm) resulted in the best correlation of outer/inner pressures, if coplanarity was achieved by an outer ring of the screw holding the transducer at the same level as the pressure-sensing membrane, thus dissipating dural wedge pressure. Using the modified screw and implanting the transducers carefully, according to the measurement of the bone thickness plus 3/8 turns, epidural ICP and simultaneous lumbar CSF pressure measurements for controlling were performed in 58 cases without any complication or adverse effects.

A close correlation was calculated for epidural and lumbar CSF pressures: $r = 0.88$, significant at the $P < 0.001$ level.
The statistical error for calculated epidural values was 11% (SEM).

Discussion

The influence of insertion-depth on epidural ICP figures has already been evaluated by different authors for different implantable epidural transducers. RYLANDER et al. (5) and MAJORS et al. (4) emphasized the importance of exact implantation depth. The phenomenon that too deep implantation yields zero values up to the 50 mm Hg range can be explained by increased membrane tension or dural wedge-pressure (5), which prevents the transducer from sensing the exact pressures. In the case the insertion is less than the thickness of the cranial bone, the membrane or dural bulging probably acts only on the center of the pressure sensing transducer membrane, thus transmitting greater forces. The above results have demonstrated that, by using the described technique, considering insertion-depth and coplanarity, ICP measurement by the present method yielded satisfactory ICP figures which compare well with CSF pressure.

Conclusions

Using transducers held by screws in the cranial bone for epidural ICP measurement, coplanarity is of great importance. Only by careful measurement of thickness of cranial bone and exact implantation within narrow limits of insertion-depth can artifacts be excluded and true epidural ICP values be obtained.

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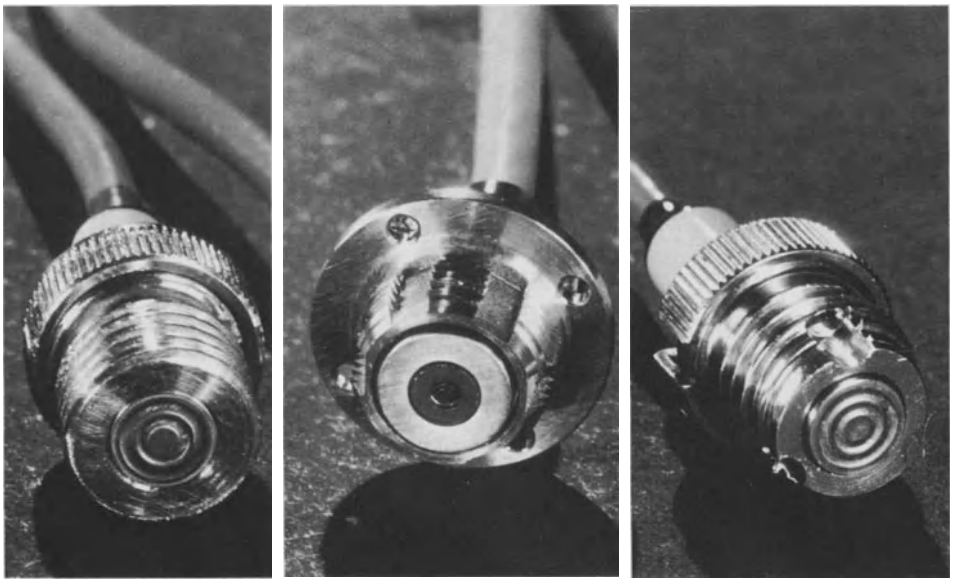

Fig. 1. Statham P 50 pressure transducer (on the right) in its original form, surpassing the screw for about 1 mm and thus being subject to non-coplanarity; wedge pressure forces are not dissipated by the outer ring. On the left Statham P 50 transducer with modified screw to ensure coplanarity, the pressure-sensing membrane being on the level of the aplanation ring. For comparison, the Philips ICP-transducer is shown in the middle, being designed so as to have a miniature pressure-sensing area in the middle, surrounded by an outer aplanation ring as one entity

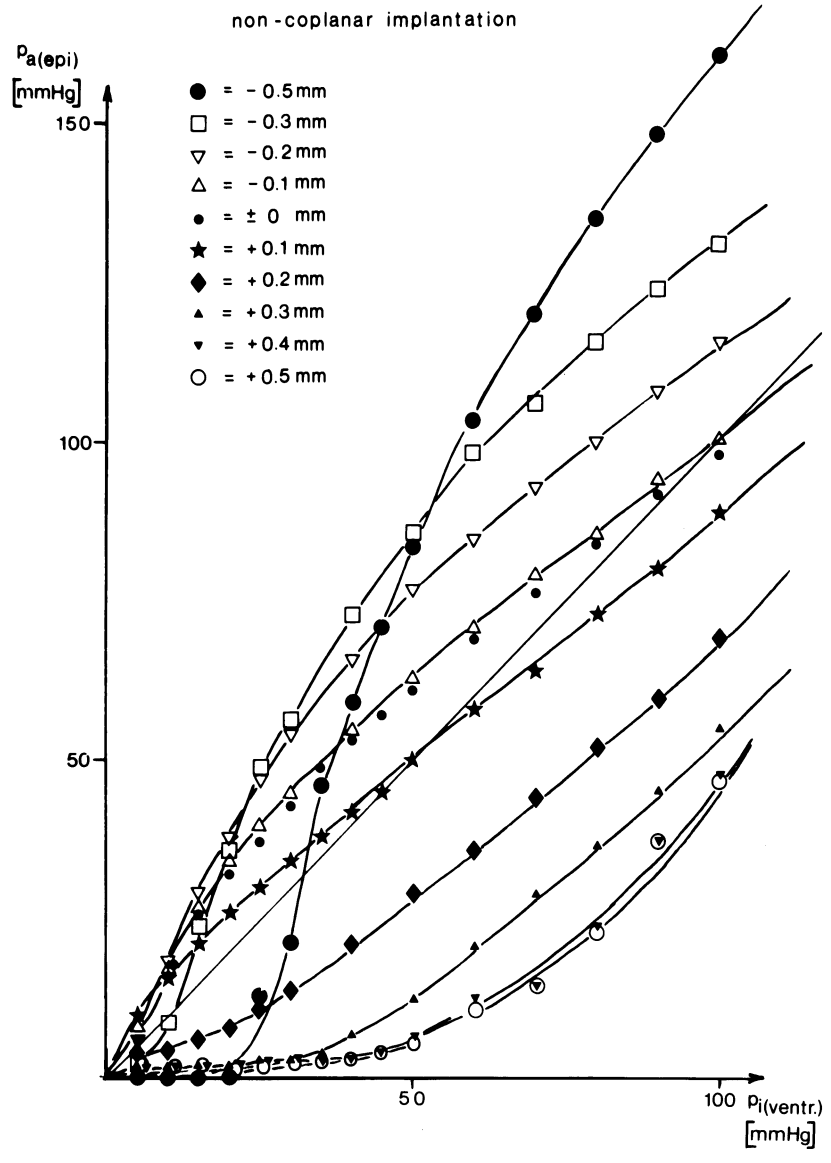

Fig. 2. The large pressure differences in case of non-coplanarity are shown at various transducer insertion depths. Especially in the physiological range important false zero-positive and false zero-negative results are obtained if coplanarity is not guaranteed and insertion-depth is varied only 0.5 mm

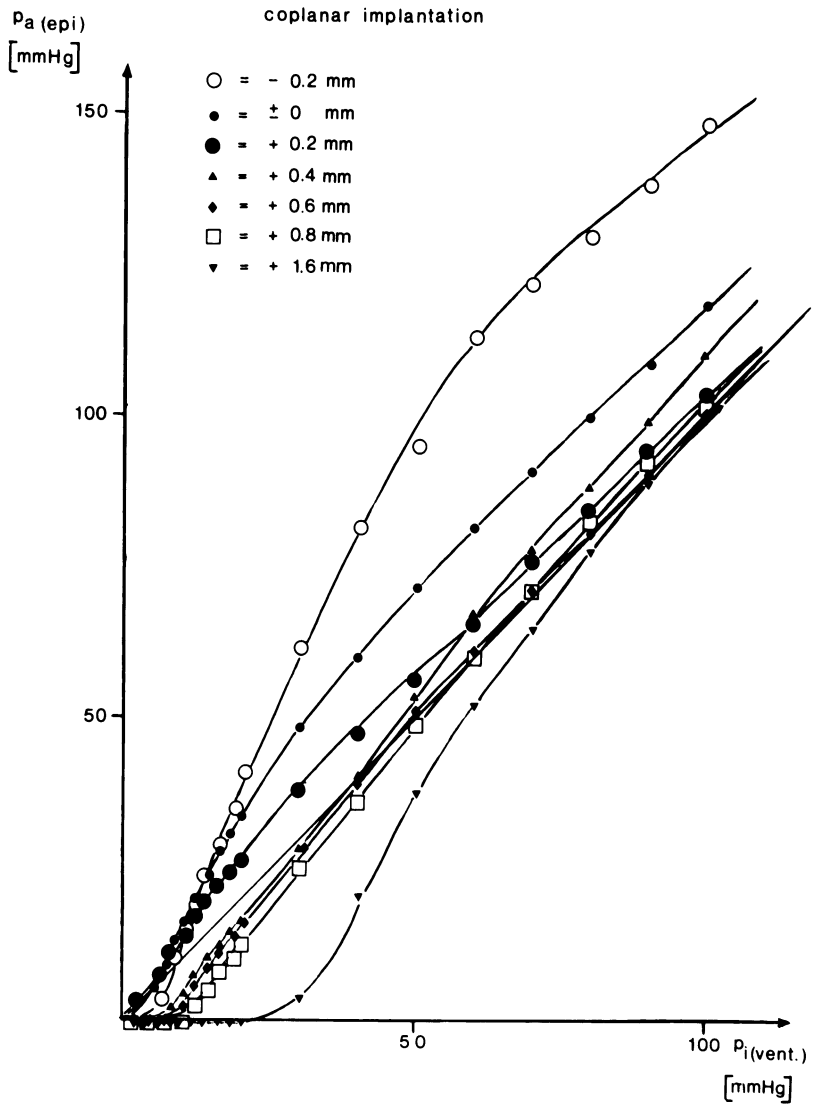

Fig. 3. The influence of insertion-depth on ICP values is shown at various implantation-depths, ranging from -0.2 mm to +1.6 mm. Coplanar application is provided, and reduces the possible degree of error

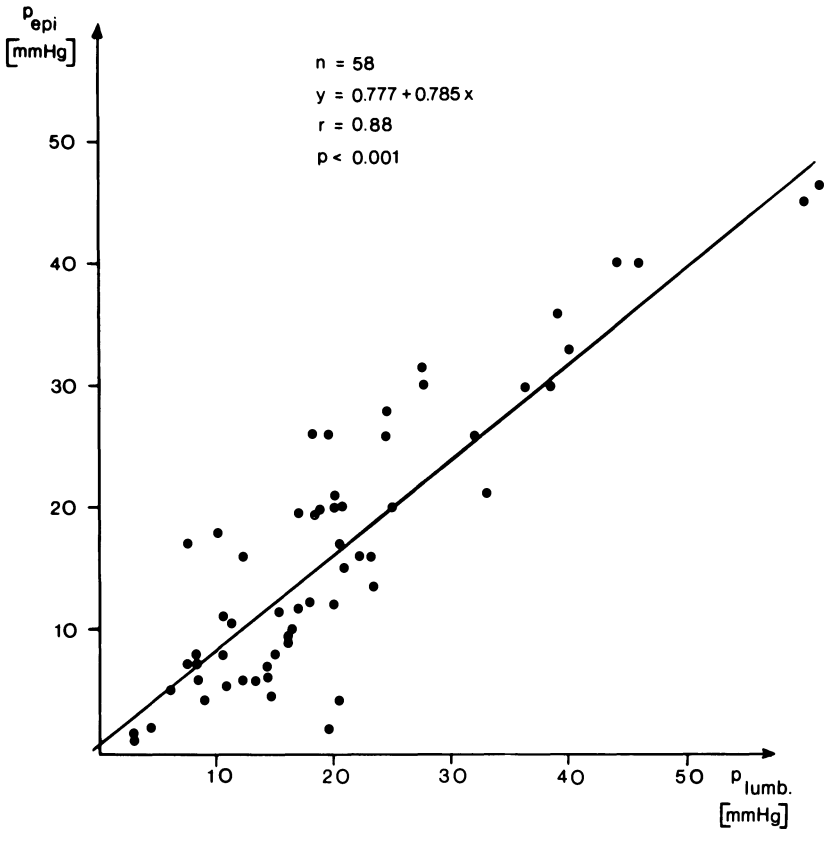

Fig. 4. The linear regression curve as calculated from 58 cases of simultaneous measurement of ICP and lumbar CSF pressure is shown. r = 0.88; P < 0.001; SEM (x) = 12.9; SEM (y) = 11.5

Measurement of Regional Cerebral Blood Volume (rCBV) by Routine Computerized Tomography (XCT) – Methods and Results[1]

R. WODARZ, M. R. GAAB, K. W. PFLUGHAUPT, and M. NADJMI [2]

Introduction

It is difficult to correlate CT findings in cases of brain injuries with the clinical state with any degree of certainty. Apart from the unmistakable findings of high and low density areas, visual analysis only allows vague paraphrases such as "relatively small ventricular system" without knowledge of the findings before injury, "light displacement of midline structures without differences of attenuation values between both hemispheres", or "suspected increase in the lucency of white matter". However, the measurement of intracranial pressure (ICP) has emphasized the importance of cerebral blood volume (CBV) in cases of recent brain injury (1, 2, 8).

Determination of CBV on the CT - scan from plasma iodine concentration (ci) and the hematocrit (Hk) before and after intravenous application of a contrast medium was already in use years ago (7, 11, 16). Also, some objections to this method were made at that time (14). Since it is more difficult to interpret our results when the blood-brain barrier is disturbed, discussion will be limited to "CBV" in the following. The results of our method, which, in part, correspond to those of other methods (4, 6, 12, 13), have led us to elaborate on this technically simple method for routine use.

Method

The difference in mean density values (Δ HE) dependent on the contrast medium in regions of interest (ROI) of identical slices (immobilized patient), the average plasma iodine concentration (ci_m), and the average hematocrit value (Hk_m) during the contrast scan we measured, and the "CBV" was determined with a programmed pocket calculator according to the following formula:

$$\text{"CBV"} = \frac{10.000 \times \Delta\ \text{HE}}{F \times ci_m \times (100 - Hk_m \times 0{,}85)}.$$

The average hematocrit value was reduced by a factor of 0.85 on the assumption that the hematocrit in the brain is only 85% of that of the peripheral blood (9, 10). This assumption of an evenly reduced cerebral hematocrit value is a factor of uncertainty in all methods of measuring CBV.

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1 Supported by grants of the VW Foundation.
2 We gratefully acknowledge the technical assistance of Mrs. Y. WAGNER.

The calibration factor F was established in a phantom experiment, by means of scans with water and protein solutions of known iodine concentration. In our system (EMI CT 1010) it amounts to 24,52 HE/mg iodine/ml. The meglumin-iotalamate (Conray 60^{R}) given intravenously as bolus (1-1,5 ml/kg of body-weight) was measured by uv-spectrometry in the serum. The linear part of the iotalamate diminution in the blood was obtained by beginning the measurement five to six minutes after the contrast medium had been given.

Results

Up to now we have studies 20 patients by this method. With one exception, all had to be sedated or anesthetized under controlled respiration because of their symptoms. Patients who moved even slightly during the investigation were excluded in order to obtain artefact-free and identical CT slices.

The results for a 56-year-old female patient with an acute Guillain-Barré syndrome may be reported as an example for visually *normal* scans (Fig. 1). The average "CBV" values are about 3 ml/100 ml. When the left and right sides are compared, the individual ROI differ by not more than 0,5 ml/100 ml on average.

The results of a 38-year-old patient five weeks after a spontaneous right fronto-basal *intracerebral hematoma* provide a good example of the *spatial resolution* of the method (Fig. 2). "CBV" values are increased, especially in the resorptive area around the bleeding, a fact which, in this phase of resorption, cannot be explained by a disturbed blood-brain barrier alone.

The "CBV" values of a 20-year-old comatose patient (Fig. 3) one day after a serious *brain injury* with increase in intracranial pressure (ICP), are higher on the whole. A decreased density of white matter, predominantly on the right, can be seen on CT (Fig. 3a). The "CBV"-values (Fig. 3b) are somewhat higher in the left than in the right edematous hemisphere. Even if we assume a possible disturbance of blood-brain barrier, this distribution of contrast enhancement suggests a lower "CBV" on the side of the edema more pronounced.

The comparison of the left and right sides, whereby the ROI often did not correspond exactly, caused some degree of uncertainty and led us to try another experiment. In three cases with *severe brain injury* without space occupying bleeding but with intermittently increased ICP, "CBV" was determined before and after *osmotherapy* (100 ml 40% sorbitol/15 min). Since ICP was continously measured in these patients, its course during "CBV" measurement could be followed. In no case was there any alteration in ICP during the "CBV" measurement nor, in particular, was there any paradoxical increase under osmotherapy (3). Nevertheless, the results show a distinct *increase in ipsilateral "CBV"* under osmotherapy (Fig. 4).

Discussion

We will not go into detail on the different methods of measuring CBV and what they can tell us (6, 7, 14). With our method it is desirable to have as large ROI as possible for a representative comparison of the sides. However, individual values for grey and white matter (7) cannot be obtained any more. Another source of error is the low Δ HE value, i.e. the low difference between the absorption values in the ROI

following injection of the contrast medium. This value can be increased by increasing the dose of contrast medium. However, in presence of a large dose of contrast medium, a temporary effect, at least, on cerebral autoregulation can be expected, a fact known from measurements of cerebral blood flow (CBF) (5, 15). A problem of the CBV method described is whether the *blood-brain barrier* remains intact for the contrast medium in cases of pathological CT findings. Up to now, larger and comparable experiments have not been able to prove whether the blood-brain barrier for the indicator used is actually as often disturbed as is theoretically assumed (14), nor has it been proved that the whole method has to be questioned by this fact.

The essential aspect of the method presented here is its application in the study of the *effect of therapeutic measures* (in our example osmotherapy), indicated for clinical reasons by simultaneous measurement of "CBV" and ICP. Until present we have only individual results; further investigations on patients with brain injury are to follow. The influence of osmotherapy, of barbiturates, hyperventilation or steroids on CBV can be important for the differentiated application of the available forms of therapy.

Summary

A method of determining "CBV" on routine CT was devised despite the theoretical and practical problems. It is relatively simple, from a technical point of view, and is feasible with every CT scanner. The current value of this method is not only the determination of CBV, of great importance in the presence of increased ICP, but also the possibility of studying, ideally with simultaneous ICP measurements, the influence of therapeutic measures such as osmotherapy or barbiturates on CBV in cases of brain swelling.

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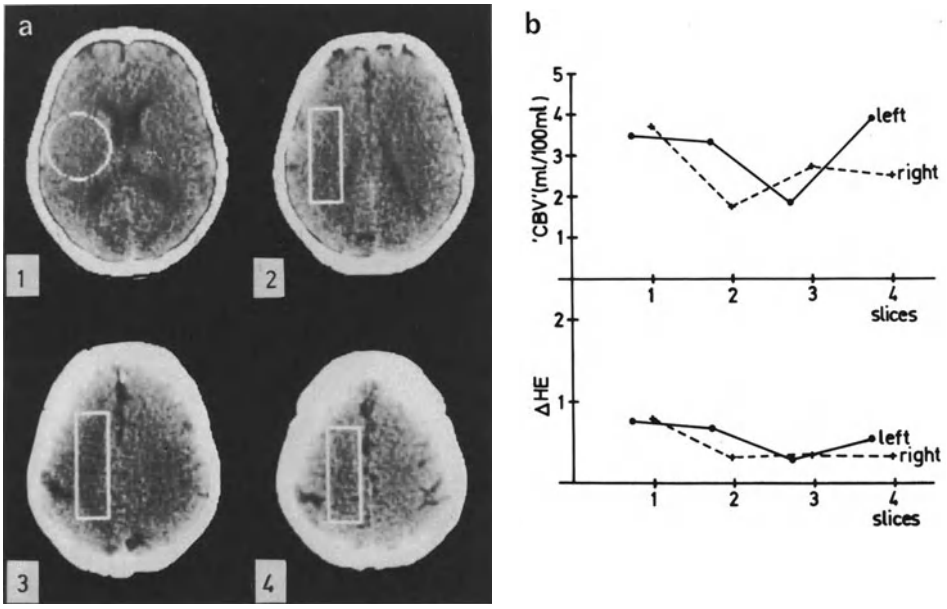


Fig. 1 a, b. *Normal "CBV":* Essentially normal CT scan in a 56-year-old female with acute Guillain-Barré syndrome (a). The pertinent Δ HE and "CBV"-values in the indicated ROI ranging between 2 and 4 ml/100 ml (b) are regarded as "normal" according to similar results in 5 other "normal" scans. (For improved clearness, ROI is outlined only on the left)

Fig. 3 a, b. *"CBV" in traumatic brain edema:* In addition to small subdural effusions over the frontal region, a traumatic brain edema is indicated by a diffuse hypodensity of the white matter in the supraventricular slices, predominantly on the right (a). Mean "CBV" (b) is elevated as compared to normal (Fig. 1). However, its values are lower on the right, in accordance with the lower density. ICP was normal during the investigation. (For improved clearness, ROI is outlined only on the left)

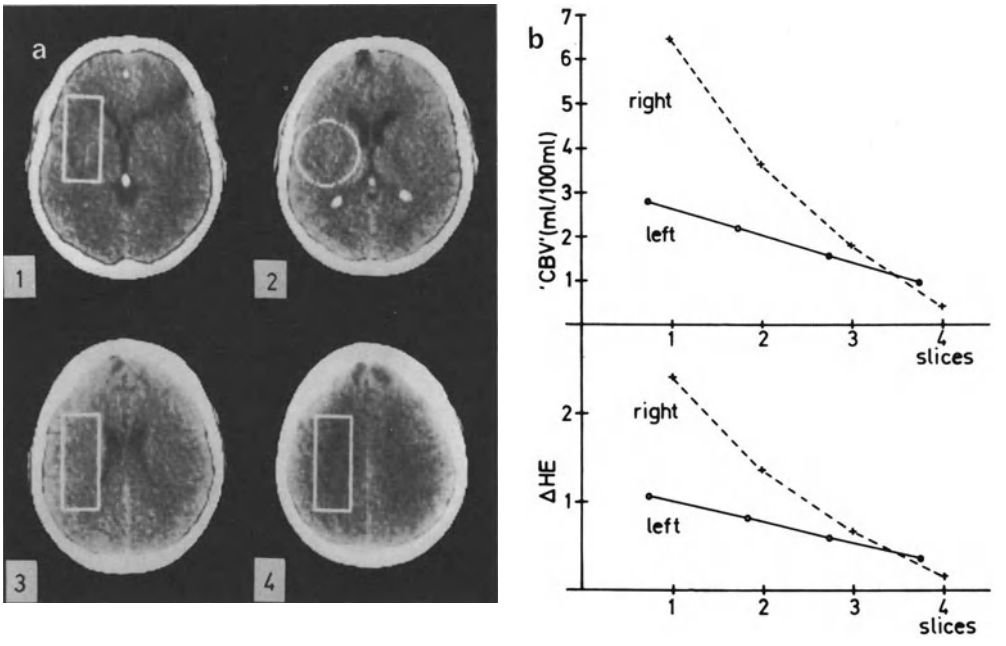
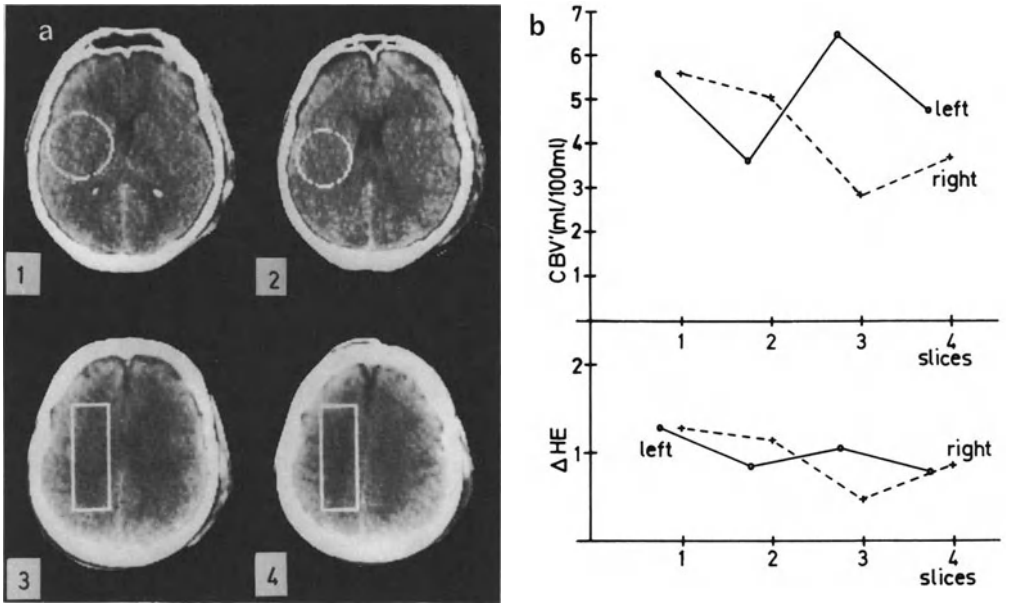


Fig. 2 a, b. *"CBV" around an intracerebral hematoma:* The area of low density around the spontaneous hematoma in the right frontal lobe of this 38-year-old patient corresponds to the normal course of resorption (a). The average "CBV" values in this perifocal hypodensity are elevated as compared to that in the corresponding left area (b). This increased "CBV" indicates resorptive activity. (For improved clearness, ROI is outlined only on the left)



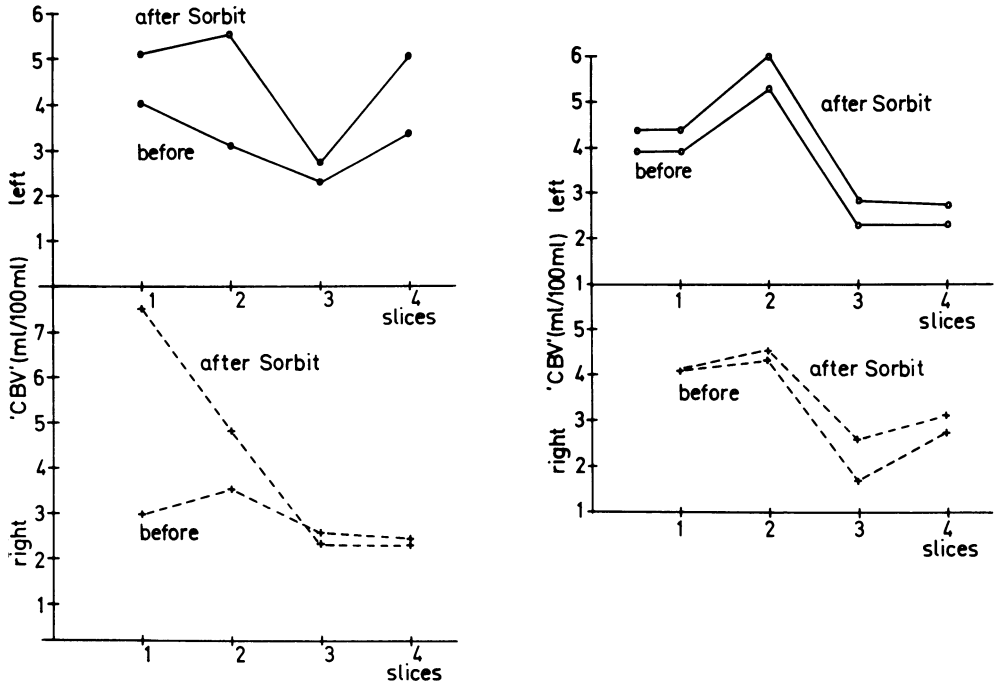


Fig. 4 a, b. *"CBV" and osmotherapy:* In a 59-year-old female (a) and a 25-year-old patient (b). "CBV" is markedly increased 5-6 days after serious brain injury with intermittent increases in ICP by osmotherapy (100 ml 40% sorbitol within 15 min)

Long-Term Results of Peripheral Nerve Sutures – A Comparison of Micro- and Macrosurgical Techniques

H. MÜLLER and G. GRUBEL

Microsurgical interfascicular suture with and without autogenous fascicle transplantation is no longer controversial (1, 2, 4, 5, 6, 7), but still needs a critical view.

Patients and Methods

Between 1968 and 1975 eighty peripheral nerve sutures were performed during 74 operations at the neurosurgical department of the University of Hamburg. Sixty cases had a follow-up long enough (Table 1). In six cases of combined lesions of the median and ulnar or radial nerves, both were sutured.

The frequency of different surgical techniques is shown in Table 2.

No patient was reeaxmined by the surgeon himself. Motor and sensory recovery were judged using modificated schedules of the B.M.R.C. and SEDDON (8, 9). We considered a useful refunction down to M 2+/S 2+ in the schedule (8) and summarized the results into bad, poor, fair and good (9).

Table 1. Localization of nerve sutures

Localization	Followed-up	(n)
Upper extremities		
Median nerve	26	(33)
Ulnar nerve	15	(19)
Radial nerve	11	(12)
Combined lesions of median and ulnar nerve	3	(5)
Combined lesions of median and radial nerve	1	(1)
Lower extremities		
Peroneal nerve	4	(4)
Total	60	(74)

Results

First, the results differed from one nerve to another independently of the technique employed. Figure 1 shows that a greater number of good and fair results were obtained with sutures of the median and radial nerves. Combined lesions and the totally unsuccessful homologous interponates are not reported in this study.

Table 2. Frequency of suture techniques

HI	7
ENS	18
IFNS	13
IFAG	42
Total	80

HI, homologous interponates; ENS, epineurial nerve suture; IFNS, interfascicular nerve suture; IFAG, interfascicular autologous grafting

Comparing the results of micro- with those of macrosurgical suture (Fig. 2), useful recovery was found in six out of eleven cases following conventional epineural nerve anastomosis. Most patients were followed-up for more than five years. On the opposite, nine out of 36 microsurgical sutures could not be evaluated definitely, i.e. further improvements could be expected. There was no reinervation in two patients of each, one having been reoperated later.

Figure 3 shows the long-term results following micro- and macrosurgical nerve anastomosis, evaluated by the SEDDON schedule. Fifteen out of 25 patients had a good or fair recovery after a microsurgical suture. Altogether the good and fair results improved with the microsurgical technique, although preoperative conditions were worse in a great number of patients. With the epineurial suture (ENS) technique, only small gaps could be bridged. The mean interval between trauma and operation was 7.4 months vs. 15.4 months for the interfascicular autologous grafting (IFAG). Three patients had a homologous interponate in early times and had IFAG 18, 19 or 26 months after the injury.

Seventy-one out of 84 cases were so-called late secondary sutures. Surgery was performed later than eight weeks after the injury. There were only 5 secondary sutures and 3 primary sutures within eight weeks after the lesion. One patient with a primary suture was followed-up: the recovery was poor. The results of all secondary sutures in relation to the interval between trauma and operation are demonstrated in Fig. 4. The cases marked with an arrow were not definitely evaluable. Two patients who had a fair or good result following suture more than 36 or 30 months after the injury (cases No. 19, 12) had one or more intact fascicles in the damaged area at surgery, so that it might have been a matter of internal neurolysis. In two cases there was no recovery although the lesion was less than six months ago, the first of these (case. No. 35) had an ENS of the ulnear nerve, the other (case No. 73) a peroneal suture.

We divided our patients into the age-groups 0-15, 16-45 and over 45 years, and found that recovery was better in the first group (Fig. 5). Two children had a bad result following peroneal suture or interfascicular suture without transplantation, possibly because of some tension at the site of anastomosis.

With the microscopic IFAG it is possible to reach a good recovery even if the critical gap-distance (10) prevents end-to-end suture. However, IFAG results were not worse in cases of a longer gap i.e. longer grafts.

The results were better with an ordinary post-operative physiotherapeutic treatment to prevent muscle contractures and atrophy.

Finally, our experience showed that patients should be followed-up at least three years to allow a definite evaluation. After three years, we found no additional recovery (Fig. 6). The mean follow-up time was 2.6 years in cases with a bad or poor recovery vs. 3.7 years in patients with fair and good results.

Discussion

The clinical results of 60 peripheral nerve sutures of the upper and lower extremities evaluated by long-term follow-up were reported. The analysis showed a superiority of microsurgical procedures with or without fascicle transplantation. However, other reports about remarkable recovery rates (more than 90% useful motor and sensory refunction (5, 7) were not confirmed. For KLINE, HUDSON (3) end-to-end repair by epineurial sutures still remains the favorite technique, according to their experiments with primates. Our good and fair results were above the 50% level with this method too, but the mean delay of repair was only 7.4 months, vs. 15.4 months with IFAG.

In general, the results were better in relation to early operation, and ordinary postoperative treatment.

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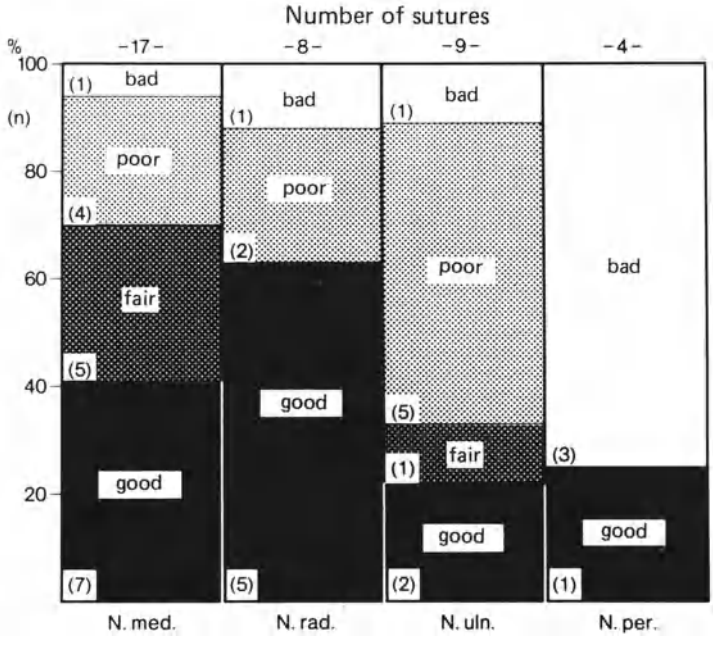

Fig. 1. Recovery of different peripheral nerves following suture

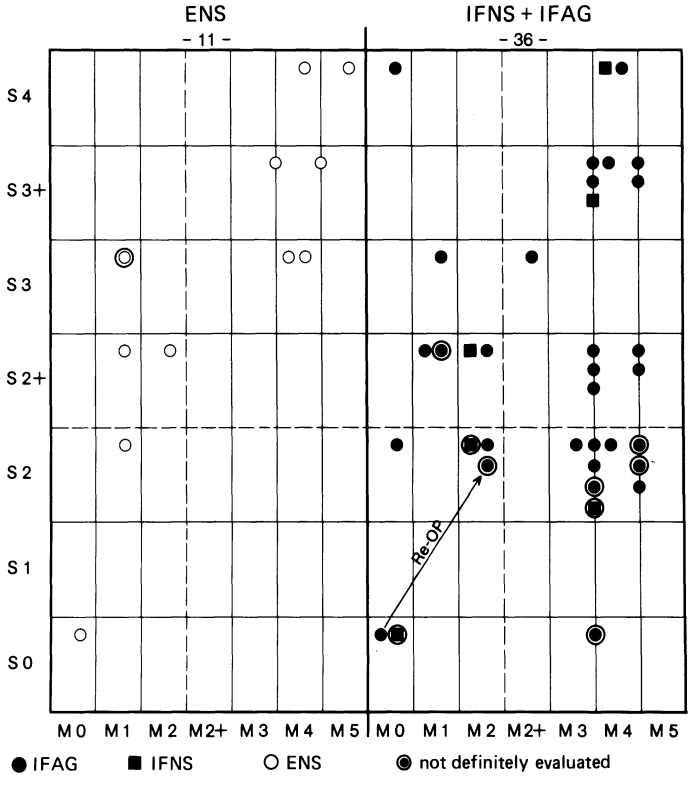

Fig. 2. Comparison of all results following macro- (left) and microsurgical (right) nerve suture

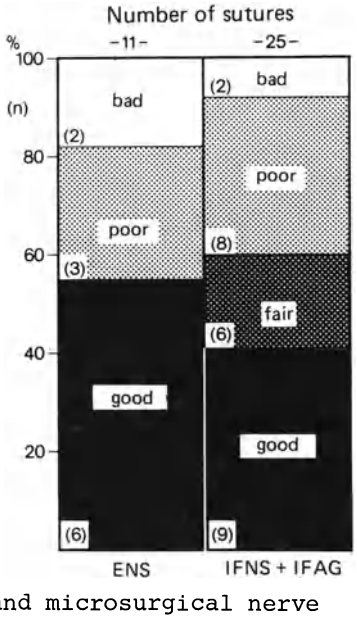

Fig. 3. Long-term results following macro- and microsurgical nerve suture

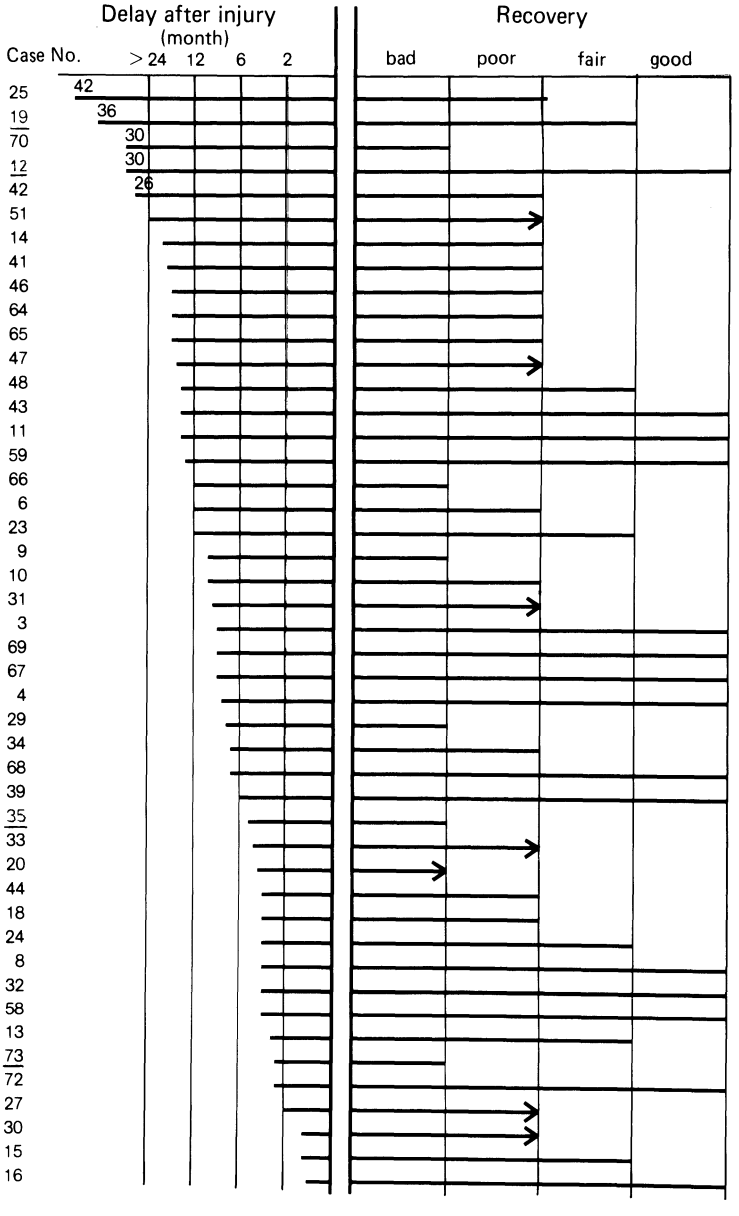

Fig. 4. Influence of post-traumatic delay on recovery following secondary suture

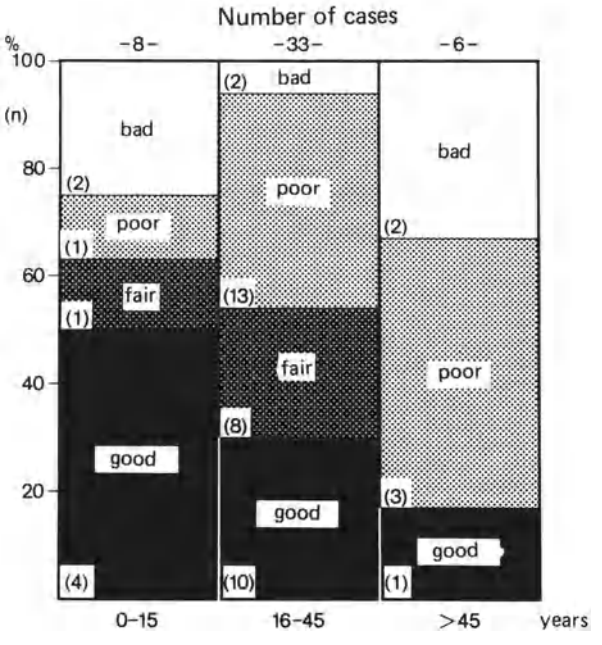

Fig. 5. Influence of age on recovery following nerve suture

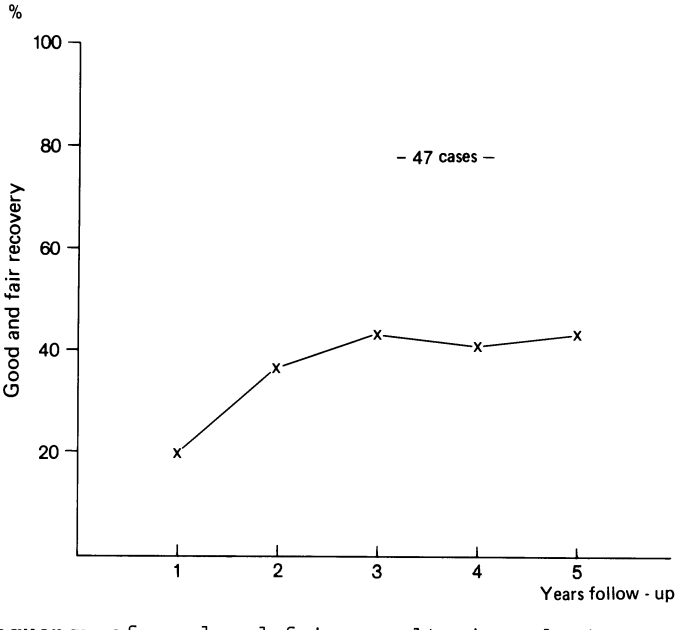

Fig. 6. Cumulative frequency of good and fair results in relation to follow-up time

Follow-Up and Results of External Drainage Therapy of Chronic Subdural Hematomas

A. HARDERS, K. WEIGEL, J. GILSBACH, and H.-R. EGGERT

Introduction

In addition to the usual craniotomy with membrane removal, various methods for treating chronic subdural hematomas are mentioned in the literature (1, 2, 5, 8, 9, 10, 11, 12, 13). Since 1976 a modified method according to JACKSON has been used in our clinic (3).

The following is a report on the follow-up and results of the first 50 patients with chronic subdural hematoma treated by external closed drainage after burr hole trepanation.

Material and Method

The patients were grouped according to the age-distribution of McKISSOCK (6). Case-histories revealed closed brain trauma in half the patients. The most frequent previous diseases were diabetes mellitus in 20% of patients, hypertonia in 16%; 18% had undergone anti-coagulant therapy; 12% suffered from alcoholism.

Following localisation of the hematoma by computerized tomography or angiography, its cavity was rinsed with Ringer's solution via 1 or 2 subdurally inserted silicone catheters. An air-free drainage-bag was used for drainage. Membrane resection was not carried out. Eleven patients were operated on under general anaesthesia, 39 under local anaesthesia. Drainage lasted an average of 8 days, the patients remained in the hospital an average of 13 days.

Follow-Up and Results

As shown in Table 1, all but two patients displayed an improvement of their neurological deficits and psychopathological changes during the stay in the hospital. There was clinical improvement in almost every case, although in 50% of the patients a residual hematoma, with an average thickness of 9.5 mm, could be verified by computerized tomography at discharge.

Hematomas recurred in ten patients during hospitalization and were treated by the same method. This complication set in on the average 15 days after the first operation. In two cases a hematoma of the opposite side was detected. One patient, who had been in a coma, prior to the operation died seven days after surgery as a result of staphylococcemia. Another patient, initially comatose, now presents the complete picture of an apallic syndrome.

Thirty-eight patients were controlled clinically and by computerized tomography after an average of 23 months. There were only neurological

Table 1. Drainage of chronic subdural hematomas. Changes in Neurological Symptoms and consciousness

	Preoperative state (n=50)	Post treatment state (n=49)	Follow-up state (n=45)
Hemiparesis	40	14	2
Cranial nerve disorders	2	1	0
Aphasia	9	3	0
Mental changes	25	11	9
Changes of consciousness			
Somnolent	11	0	0
Stuporous	8	0	0
Comatose	6	1	1 Apallic syndrome

control findings in another seven patients. Four patients died of other illnesses in the meantime. Autopsy revealed no connection to the subdural hematoma treated surgically.

As shown in the table, the neurological and the psychopathological status improved markedly in all cases. In a subjective assessment of their own improvement three patients gave the grade "very good", 18 said "good", and three patients were not satisfied with the result of the treatment.

CT-controls at the time of the follow-up study showed no residual hematomas overlying the affected hemispheres in any of the 38 cases, although 25 patients had residual hematomas at the time of discharge. The deepened cortical relief of both hemispheres constituted a particular criterion for the pathological-anatomic changes. In only two cases did the control examination detect a clearly flattened cortical relief when comparing both sides. In two other cases atrophy of the affected hemispheres had increased. Disturbances of cerebrospinal fluid (CSF) resorption with subsequent hydrocephalus did not occur.

Discussion

As repeatedly reported in literature, surgical treatment of displacing subdural hematomas is undoubtedly superior to conservative therapy. What seems to be decisive here is halting the displacement and not the removal of the hematoma membrane, as shown by detailed examinations by SVIEN (12). The author describes single burr-hole trepanation with hematoma-drainage, and achieves better results than with craniotomy and membrane resection. RAND (8) and BURTON (2) arrive at the same conclusions. Needle-trepanation as reported by NECRON (7) and TABADOR (13) has been abandoned.

Closed bag drainage, described by JACKSON (4) and slightly modified by us, provides a form of therapy of chronic subdural hematomas that puts less strain on the patient since it is usually performed under local anaesthesia. The single disadvantage of this method appears to be the relatively high reoperation rate of 20%. However, SVIEN (12) also reports a similarly high percentage.

We consider the low mortality rate and the good neurological and psychopathological results to justify this as the method of choice. In addition, CT-controls show complete restitution of the cortical relief in the large majority of patients. In none of the 38 patients re-studied by CT could residual hematomas or CSF disturbances with subsequent hydrocephalus be detected. This fact justifies the assumption that the remaining hematoma membrane does not necessarily result in recurrence.

Conclusion

Because of the good neurological and psychopathological results, and the CT-findings, we consider the modified bag-drainage of chronic subdural hematomas according to JACKSON to be an adequate form of therapy with minimal strain on the patient.

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New Aspects of Pathogenesis and Therapy of the Cubital Tunnel Syndrome

H. ASSMUS

In the past, subcutaneous or submuscular ventral transposition was supposed to be the method of choice in treating the entrapment neuropathy of the ulnar nerve at the elbow (1, 3, 4, 5, 7). From the hypothesis that the nerve was irritated in its pathologically altered bed in the sulcus ("sulcus-ulnaris-syndrome"), it appeared necessary to remove the nerve from this bed.

Angloamerican authors, however, have replaced this concept by a new one, implying a common compression syndrome in the cubital tunnel (6, 9, 10). They reported good clinical results after simple division of the fibrous roof of the cubital tunnel. Nerve conduction studies in patients operated on by this procedure have not yet been reported.

Material and Methods

Twenty-eight patients have been treated by this method of dividing the aponeurosis between the heads of the flexor carpi ulnaris without translocation of the nerve. One third of our patients had osteoarthritic or post-traumatic changes of the elbow joint, another third showed abnormalities such as recurrent subluxation or additional factors affecting the nerve, such as radiculopathy or alcoholic neuropathy, and the last third was suffering from the idiopathic form of the disease with no obvious abnormality. At first, some of the idiopathic cases seemed to be simple pressure palsies, but showed no spontaneous tendency to improve.

The diagnosis of the ulnar nerve entrapment was confirmed by electromyography in all cases. Motor conduction velocity (c.v.) was determined for three segments of the nerve as described elsewhere (1, 2). The diagnosis was accepted only if the c.v. was diminished by at least 10 m/sec in the elbow segment as compared to the other segments. Clinically, a local tenderness had been found at the site of compression in all cases. In 80% muscle wasting was apparent.

All patients have been operated on in our outpatient department under regional anaesthesia and in a bloodless field, by application of a pneumatic tourniquet. After a small cutaneous incision of about 6-8 cm between the olecranon and the medial epicondyle, the ulnar nerve was exposed in the sulcus. Then, the fibrous arch between the two heads of the flexor carpi ulnaris was divided and resected. In a few cases only, it has been readapted with two sutures beneath the nerve. Since the nerve was left in his bed, local blood vessels have not been divided, and the sensory branch to the elbow was preserved. After thorough hemostasis with the bipolar coagulator the wound was closed and the elbow bandaged in extension for 10 days.

Results

Intraoperative movement of the elbow joint showed that with flexion of the elbow the aponeurotic band was stretched and the cubital tunnel thus decreased in volume (Fig. 1). Thickening of the band and elevation of the floor of the tunnel in cases of osteoarthritis, or other changes of the elbow joint which press the nerve against the sharp edge of the band, seemed to have an additional pathogenetic effect. The last mechanism also seemed to be responsible for the recurrent subluxation of the ulnar nerve (Fig. 2).

Electromyographic follow-up studies of 24 clinically improved cases (two patients remained unimproved, in two the follow-up period is too short) revealed a continuous and marked increase in c.v. across the elbow segment. This improvement started immediately after operation. Within the first postoperative year the mean values became almost normal (Fig. 3). At the same time, the amplitudes of the muscle action potentials increased. Only in two cases, in which no clinical improvement was observed, did the c.v. remain unchanged. In no case the c.v. became worse.

Discussion

Several authors have demonstrated that subcutaneous or submuscular ventral transposition of the ulnar nerve is an effective therapy of ulnar neuritis at the elbow. Extensive mobilisation of the nerve, however, might not be without harm for an altered nerve. We have previously shown that c.v. became even worse immediately after transposition (1). This operating procedure is followed by greater morbidity because of the large wound, the division of the muscle mass implying a longer immobilisation by a plaster-of-Paris, and of more frequent complications such as postoperative kinking of the nerve. The much smaller procedure of simple decompression is without serious complications or morbidity, and can be performed in the outpatient department. Thus, the indication for surgery may also include patients who seem to suffer from simple pressure palsies but who show no spontaneous recovery within two to three months. Very often these cases may be subclinical compression syndromes with or without mild arthrogenic changes, in which the occurrence of a minor injury can trigger the manifestation of ulnar palsy. In cases with severe osteoarthritis, however, in cubitus valgus deformity, and in some cases with recurrent subluxation of the nerve, we prefer the anterior transposition of the ulnar nerve. However, also in such cases decompression of the cubital tunnel is the most important act.

Conclusion

Clinical, intra-operative and electromyographic studies in cases of entrapment of the ulnar nerve at the elbow ("ulnar neuritis", "late ulnar palsy", "sulcus-ulnaris-syndrome") revealed that the pathologically altered cubital tunnel is the most important pathogenetic factor ("cubital tunnel syndrome"). Clinical observations of improvement of the ulnar palsy following simple excision of the aponeurotic band between the two heads of the flexor carpi ulnaris were confirmed by our electromyographic follow-up studies. These revealed a marked and continuous increase in c.v. of the ulnar nerve across the elbow segment leading to essential normalization within twelve months after surgery. In all cases, except those with severe osteoarthritis, cubitus valgus and some cases of recurrent subluxation, simple decompression

of the ulnar nerve is an entirely satisfactory substitute for the more complicated and extensive procedure of ventral transposition of the ulnar nerve.

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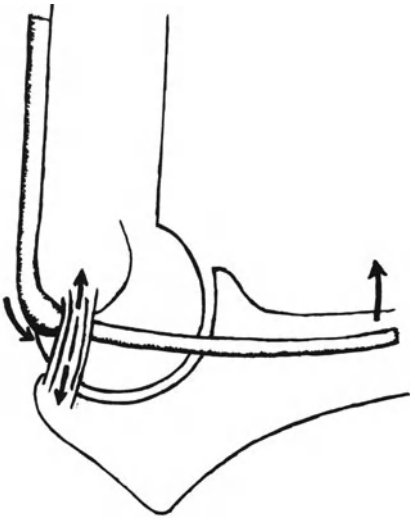

Fig. 1. Bending of the elbow joint results in stretching of the fibrous band between the olecranon and the medial epicondyle (or the two heads of the flexor carpi ulnaris) and acts as a compressing agent against the ulnar nerve in the cubital tunnel

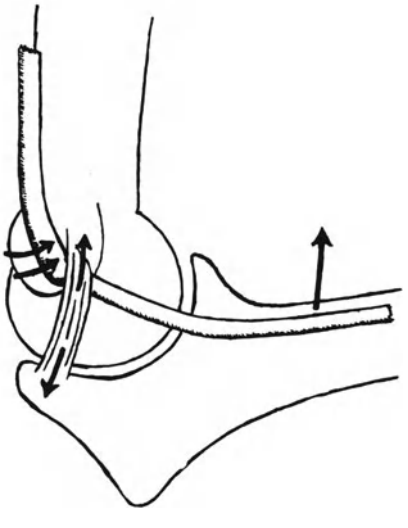

Fig. 2. In recurrent subluxation of the ulnar nerve the sharp edge of the fibrotic band also acts as the main pathogenetic factor

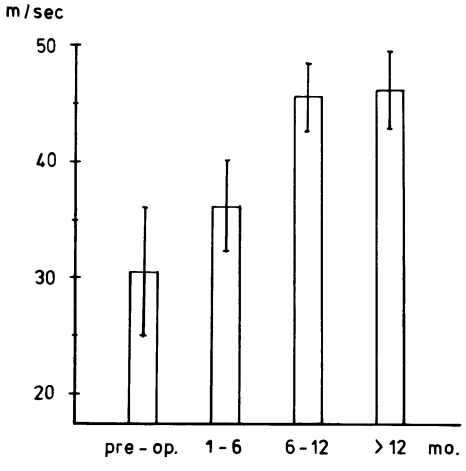

Fig. 3. Electromyographic follow-up studies reveal a marked and continuous increase in c.v. starting immediately after surgery and reaching almost normal values after one year (mean values and standard deviation of 24 patients)

Influence of Thiopental on Post-Operative Blood Pressure Following Surgery Under Induced Hypotension

A. SPRING and G. SPRING

Introduction

Sodium nitroprusside and nitroglycerin have proven effective for the reduction of blood pressure during neurosurgical procedures because their effects are easily controlled (5, 8, 11, 15). An undesirable side-effect is a significant postoperative increase in blood pressure (4, 7, 16). Empirically, we found a way to lower or to abolish these reactions by means of thiopental.

Material and Approach

Fifty-seven patients were operated on for cerebral aneurysms and arterio-venous malformations under hypotension induced by sodium nitroprusside, nitroglycerin or a combination of the two substances. In 29 (group I) neuroleptanalgesia (fentanyl and droperidol) was used. In the other group (II) (28 patients) thiopental anesthesia was used. In both groups induction consisted of 4 mg/kg thiopental given intravenously. Thiopental anesthesia was maintained with 2-3 mg/kg/h, injected continuously by means of a perfusor. The radial artery was cannulated for monitoring of arterial pressure. Pressure differences were compared by STUDENT's t-test.

Results

Group I (neuroleptanalgesia) showed a significant postoperative blood pressure increase of 20-40% above the preoperative baseline (Fig. 1). In some cases, blood pressure values of 250 mm Hg were reached. This obvious rebound-effect persisted for several hours. The type of hypotension (with sodium nitroprusside and nitroglycerin alone or the combination of the two substances) had no influence on this rebound-phenomenon. Once this rebound-phenomenon has been triggered, it is difficult to manage with antihypertensives. Nitroglycerin given at this time sometimes has a moderate positive influence. The use of clonidine is risky. High doses are necessary to lower blood pressure. Abrupt falls of blood pressure may occur. The minimal effect of these procedures are shown in Figure 1.

Postoperative hypertensive blood pressure reactions can be avoided or significantly reduced, if thiopental is continuously employed during surgery. The positive effect of this measure is shown in Fig. 2. The postoperative increases in blood pressure are less than 10-20% above preoperative values. Excessive increases in blood pressure were not observed. Additional treatments were not necessary to lower the blood pressure.

Discussion

Sodium nitroprusside and nitroglycerin are commonly used to induce hypotension (5, 8, 11, 15). The mean sites of action are the vascular smooth muscles. An undesirable side-effect is a significant increase in blood pressure after the withdrawal of these agents (4, 7, 16).

MILLER et al. (10) found high plasma-renin activity after experimental application of sodium nitroprusside. The release of renin generates the hormone angiotensin II. Angiotensin II increases arterial pressure by producing vasoconstriction and causes the release of aldosterone, a hormone responsible for salt and water retention. Rats pretreated with the angiotensin-antagonist saralasin, showed a deleterious fall of blood pressure. After hypotension with sodium nitroprusside the release of renin is an attempt to restore normal blood pressure (6).

KHAMBATTA et al. (7) confirmed these results in men who underwent hypotension induced by sodium nitroprusside during anesthesia. After discontinuation of hypotension, the increased plasma-renin activity declined slowly to normal values.

Other causes for the withdrawal-symptoms may be an increase of catecholamine release or an activation of the vasomotor center (1, 2, 13).

For these reasons, application of clonidine or nitroglycerin had no sufficient effect. As shown, the postoperative hypertensive blood reactions can be avoided or significantly reduced if thiopental is continuously employed during surgery. The positive effect of this measure indicates the value of the use of barbiturates as prophylaxy and therapy of central sympathetic disturbances (3, 9, 14).

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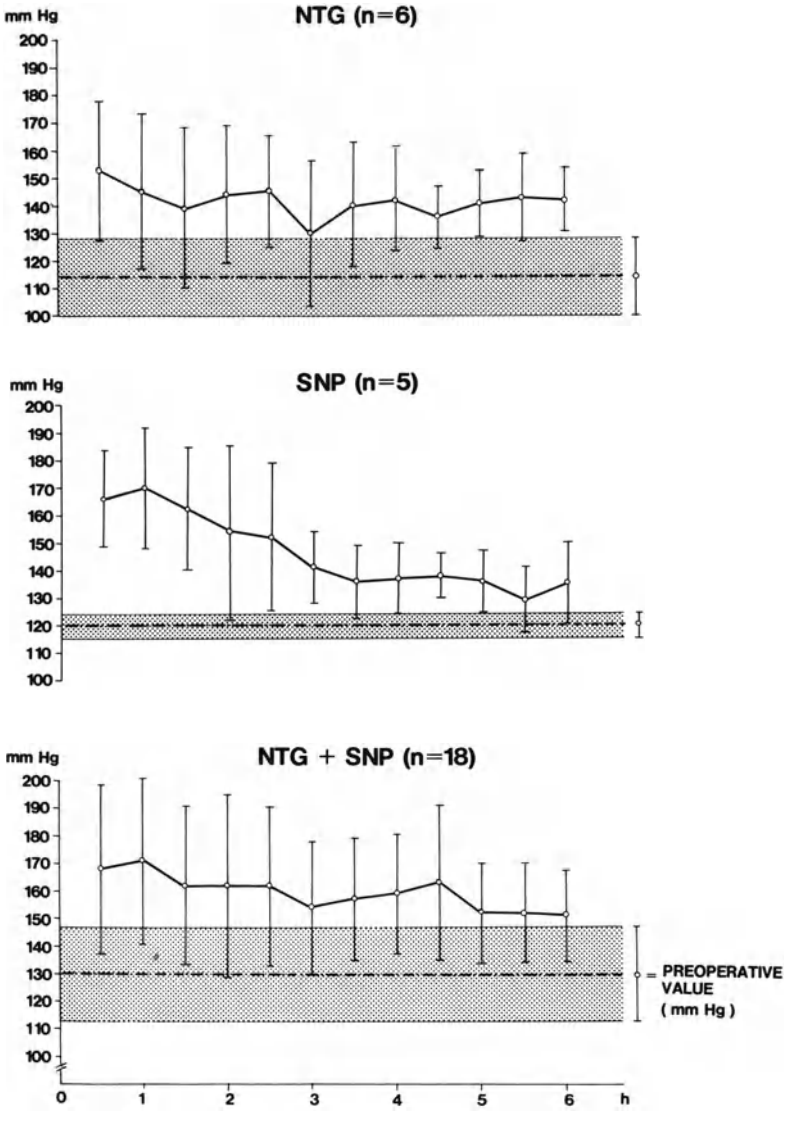

Fig. 1. Postoperative blood pressure reactions (mean ± SD) following neurosurgical operations in deliberate hypotension and neurolept-analgesia. Hypotension was induced by nitroglycerin (= NTG), sodium nitroprusside (= SNP) or a combination of both

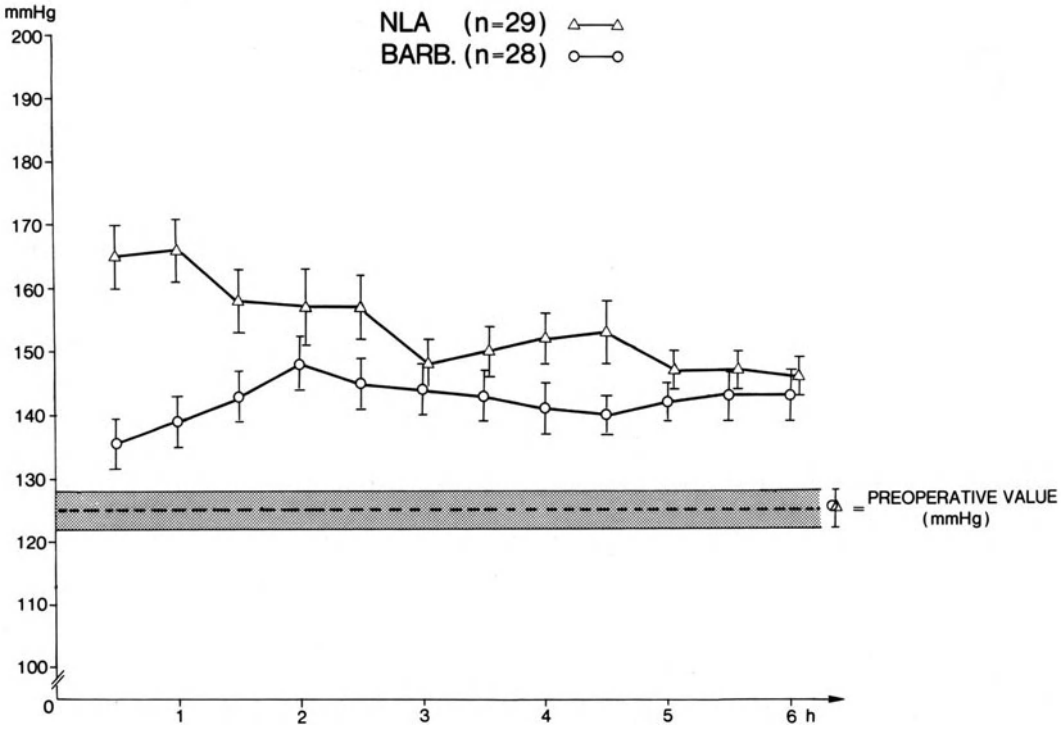

Fig. 2. Postoperative blood pressure reactions (mean ± SE) following neurosurgical operations in hypotension. Anesthesia was maintained with neuroleptanalgesia (= NLA) or the barbiturate (= BARB) thiopental

Preliminary Results of Intracavitary Irradiation of Cystic Craniopharyngiomas by Means of Stereotactically Applied Yttrium-90

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Introduction

Craniopharyngiomas are histologically benign tumors, which can be divided in 3 groups (9): (1) Predominantly, cystic, with a large solitary cyst (about 60% of all cases). (2) Cystic, often polycystic, with an appreciable solid portion (about 30% of all cases). (3) Predominantly solid, no cysts observable. The main pathophysiological factor in the development of clinical symptoms are usually the cysts, whereas the solid, often calcified portions in tumors of group 1 seem to be of less importance. Attempts at radical microsurgical removal of these cysts are often followed by severe hypothalamic disorders, recurrences are frequent. Evacuation of the cyst by puncture is usually followed by rapid refilling. Conventional radiotherapy has been found to be more effective than previously assumed. High-dose irradiation may cause complete destruction of the tumor, but persistent hypothalamic and optic disorders are to be encountered (7).

A completely different therapeutic approach has been introduced by several groups in the early fifties: the stereotactic puncture and evacuation of the contents of the cyst and the instillation of radioactive agents (8, 6). The results were inconsistent and often discouraging until LEKSELL et al. (9) and BACKLUND (1, 2) had developed a standardized radiosurgical method of treatment of cystic craniopharyngiomas, which is in routine use at Karolinska-Institute, Stockholm, since 1967 and in our department since 1 year.

Material and Approach

If there is clinical and radiological evidence of a predominantly cystic craniopharyngioma, the first step in the therapeutic program is stereotactic puncture of the center of the cyst. This simple procedure is performed not only in cases in which the presumed cysts appear hypodense in CT, but also in iso- or hyperdense lesions, which, in some cases, were shown to be cystic as well (3, 11). For determination of the target point, the outlines of the solid and the cystic parts of the tumor are calculated by computer from the CT-slices and transferred to the stereotactic X-ray films according to a procedure recently developed by our group, which will be described elsewhere. Carotid angiography is essential for safe puncture. The approach has to be chosen according to the pattern of vessel displacement.

After reaching the center of the lesion, aspiration is performed and, if typical craniopharyngioma-fluid is obtained, 1 or 2 ml are aspirated and replaced by the same volume of Technetium-99 solution. This fluid is mixed with the cyst-fluid by several aspirations and reinjections. Thereafter, 1-2 ml of the mixture are aspirated. By quantitative de-

termination of the gamma-emission of this mixture, the exact volume of the cyst is determined (2) and compared to the value, calculated by computer from the CT-sections (4). According to the volume of the cyst, the activity of colloidal Yttrium-90 necessary for achieving an irradiation of every point of the inner surface of the cyst with 20 000 rads is calculated (10), injected into the cyst and mixed with the cyst-fluid. Yttrium-90 is a pure β-emitter with a mean energy of 0,93 MeV, a medium half value layer in soft tissue of 1,1 mm and a physical half life of 64 h.

Both 3 and 24 h after operation a gamma-scintigraphy is performed, which allows to visualize selectively the distribution of the gamma-emitter Technetium-99 and the "Bremsstrahlung" of the Yttrium-90. Thus, a possible leakage with escape of radioactive fluid can be detected and managed by evacuation of the cyst. Twelve to 14 days after the operation, when irradiation is practically terminated, a CT-control is performed. If there has been a hypersecretion during the time of irradiation, which rarely occurs, the cyst is partially evacuated by re-puncture (1, 2). An essential prerequisite for the therapeutic success is that the volume of the cyst is kept constant during the operation and the time of irradiation. Homogeneous irradiation is thus achieved and rapid unphysiological decompression of the surrounding structures is avoided.

Since May 1979 10 patients have been treated by our group using the technique described above (1, 2, 9). Nine patients belonged to group 1, 1 patient belonged to group 2. Every patient suffered from severe neurological symptoms.

Results

In 8 cases out of a total of 9 in group 1, the Yttrium-90-instillation caused an arrest in the growth of the cysts, which was followed by a considerable shrinkage during the postoperative weeks or months. This shrinkage often led to a marked amelioration or to disappearance of the clinical symptoms. A CT example of a typical course is given in Fig. 1.

One patient with a large solid tumor and 2 cysts of extreme size (160 and 40 ml respectively), was operated on in a very bad clinical condition and died from pneumonia after 3 weeks. In 1 patient of group 1 the puncture caused a frontal intracerebral hemorrhage. Operation was not necessary since it was not space-occupying. In another patient of group 1, a further worsening of the preoperative marked bilateral reduction of visual acuity occurred 2 months after the Yttrium-90-instillation, in spite of a decrease in cyst-volume from 31 to 3 ml. This side-effect was completely reversible by osmo- and oncotherapy. Side-effects were observed in no other case. In the single patient of group 2 another small cyst developed from the tumor matrix 10 months after the treatment of the first cyst.

Discussion

The main factor limiting the possibilities of conventional neurosurgery in the treatment of cystic craniopharyngiomas is the firm adherence of the cyst-walls to surrounding hypothalamic and optic structures due to small papillary tumor-extensions and glial reactions (5, 1). This explains the frequent recurrences and the often marked side-effects after conventional operations. The fact that the β-irradiation of

Yttrium-90 is limited to a tissue-layer of 3 mm allows the application of doses of 20 000 rads to the inner surface of the cyst-wall. Thus, a selective lethal irradiation of the wall of the cyst is achieved.

The main drawback of this method is the possibility that other cysts may develop from the solid part of the tumor. This is true specially for predominantly solid tumors, as was the case in one of our patients. According to the experience of LEKSELL and BACKLUND (9, 2, 3), both the development of new cysts and further growth of the relatively small solid parts in tumors of group 1 are rare after Yttrium-instillation in a large solitary cyst. In such cases the solid parts must be operated on conventionally or treated by external irradiation.

The risk of the stereotactic puncture is as low as in standard stereotactic procedures. In the series of BACKLUND (3), radiation injuries of the optic pathways occurred in about 4% of the cases. A delayed, radiation-induced local edema may have been the cause of the further transient deterioration of visual acuity in 1 of our patients of group 1, completely reversed by osmo- and oncotherapy. Another possible explanation is a minute displacement of the already strongly impaired preoperatively optic nerves, due to the shrinkage of the cyst.

Our data are in accordance with the findings of BACKLUND (3) in a series of about 90 patients treated within the past 13 years. Our results indicate that this method is a true alternative to microsurgery and conventional radiotherapy, and that good results can be expected in monocystic tumors with a relatively small solid part.

Summary

Both microsurgery and external irradiation of cystic craniopharyngiomas are loaded with considerable problems. A totally new therapeutic approach is the method of intracavitary high energy β-irradiation of the cyst wall by means of stereotactically instilled colloidal Yttrium-90. This method, developed by LEKSELL and BACKLUND (1, 2, 9), is in routine use in our department since 1 year. The method and the preliminary results obtained in 10 patients are reported and discussed.

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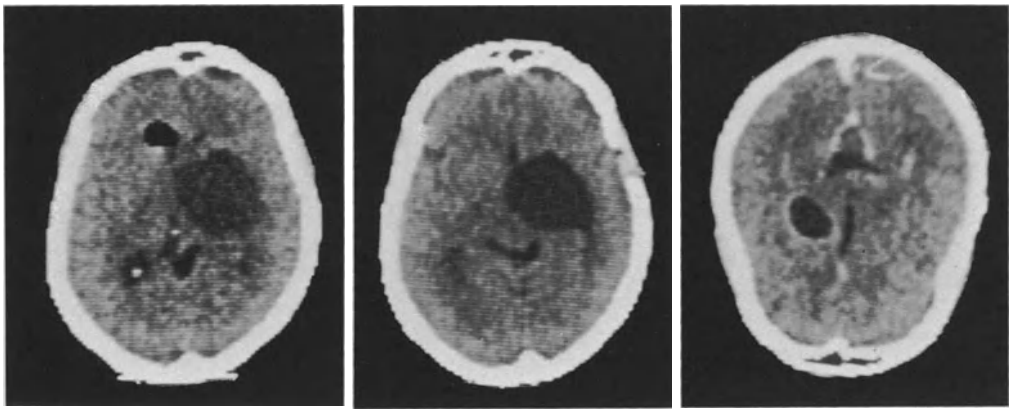

Fig. 1. CT-controls of a craniopharyngioma-cyst, treated by instillation of Yttrium-90. *Left upper cut:* Preoperative state. *Right upper cut:* State 14 days after operation. *Lower cut:* State 6 months after operation. Note the gradual shrinkage of the cyst

Psychometric Follow-Up Studies in Patients with Occlusive Disease of the Cerebral Arteries Treated by Extra-Intracranial Arterial Anastomosis

R. BOLLBACH, H. WASSMANN, K.-H. HOLBACH, and T. PAYK

Introduction

The extra-intracranial bypass operation can lead to a constant improvement of cerebral blood flow in occlusive arterial disease of the brain. It remains unclear whether it is possible, by this means, to prevent transient ischemic attacks and to influence positively neurological impairment. However, the patient often regards the decrease of intellectual functions to be more drastic than the sensomotoric deficiencies.

Although some authors report an improvement of psychic symptoms following microneurosurgical anastomosis (5, 11), there are hardly any systematic studies concerning this question (4). We therefore evaluated the intellectual functions of patients who underwent a bypass operation in correlation to EEG-changes by means of standardised psychometric testing.

Methods

Twenty-seven patients, with an average age of 49,9 years, with internal carotid or middle cerebral artery occlusion were selected for the extra-intracranial bypass operation. The apoplectic insult had occurred on an average of 5,6 months prior to surgery. A few days before, as well as 2 and 6 months after the operation, each patient was given the following series of psychometric tests:
the *d2-Test* (2), the main concern of which is to evaluate the patient's ability to discriminate quickly and precisely a range of details,
the *Revisionstest* (6), by which the patients are to solve quickly a series of arithmetic problems,
the *Konzentrations-Leistungs-Test* (KLT) (6), in which more complicated arithmetical questions are given,
the *BENTON-Test* (1) for the visual short term memory and
the *digital span* (ZN), a subtest of the Wechsler Adult Intelligence Scale (10), which measures attention and immediate memory.
At the same time EEG-changes were recorded by means of the digital interval- and amplitude analysis (8, 9).

Results

The following example illustrates the procedure: three months before admission, the 54-year-old patient had suffered a temporary left-sided hemiparesis and a persistent lethargy and impairment of memory. Occlusion of the right internal carotid artery was diagnosed by angiography.

The relative changes in the main test parameters increased noticeably two months after surgery (Fig. 1). In all tests, with exception of the KLT, further improvement was still observed after 6 months.

Computerized EEG-analysis revealed a significant increase in electrical brain activity, particularly over the affected region, in the alpha-range and on the first postoperative examination (Fig. 2).

Similar evaluation of the 27 patients showed a significant increase in general achievement (GZ-F) in the d2-Test, whereas the failure rate (F%) dropped (Table 1). The improvement in the Revisionstest as well as in the digit span (ZN) occurred mainly in the first two postoperative months. The failure rate in the BENTON-Test (failure rate) showed a statistically significant decrease. Only in the KLT was the observed improvement comparatively poor and statistically nonsignificant.

In correlation to the psychometrical results, the electrical activity of the brain rised significantly in the alpha-range during the first two postoperative months.

Discussion

Our findings indicate that there is a relationship between the observed increase in intellectual function and cerebral blood flow improved by surgery. This presumption is based on the following facts:

a) little spontaneous improvement of neurological impairment can be observed (7) after an interval of 5.6 months

b) the clearest psychometric changes were detected in the early postoperative phase, and

c) there was a correlation between the data compiled by computerized EEG-analysis and the psychological testing.

Table 1. Relative psychometric changes in 27 patients two and six months after bypass surgery

n = 27	Changes 2 months postoperative Δ %	Changes 6 months postoperative Δ %	Parameter
d_2	+ 17.3 ($p < 0.001$) - 42.9 ($p < 0.05$)	+ 26.7 ($p < 0.001$) - 51.8 ($p < 0.001$)	GZ - F F %
Rev.	+ 16.5 ($p < 0.001$)	+ 16.4 ($p < 0.05$)	Total score
KLT	+ 9.3 ($p < 0.1$)	+ 12.1 ($p < 0.2$)	RW (L)
ZN	+ 9.7 ($p < 0.1$)	+ 14.0 ($p < 0.01$)	Total score
BENTON	- 13.6 ($p < 0.05$)	- 21.0 ($p < 0.01$)	Failure rate
EEG-analysis	+ 45.6 ($p < 0.01$)	+ 41.7 ($p < 0.01$)	EPE a-activity

GZ-F, general achievement; F%, relative failure rate; Rev., Revisionstest; KLT, Konzentrations-Leistungs-Test; RW (L), total score; ZN, digital span; EPE, electrical power equivalent

Conclusion

Psychometrical and EEG-analytical follow-up studies performed on 27 patients with occlusive cerebro-vascular disease provided evidence that anastomosis of superficial temporal artery to middle cerebral artery may contribute to an improvement of impaired intellectual function and of electric brain activity.

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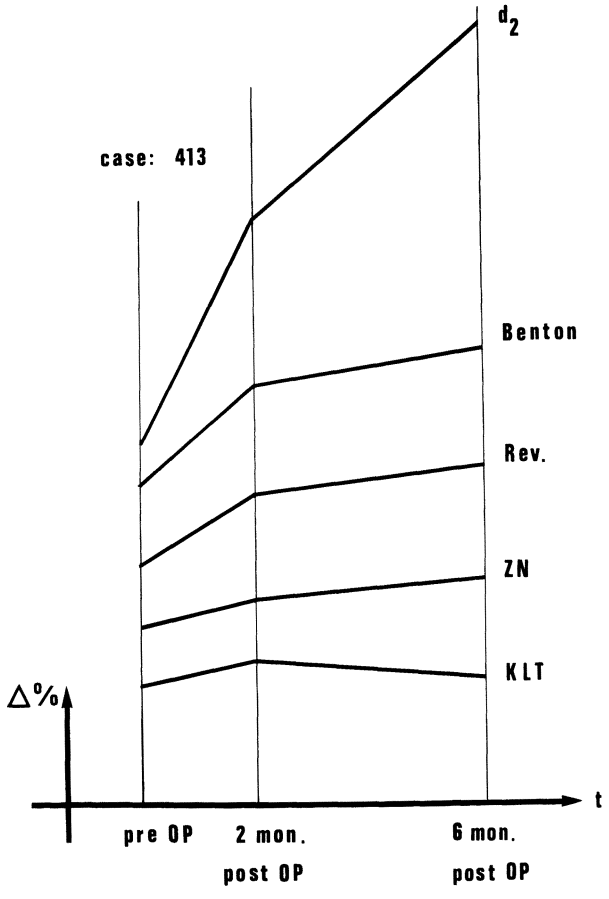

Fig. 1. Relative changes in the main psychometric parameters in a 54-year-old patient with occlusion of the right internal carotid artery treated with extra-intracranial arterial anastomosis.

(Rev., Revisionstest; ZN, digital span; KLT, Konzentrations-Leistungs-Test)

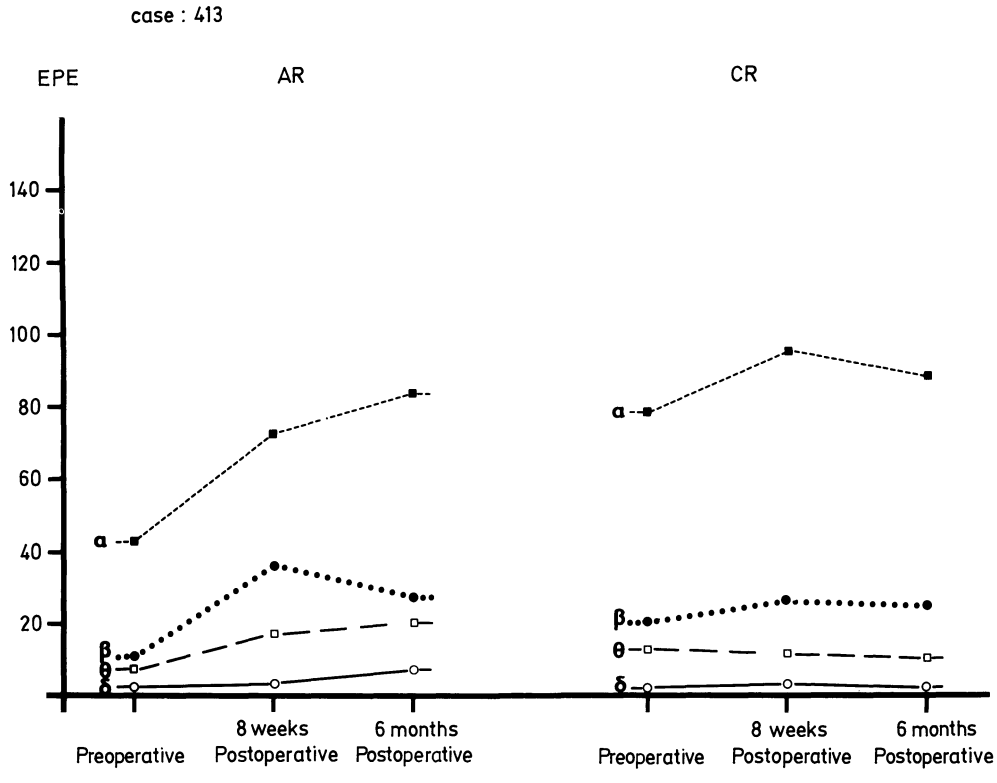

Fig. 2. Changes in electrical brain activity of the same 54-year-old patient after bypass-operation.

(EPE, electrical power equivalent; AR, affected region; CR, contralateral region)

The Importance of Computerized Tomography for the Indication of Surgical Treatment of Cerebrovascular Insufficiency

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Introduction

Findings of computerized tomography (CT) in patients with cerebral ischemia were analyzed to clarify the validity of this technique for the indication and timing of neurosurgical intervention in occlusive cerebrovascular disease. One important point is to exclude silent recent infarction in patients who had suffered a shortlasting fully reversible neurological deficit. This question became interesting on the one hand, because of increasingly detailed knowledge on the morphological development and healing of cerebral infarction as observed by CT (3, 5, 7-10, 12, 14, 15, 18-22, 24). On the other hand, some discrepancy between the clinical course of ischemic episodes and CT-findings raised the question as to the reliability of visualization of infarcted areas shown by CT.

Another important point is the ability to predict the success of surgery from the size and location of infarcts, since there are patients with a completed stroke whose neurological deficit improves impressively shortly after operation, whilst others remain unchanged.

Material and Approach

During the last six years, 121 patients underwent cerebro-vascular surgery for cerebral ischemia; carotid thrombendarterectomy at the neck (TEA) was performed in 76 patients; extracranial-intracranial arterial bypass (EIAB) in 53. Both interventions were done in 8 cases. Pre- and postoperative follow-up by CT and neurological symptoms were obtained from 58 patients, the initial CT being performed for detection or exclusion of a suspected recent infarction. One ml of 65% Urovist^{R} per kg body weight was regularly administered intravenously for contrast-enhancement. In patients with a completed stroke clinically CT was repeated at regular intervals until the healing of an infarct was verified by absence of contrast enhancement. Postoperative improvement of symptoms was only considered as such when occurring within 24 hours.

Results

Cerebral infarction was demonstrated by CT (typical contrast enhancement during the second to third week after the insult) in 40 out of 45 patients with clinical signs of completed stroke (CS). In these 40 cases, the density of the infarcted area on plain scans decreased progressively within 5-12 weeks (mean 8 weeks). At this time, the planned surgical interventions were performed. In one case, an area of decreased density was found at the first investigation 4 weeks

after stroke that became completed. The patient was operated on for carotid stenosis at the neck six weeks after the stroke. Control CTs 6 and 12 weeks following the stroke were normal (Fig. 1a,b), the symptoms remaining unchanged. In four patients with CS, no infarction was seen on the initial CT; in two of them, a small infarction was found until week 3, whereas this finding was absent in the scans of the remaining two patients. Nine patients with CS had an infarcted area in the central region. CT was normal in 12 patients suffering from transitory ischemic attacks (TIA's) or persistent reversible ischemic neurological deficits (PRIND). However, a medium-sized temporal infarction was shown in one patient with TIA.

Eight patients with CS improved neurologically within 24 hours following EIAB. Interestingly, such rapid amelioration was never observed following TIA. Six patients had a cortical infarction: large infarctions were seen in 3 cases aged 17, 21 and 43 years, medium-sized infarctions in the other 3 cases aged 49, 51 and 59 years. The 17-year-old female patient took an interesting course following acute hemiplegia. CT revealed a massive recent infarction, which increased its volume until 3 months later and then stabilized (Fig. 2a). An EIAB was performed to bypass a stenosis of the syphon and hemiplegia dramatically improved the day following surgery. Control CT 5 weeks after operation showed that the area of infarction was unchanged (Fig. 2b).

One patient aged 29 improved despite a small central infarction. Another patient's hemiparesis also improved, the infarction being undetected by CT.

Discussion

Cerebrovascular surgery aims at (a) ameliorating a neurological deficit ("therapeutic indication") and (b) preventing a recurrent stroke ("prophylactic indication"). Evidently the second point applies to patients with mild CS only. Amelioration of neurological symptoms was observed only in about 50-60% of the cases with CS (1, 6, 11, 17, 23, 25). The reason for dramatic neurological improvement shortly after a bypass procedure is still unknown, although the border zone around infarcted areas might play an important role. The selection of patients who would profit from an operation has been performed by measuring cerebral blood flow (4, 16, 26) or by administration of hyperbaric oxygen (13). The present results evidenciate the prognostic value of CT in combination with age and neurological symptoms. Thus, patients over 50 years of age only improved if they had small or medium-sized cortical infarctions, and never with central infarction. The likelihood of amelioration in patients under 50 was not related to size and location of the infarction.

Moreover, CT may even be a must for precise timing of surgery in cases of silent infarction. Areas of decreased density in the CT-scans of patients with TIAs are known from literature (2, 20, 21, 26). All patients suffering from TIAs should therefore have a CT-scan shortly prior to operation so as to avoid the risk of overlooking a silent infarction or a postoperative bleeding into a recently infarcted area as occurs spontaneously in about 35% of infarctions (2).

A definite advantage of CT is found in patients with completed stroke, where early diagnosis becomes possible this non-invasive technique. This allows the avoiding early angiography, an increased risk in such patients (2).

A further advantage of a follow-up CT-scan can be seen in the more precise timing of operation when symptoms improve rapidly following a stroke. Here, in a few instances, early normalization of the CT-scan within 2-3 weeks allows earlier surgery and provides a lower risk of recurrent stroke while waiting for surgery. As an additional sign in these rather rare cases, the well defined enhancement after injection of contrast medium as usually occurs in areas of ischemic infarction during the second and third week (27, 28) is very faint.

Thus, neurological signs of a completed stroke must be interpreted as a consequence of cerebral infarction, even in the presence of a negative CT. Surgery should not be performed earlier than 6-8 weeks following the stroke, when healing of an infarct is usually completed.

In the same way a waiting period of 6-8 weeks is necessary in a neurologically normal patient with recent infarction present in the CT.

Conclusion

Criteria may be summarized as follows.

1. TIAs + normal CT - operation as early as possible.
2. TIAs or CS or SE + recent infarction on CT - wait until healing of infarct (6-8 weeks).
3. CS + normal CT - infarction absent in CT - wait for 6-8 weeks, then repeat CT.
4. Mild CS + small cortical infarction in patients over 50 - operation for therapeutic and prophylactic reasons.
5. Mild CS + massive infarction or central infarction in patients over 50 - in theory prophylactic operation, not done practically; in patients under 50 - operation for therapeutic and prophylactic reasons.
6. Severe CS + massive infarction in patients under 50 - therapeutic operation; in patients above 50 - operation contraindicated.

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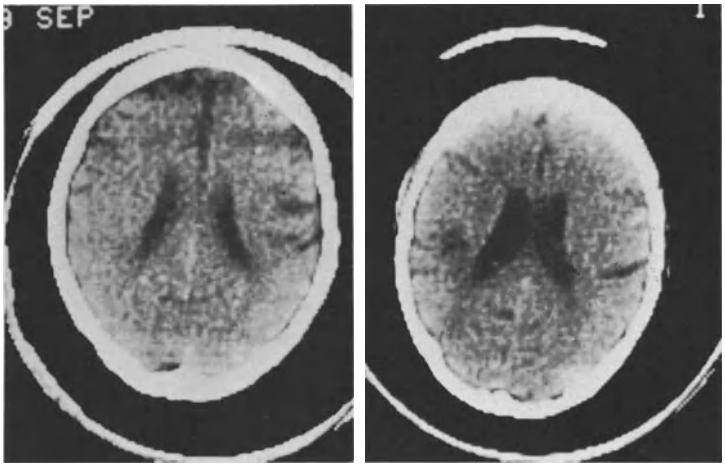

Fig. 1. a Small left temporal infarction 4 weeks following stroke. b 12 weeks after stroke and 6 weeks after thrombendarterectomy, the area of decreased density has vanished, yet right-sided hemiparesis is unchanged

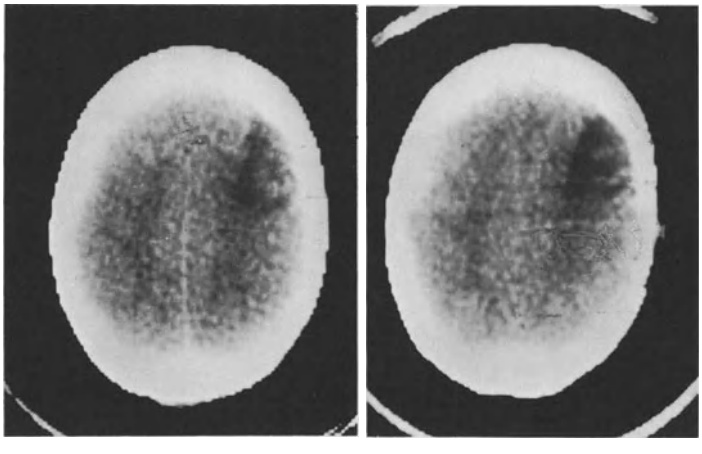

Fig. 2. a Massive old infarction in the right frontotemporal region 3 months after the stroke, the patient suffering from hemiplegia. b Five weeks later, the picture is more or less unchanged. However, the patient's neurologic deficit improved dramatically on the day following surgery

Management and Prognosis of Delayed Posttraumatic Intracerebral Hematomas

W. I. STEUDEL, J. KRÜGER, and H. HACKER

Since introduction of the term "late traumatic apoplexy" by BOLLINGER, 1891, delayed posttraumatic intracerebral hematoma has been a familiar clinical syndrome. However, the duration of the interval between the accident and the manifestation of the hematoma has remained unknown (1-4, 6-10, 15, 17, 19, 23).

An intracerebral hematoma can be directly visualized only since the introduction of computer-tomography (CT). The time of occurrence of secondary changes can be precisely determined by follow-up studies (5, 8, 12, 13, 16).

The clinical course, prognosis and treatment of this type of hematoma is analysed in 15 cases and compared with data in the literature.

Patients and Methods

From March 1977 until October 1979, 476 patients with head injuries were admitted. Of these, 60 were investigated several times with CT. These were 12 women and 48 men aged 15-88 years (mean age 39.6 years). Of these, 60 were followed up with CT, 15 showed a delayed intracerebral hematoma: 3 women and 12 men from 15-65 years old (mean age 38.6 years).

CT was performed with the SIRETOM I (matrix 128x128) and repeated every third day when the patient remained comatose or deteriorated clinically.

Results

CT and Clinical course: Twelve of the 15 patients with a delayed intracerebral hematoma were comatose and three somnolent on admission. CT was performed a few hours after the accident, and only in one case after four days (Table 1, see pp. 418 and 419).

An extracerebral hematoma was removed seven times. Initial CT was negative in only one case. With one exception (case No. 1), the interval between the first CT and the demonstration of a delayed intracerebral hematoma was less than one week. Delayed hematomas could be demonstrated six hours after the trauma in one case and 24 h after the trauma in eight cases, twice on the third day, three times on the sixth day and once on the ninth day. The hematomas were localized nine times in the frontal lobe and ten times in the temporal lobe. Only in one case was the hematoma found in the occipital and once in the parieto-temporal region. Multiple hematomas were present six times. The delayed intracerebral hematoma occurred after removal of an epidural or

subdural hematoma in five cases, three times on the opposite side and once after evacuation of an epidural hematoma in the posterior fossa (case no. 2). Delayed intraventricular bleeding was shown in addition in two cases.

Demonstration of the delayed intracerebral hematoma was not preceded by clinically appreciable alteration of the level of consciousness in ten cases (Table 1, p. 418/419). Signs of hemiparesis or deterioration of consciousness occurred five times.

Prognosis: As regards prognosis, the patients were subdivided into three groups according to the follow-up CT findings (Table 2):

Group 1: Patients with a singe delayed intracerebral hematoma (cases no. 1, 3, 4, 12). Three of these four patients survived.

Group 2: Patients with an extracerebral hematoma and a single intracerebral hematoma (cases no. 2, 6, 9, 14, 15). Two of these five patients died.

Group 3: Patients with multiple hematomas (cases no. 5, 7, 8, 10, 11, 13). All these patients died.

Thus, prognosis is favorable in the first and second groups.

Treatment: The delayed intracerebral hematoma was removed in six patients; four of these survived. The patients who were not operated on had multiple hematomas, mostly left frontal and temporal, and were not operated on because of the severe neurological deficits to be expected. The treatment of brain edema was carried out seven times with a high-dose, six times with a lower-dose and twice without corticosteroids. A definite influence of corticosteroid treatment on the development of delayed intracerebral hematoma was not discernible (taking into account the small number of our cases).

Table 2. Prognosis of delayed posttraumatic intracerebral hematoma (ICH)

	DIAZ, 1979 (n = 9)	STEUDEL, 1980 (n = 15)
Group 1		
Single ICH	●●●o	●●●o
Group 2		
Extracerebral hematoma and single ICH	●	●●●oo
Group 3		
Multiple ICH	oooo	ooooo o

● = surviving patient

Discussion

The criteria of a delayed posttraumatic intracerebral hematoma according to DIAZ et al. (1979) are fulfilled when (1) A history of head injury producing transient or permanent loss of consciousness, focal

Table 1. Summary of clinical cases

No. of case	Age	Sex	Level of consciousness	Interval findings	Computer-tomography on admission (Interval from trauma)	Follow-up scan	Surgery	Outcome
1	44	M	Somnolent	Coma	Rt temporal contusion (3h)	RT temporal ICH (9 days)	ICH	Survived without deficit
2	41	M	Comatose	Unchanged	Cerebellar EDH (1 h)	Lt frontal ICH (6 days)	EDH, ICH	Survived with minimal deficit
3	42	M	Comatose	Unchanged	Negative (3 h)	Lt occipital ICH (6 days)	No	Died on the 8th day
4	33	M	Comatose	↑Lt pupil, decerebrate	Lt temporal contusion (1 h)	Lt temporal ICH (24 h)	ICH	Survived with aphasia
5	34	F	Comatose	↑Rt pupil	Rt fronto-temporal contusion (2 h)	Multiple ICH, lt & rt (24 h)	Rt frontal ICH	Died on the second day
6	27	M	Somnolent	Unchanged	Lt temporal EDH (4 days)	Lt temporal ICH (6 days)	EDH	Survived with no deficit
7	15	M	Comatose	Unchanged	Lt & rt frontal contusion (2 h)	Lt & rt frontal ICH (3 days)	No	Died on the 6th day
8	56	M	Comatose	Unchanged	Lt temporal EDH, rt SDH (2 h)	Bifrontal and rt temporal ICH (24 h)	EDH, SDH	Died on the 28th day
9	44	M	Comatose	↑Both pupils, decerebrate	Lt SDH (3 h)	Rt temporo-parietal ICH (24 h)	SDH, ICH	Died on the 14th day

10	15	M	Comatose	Unchanged	Lt fronto-temporal contusion (2 h)	Lt fronto-temporal & rt frontal ICH (24 h)	No	Died on the 8th day
11	27	F	Comatose	↑Both pupils decerebrate	Bifrontal contusion (2 h)	Bifrontal ICH (24 h)	No	Died on the second day
12	43	M	Somnolent	Unchanged	Rt SDH (12 h)	Rt frontal ICH (3 days)	SDH, ICH	Survived with deficit
13	65	M	Comatose	Unchanged	Lt fronto-temporo-occipital contusion (2 h)	Lt fronto-temporal ICH (24 h)	No	Died on the 12th day
14	43	M	Comatose	Unchanged	Rt temporal EDH (2 h)	Lt temporal ICH (3 days)	EDH	Died on the 8th day
15	23	F	Comatose	Unchanged	Rt temporal EDH (2 h)	Lt temporal ICH (24 h)	EDH	Survived with severe deficit

ICH, delayed intracerebral hematoma; EDH, epidural hematoma; SDH, acute subdural hematoma

neurological findings is present. (2) There is an interval of less than two weeks between the injury and the development of delayed hematoma. All our patients meet these conditions. The interval in our patients is more than one week in only one case. It should be emphasized that in this patient CT was repeated only on the ninth day.

The localization of delayed intracerebral hematomas is mainly in the frontal and temporal region, corresponding to the coup and contrecoup mechanism (22). Our results agree with those of other authors (8).

Prognosis depends on the severity of the clinical picture. Classification according to the CT finding, suggested by LANKSCH et al. (1978), is useful. We have adopted it in a modified form (Table 2). Single hematomas have the best prognosis. A favorable course is also shown by patients initially operated on for an extracerebral hematoma and in whom the intracerebral hematoma appeared afterwards. CT follow-up examinations, which we performed every third day in cases of persistent unconsciousness, has proved useful here.

Pathogenetically, a large number of factors are considered in the genesis of a delayed intracerebral hematoma: vascular mechanisms are at the forefront. BOLLINGER (1891) originally attributed this type of hemorrhage to progressive cerebral malacia due to the trauma: the hematoma occurs when the vascular wall is included. Other authors regard the contusion or laceration as a prior condition, followed by hypoxia, hypercapnia or venous congestion which leads to bleeding (2). In one of our cases (no. 3), with a left occipital hemorrhage, a partial thrombosis of the superior sagittal sinus could be demonstrated by angiography.

Other authors attribute the delayed hematoma to vasoparalysis (11) or to a traumatic aneurysm (21). Our present CT with the matrix 128-128 does not permit any statement with regard to alterations due to blood vessels. Since an intracerebral lesion can already be demonstrated in the affected area at the initial examination, we can assume that local factors (especially a focus of contusion with lacerations) are the basis of a delayed intracerebral hematoma. This is confirmed by pathologic-anatomical findings, which show that secondary lesions involve alterations of ganglion cells, anemic and hemorrhagic necroses and diapedetic hemorrhages (18, 20).

Conclusions

Delayed posttraumatic intracerebral hematoma has become detectable very much more frequently since introduction of follow-up CT scans. The delayed hematoma usually appears during the first three days after injury. All patients in whom a space occupying lesion is present due to the hematoma, should be operation on. Prognosis is favorable in patients with single hematomas.

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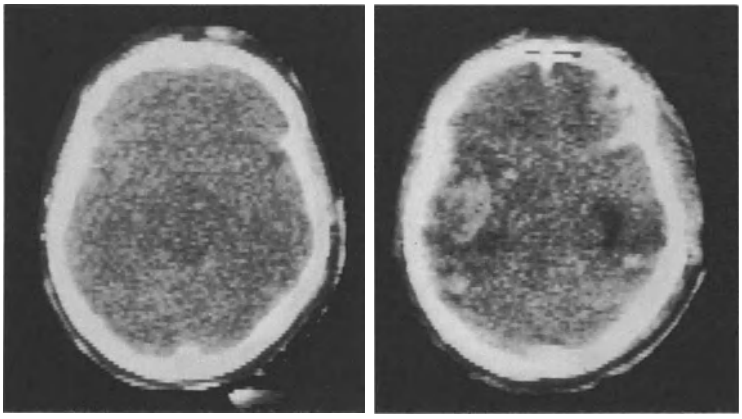

Fig. 1. a CT (1 h after the accident) in a 33-year-old man: sign of generalized brain edema with fine left temporal hemorrhagic foci. b CT 24 h later, after clinical deterioration with a large contusion hematoma on the left and signs of temporal herniation with widening of the right temporal horn. After removal of the hematoma, the patient recovered rapidly and survived with an aphasia

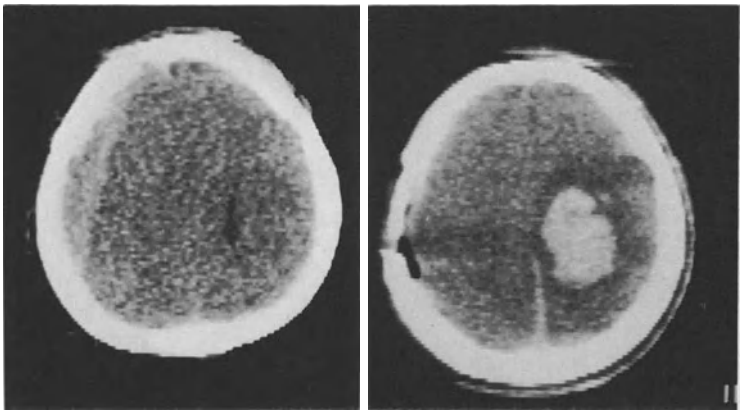

Fig. 2. a CT 2 h after a traffic accident in a 44-year-old man with an acute subdural hematoma on the left side. b CT 24 h later, after revomal of the hematoma. Large intracerebral hemorrhage in the right hemisphere. After removal of this hematoma, the condition did not improve, and the patient died 14 days later

Prophylactic Treatment of Peptic Ulcers, Gastric Dilatation, and Gastric Secretion in Head Injury

H. J. KLEIN

Introduction

The occurrence of acute gastric ulceration and bleeding, and the loss of large amounts of gastric secretion secondary to intracranial disease and to severe head-injuries is a well-known phenomenon to all neurosurgeons. The first connection between head-injury and oesophago-gastro-duodenal ulceration was noted in 1772 by JOHN HUNTER (3). Although the syndrome was extensively described by ROKITANSKY in 1849 (7), it was HARVEY CUSHING (2) in his famous Balfour Lecture of 1932, who suggested the existence of a primary parasympathetic center in the diencephalon which exerts direct influence on the vagal nuclei of the brain-stem. Stimulation of this center would produce excessive vagal activity leading, in turn, to increased gastric motility and hypersecretion of acid and pepsin. This induced hypersecretory state produces ulceration, bleeding and perforation. Since the upper gastro-intestinal hemorrhages and ulcerations following surgical procedures, especially for head injuries, are frequently fatal (8, 4), postoperative management has to take into account their incidence. The aim of this study was to compare and to prove the effect of two modern antacid drugs in the prophylactic treatment of peptic ulcers and of secretion-loss following head injury. We used the drugs CIMETIDINE ((Tagamet) and PIRENZIPINE (Gastrozepin). The pharmacological effect of CIMETIDINE (C) is the inhibitoring of H_2-sensitive receptors whereas PIRENZIPINE (P) is an anticholinergic drug of the muscarine-like inhibiting type (1).

Material and Approach

In a controlled study 83 patients with surgically treated head injuries were given either C, P, or a placebo according to a randomization score. Those patients in the placebo group who developed signs of gastrointestinal bleeding were immediately treated with one of the drugs studied, also according to a randomization score. All patients had the same basic therapy, consisting of the same infusions, the same dosage of dexamethasone, and osmotic and oncotic drugs. The diagnosis of stress ulcers, gastrointestinal bleeding and secretion-loss was based on the quantity and colour of the gastric secretion (via suction by the nasogastric tube), gastric acidity, pulse, blood pressure, hematocrit, hemoglobin, hematemesis, melena and macroscopic inspection of faeces. Patients treated with C received 5x200 mg daily, intravenously, whereas in the P-group the drug was given in a dosage of 3x10 mg daily. The sutdy excluded patients older than 70 years, those with liver cirrhosis, and those having a previous treatment with anticoagulating drugs.

Results

Our results were obtained from 54 patients (the others either died very soon or did not need intensive care any longer). Eight of 54 patients developed signs of gastrointestinal bleeding (14,81%). Four of these were in the placebo group (16,67%). Of those patients who were placed on C (13) four developed gastrointestinal bleeding (30,77%), whereas in the group with P (17) no bleeding occurred. Two of the four patients with bleeding and without specific therapy received C immediately and the symptoms disappeared at once; the other two patients died in a decebrate state before this treatment started. In all patients with a poor outcome the critical phase of increased gastric secretion occurred between the fifth and the eight postoperative days. The patients treated with P had the lowest gastric secretion rate, lowered down to almost 150 ml daily at the third postoperative day. In the critical phase of generally increased secretion, the secretion-loss with P-treatment did not exceed more than 261 ml daily. Patients placed on P who had a good functional outcome produced the smallest amounts of gastric secretion. In the same group, in the patients with a poor outcome, P did not prevent the critical augmentation of secretion between the sixth and the eighth postoperative days. Nevertheless, during this period the secretion-loss was lower than in patients treated with C or placebo (Fig. 1, 2). After the ninth postoperative day there was no difference between patients without a specific therapy and those placed on P in the group with a good outcome (Fig. 3). In both groups we observed a very low secretion-amount after the ninth day.

Patients managed with C (Fig. 4) and with a good clinical outcome, had a lower secretion-rate than those managed with P only at the second and third days. In the later course we observed a second increase with large quantities of gastric secretion in the C group after the fourth day.

In the group with C treatment and a poor outcome, there was no reduction of gastric secretion during the whole period as compared to the placebo group. Also, with the use of C we saw no reduction of secretion-loss after the fourth postoperative day. In patients treated with placebo, and with a good clinical course we could notice a lower amount of gastric secretion than in the corresponding group who had been treated with C.

Discussion

We found no correlation between the degree of gastric acidity and the clinical course even if decerebrate rigidity was present. This means that, in our material, the correlating factor was not hyperacidity but hypersecretion. This corresponds to the results of other authors (5, 8). A possibility to explain the good results of the prophylactic treatment with an anticholinergic drug is that the gastric erosions and hemorrhages, as well as gastric hypersecretion, are due to stimulation of the parasympathetic center through efferent fibers contained in the vagus nerve (2).

Other authors have stimulated the vagal nuclei directly with inlying balloon pressure on the floor of the fourth ventricle (6). They concluded that gastric acid hypersecretion after severe head injury may be due to direct pressure stimulation of vagal nuclei rather than to hypothalamic stimulation as suggested by CUSHING. Hypersecretion in

patients with surgically treated head injuries can be considered as a result of central vagal stimulation due to direct vagal compression by a space-occupying mass or by a global increase in intracranial pressure, and as an additional sign which documents important brainstem functions.

Conclusion

The prophylactic management of patients with surgically treated head injuries with P was able to reduce the gastric secretion-loss more markedly and continuously than a comparable management with C. Furthermore P was able to prevent neurogenic ulcers of the gastrointestinal tract.

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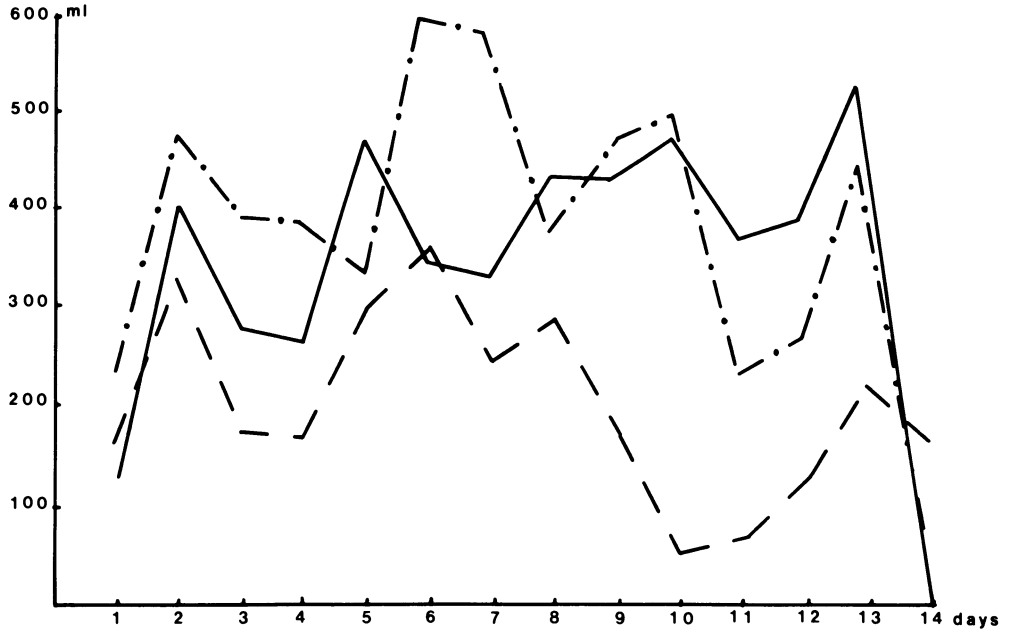

Fig. 1. Gastric secretion in patients with poor outcome.—— = placebo; -.-.- = Cimetidine; ---- = Pirenzipine

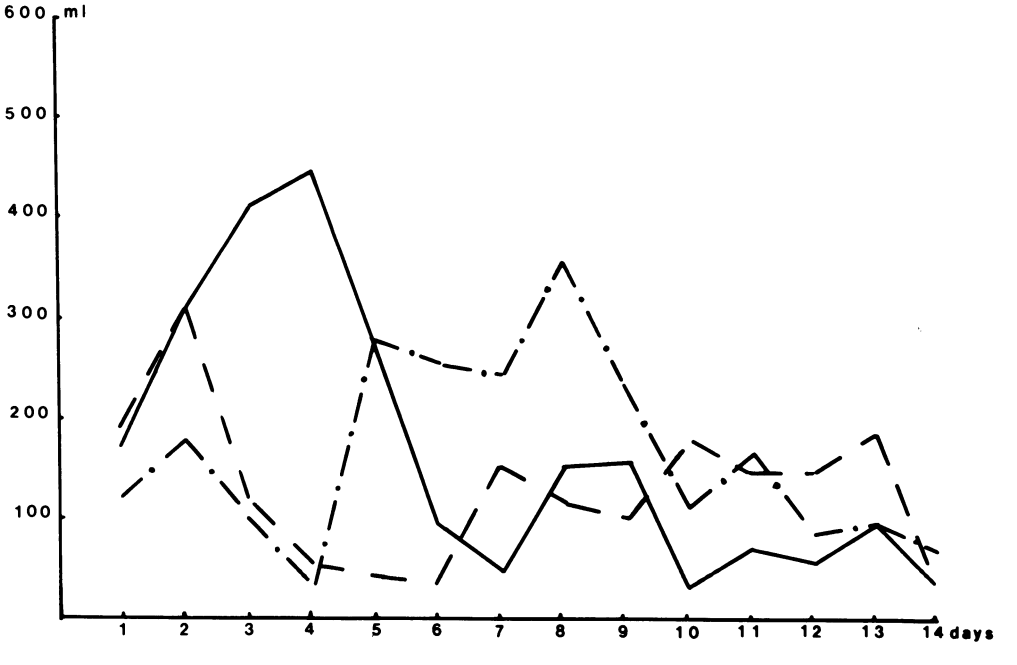

Fig. 2. Gastric secretion in patients with favorable outcome. —— = placebo; -.-.- = Cimetidine; ---- = Pirenzipine

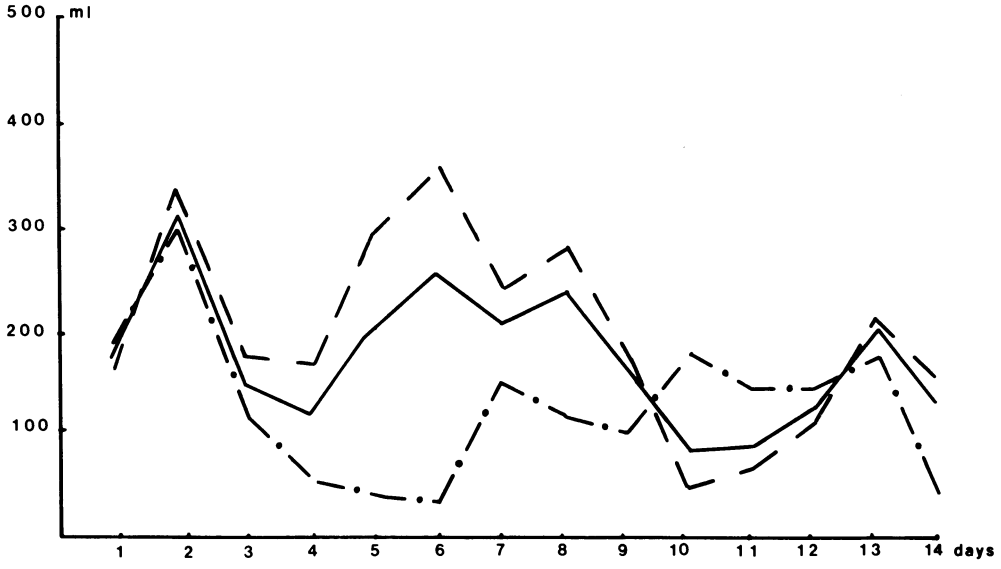

Fig. 3. Gastric secretion in patients treated with Pirenzipine.
—— = complete group; -.-.- = patients with favorable outcome;
---- = patients with poor outcome

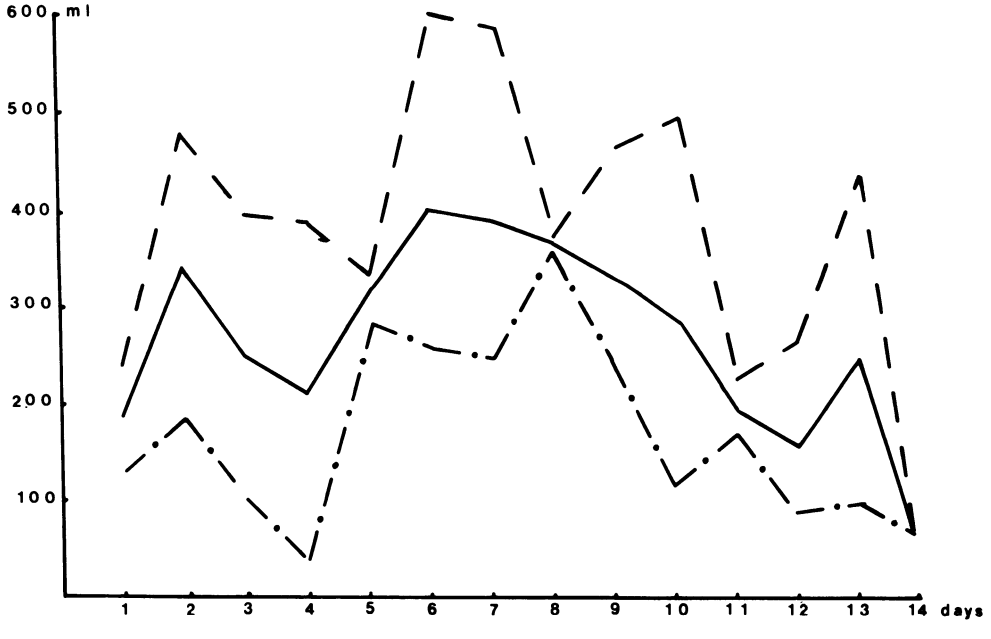

Fig. 4. Gastric secretion in patients treated with Cimetidine.
—— = complete group; -.-.- = patients with favorable outcome;
---- = patients with poor outcome

Unusual Development of Chronic Subdural Haematomas After Cerebrospinal Fluid Shunting

H. ALTENBURG, M. BRANDT, and P. BÖHM

The introduction of cerebrospinal fluid (CSF) shunting systems in the treatment of hydrocephalus was an incontestable progress, although these procedures still have the highest complication-rate in neurosurgery (4, 5). Most usual complications are drainage insufficiency and infection.

Additionally to a remarkable sensitivity to minimal intracranial pressure (ICP) elevations, to the negative-pressure syndrome, to ventricular collapse and to slit ventricles, chronic subdural haematomas are thought to be the most severe sequels after CSF drainage (3, 6, 9, 11, 12). In the recent literature the incidence of subdural haematomas appears to be about 5% (1, 6), after shunting of normal pressure hydrocephalus (NPH) in adults even about 23% (9, 12).

Chronic subdural haematomas, effusions, callus, and other complications, often without any specific clinical symptomatology, are discovered more frequently within the last years due to routine computerized tomography (CT) (7, 8, 10).

The development of chronic subdural haematomas after CSF drainage is due to the increase of negative intraventricular CSF pressure values. After ventriculo-atrial or peritoneal CSF drainage there is a duplication of the average negative values by a syphon effect (9, 11) in the upright position.

It is our aim to discuss the indication for the operation of hydrocephalus due to non-tumoural aqueduct stenosis or obstruction, as well as the treatment of the abofe mentioned severe complications.

Case 1, male, 22 years old: In follow-up studies after CSF drainage for hydrocephalus, due to aqueduct stenosis, the development of a bilateral subdural haematoma, which was mentioned to be an adaptive mechanism, was observed. Regarding clinical improvement, an excepting attidute with adequate controls seemed to be justified (Fig. 1).

Case 2, male, 8 years old: This was an accidental discovery. Three years after CSF drainage for hydrocephalus due to aqueduct obstruction, a massive chronic subdural haematoma over the left hemisphere was found in a first routine CT control. There were no signs of raised ICP and no clinical symptomatology. Nevertheless, the operative treatment of this unusually thick intracranial haematoma was found to be indicated. After trepanation and nearly total evacuation of the completely organized subdural haematoma, which was about 6-7 centimeters in diameter, postoperative life-threatening disturbances of ICP with central dysregulations and changing variations of consciousness were observed. A few days later there was a total remission of midline shifting, later leading to the partial development of a callus in the *bi*lateral compen-

satory chronic subdural haematoma. Ten months after surgery the situation was reached as seen in the preoperative CT. The child is perfectly well (Fig. 2).

Case 3, female, 52 years old: This is an example of eventually fatal outcome following CSF drainage for NPH due to aqueduct stenosis proven by ventriculography. Preoperative clinical signs: psychic alteration and severe ataxia. A high-pressure SPITZ-HOLTER valve was inserted. Postoperatively there was clinical improvement, but an extracerebral fluid collection over the left hemisphere was seen already after one week.

Two months later she fell at home and was brought again as an emergency case with unconsciousness and right-sided hemiparesis. Now a massive, space-occupying chronic subdural hematoma over the left hemisphere with fresh blood clots (Fig. 3) and midline shifting was seen in CT. The patient was operated on immediately. The hematoma was evacuated and the membranes removed. After this there was a shortlasting improvement. Instead of repeated operative procedures during the following two weeks, for some of the above mentioned complications, she died of central dysregulation due to reactive brain edema and a contralateral space-occupying subdural hematoma.

Case 4, female, 9 years old: Following a shunting procedure for hydrocephalus due to aqueduct stenosis, life-threatening postoperative complications such as ventricular collapse, slit ventricles, bifrontal air collection, disturbances of consciousness, and vegetative signs were observed. After occlusion of CSF drainage system, a marked hydrocephalus was again found in the CT three days later. A Hakim medium-pressure valve was inserted. Normalization of ventricular size and clinical improvement leading to total restitution were observed (Fig. 4).

In conclusion, there is the question as how to avoid the above mentioned complications and side-effects due to hyperdrainage of CSF (3).

All extracranial CSF shunts aim at coping with these problems. Medium and, especially, low-pressure valves seem to favor overdrainage phenomena. High-pressure systems can not prevent it. We have no experience with the antisyphon device of PORTNOY et al. (11). Larger reports on this method have not been published as yet. Is there a fundamental need to measure intraventricular CSF pressure before shunting in order to find out the correct valve system? Is there a renaissance of TORKILDSEN's ventriculo-cisternostomies in the management of patients with non-tumoural aqueduct stenosis and NPH (2), who have been accustomed to low intracranial pressure for many years?

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Fig. 3. Space-occupying chronic subdural haematoma, due to CSF drainage 2 months ago ▷

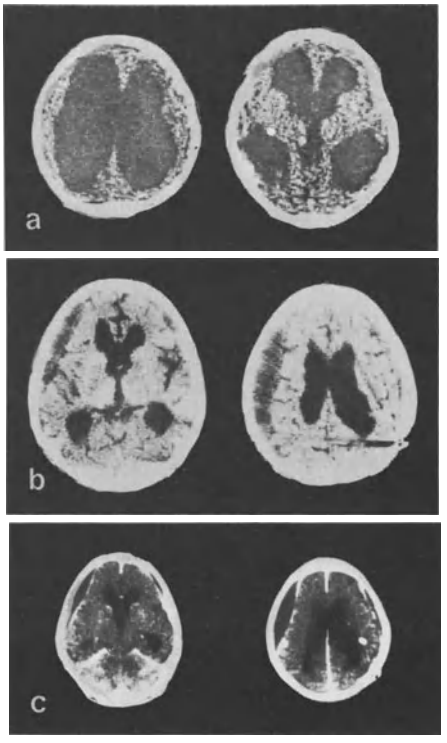


Fig. 1 a-c. CT follow-up before (a) and after (b, c) CSF-drainage. Expecting attitude, adequate controls

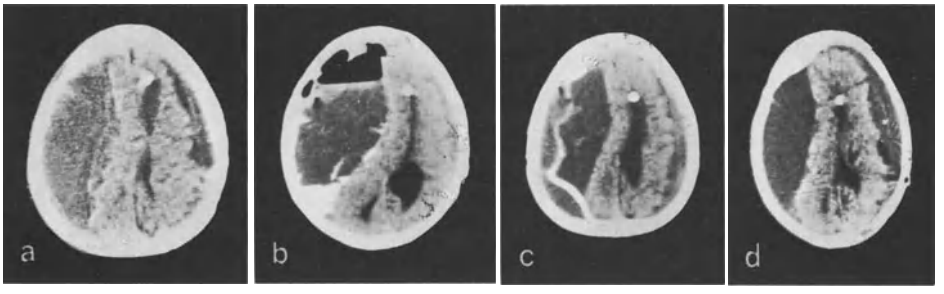
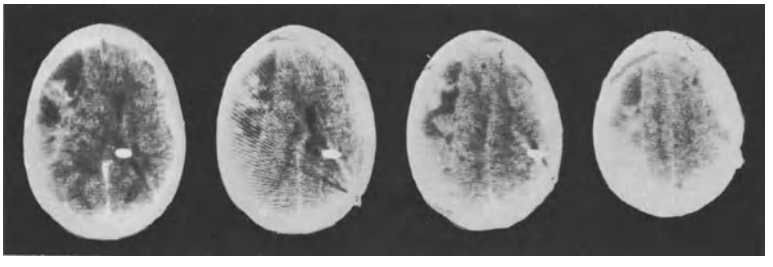


Fig. 2 a-d. CT observations before (a) and after (b-d) surgical evacuation of a space-occupying chronic subdural haematoma. CSF-drainage was instituted 3 years ago



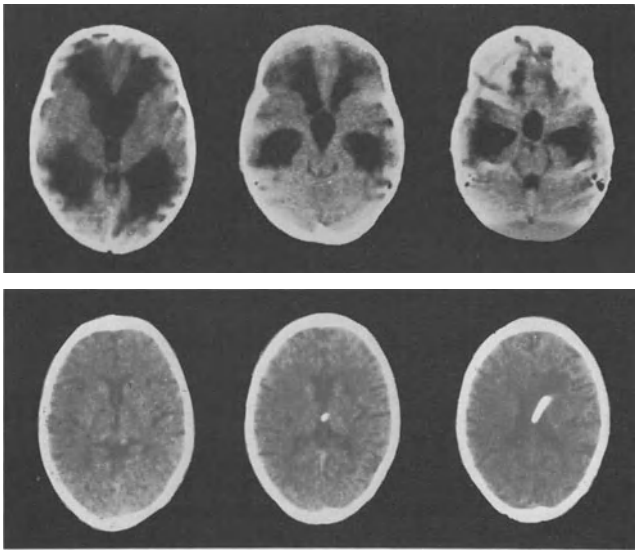


Fig. 4. Pre- *(left)* and 2 months postoperative *(right)* CT. Note subependymal periventricular edema *(left)*

The Role of Ventricular Fluid Viscosity in the Treatment of Hydrocephalus

K. E. RICHARD, R. HELLER, and R. A. FROWEIN

The hydrodynamic properties of the shunt systems used nowadays in the treatment of hydrocephalus have been submitted to repeated tests (1-4, 7). Studies were made on the influence of CSF protein content upon the function of the valve systems (4, 7). It turned out that the flow-rate of the slit valve systems inversely diminished to increasing protein content. On the other hand, the flow-volume response of the ball-spring systems as developed by HAKIM proved to be independent on CSF protein content.

During the last years, the RAIMONDI peritoneal one-piece shunt system (6) with slit valves has been increasingly used in our hospital, particularly in patients with tumoral hydrocephalus, restricted operability, and pathological ventricular fluid. Therefore, it seemed necessary to investigate the effect of CSF properties altered by admixture of serum, fibrinogen, or red-cells on CSF-viscosity and function of the RAIMONDI system.

Methods and Results

1. Ventricular Fluid Viscosity Under Pathological Conditions

Viscosity was measured by a KPG^{R}-Ostwald Microviscometer (Schott Geräte GmbH) at 37 $\pm$ 0.1^{o} C.

Under normal conditions the relative viscosity *(rV)* of the ventricular fluid *(VF)* was in the range of 1.005-1.015. The higher normal values previously reported were measured in lumbar fluid exclusively (5).

When human albumin, serum, plasma, or red-cells were added to VF of normal viscosity, the rV equally increased up to a protein content of 0.2 g/100 ml, respectively to a hemoglobin content of 0.2 g/100 ml (Fig. 1). Beyond this limit, however, rV increased steeper after admixture of plasma or red cells than after admixture of human albumin or serum. After hemolysis of red cells rV exceeded 1.06.

2. VF - Viscosity and Shunt-Flow

The influence of VF-rV upon flow-time within the RAIMONDI system (closing pressure 5-9 cm H_2O) was established by determination of the time the fluid took to pass from 15 to 10 cm H_2O inside a gauge-glass set before the system.

rV-increases even above 1.06 did not lead to a measurable prolongation of the flow-time.

3. VF - Viscosity and Popping Pressure

The slit valves opened at hydrostatic pressures between 3 and 8 cm H_2O, independently of the rV-level, respectively of the kind of admixture.

4. VF - Viscosity and Fluid Pressure Within an Experimental Set-Up

Inside a skull-like model, a balloon wrapped into foam rubber was perfused for 6 hours with fluid to which human albumin, serum, plasma, or red cells were added in an increasing concentration (Fig. 2).

The rV of the perfusion fluid was gradually augmented up to the extreme pathological range of 1.12-1.30 in intervals of two hours (Fig. 3). Within each rV-level the perfusion volumes were increased from 12 ml/h over 30 ml/h up to 60 ml/h according to possible rates of CSF production. An increase of perfusion-rate always led to a perceptible augmentation of the fluid pressure. On the opposite, the fluid pressure rose little with increasing rV, i.e. 2 Torr at most, independently of admixture of human albumin, serum, plasma, or red-cells to the fluid. In comparison, when the drainage was performed via a PUDENZ slit-valve with a closing pressure of 6-9 cm H_2O, a slightly more distinct increase of the fluid pressure, reaching 5 Torr at most, was measured (Fig. 4). Steep increase occurred when air bubbles passed.

Even at a long-term perfusion, up to 12 h, no variations of the shunt-capacity could be observed: fluid pressure kept unchanged.

Conclusion

RAIMONDI's one-piece system proved to be a device functionally insensitive to hyperviscosity, independently of whether hyperviscosity was caused by an admixture of serum proteins or red cells. Even a pleocytosis up to 5000/3 white cells should not have an influence upon the flow-rate via this system (5).

Under the conditions of VF-fluid hyperviscosity the pressure-flow relationship of the RAIMONDI shunt resembles the one of the ball spring assemblies, which have the greatest flow-capacity when the protein contents are high (4, 7). This insensitivity of the one-piece shunt system towards alteration of the VF-viscosity is due to an improvement of the flow characteristics by decrease of turbulence and more numerous and lengthened valve slits.

Summary

The RAIMONDI one-piece system proved to be a device hydrodynamically insensitive to hyperviscosity, independently whether it was caused by admixture of protein, fibrinogen or red cells.

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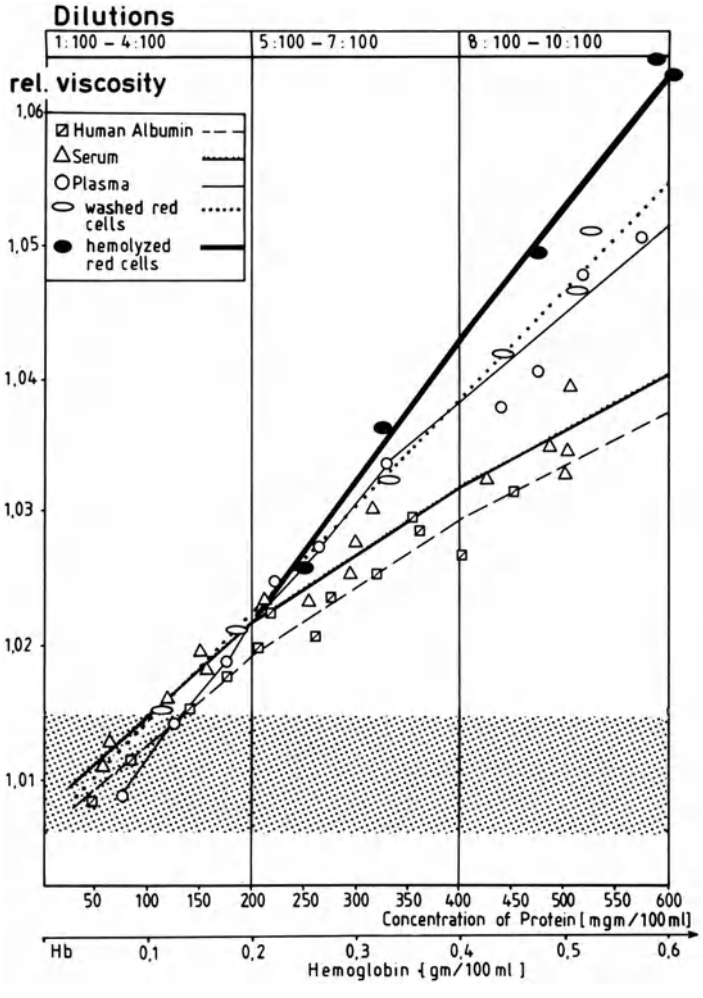

Fig. 1. Relative *viscosity* of *ventricular fluid* after *admixture* of human albumin, serum, plasma, or red cells (non hemolysed, hemolysed) in increasing concentrations

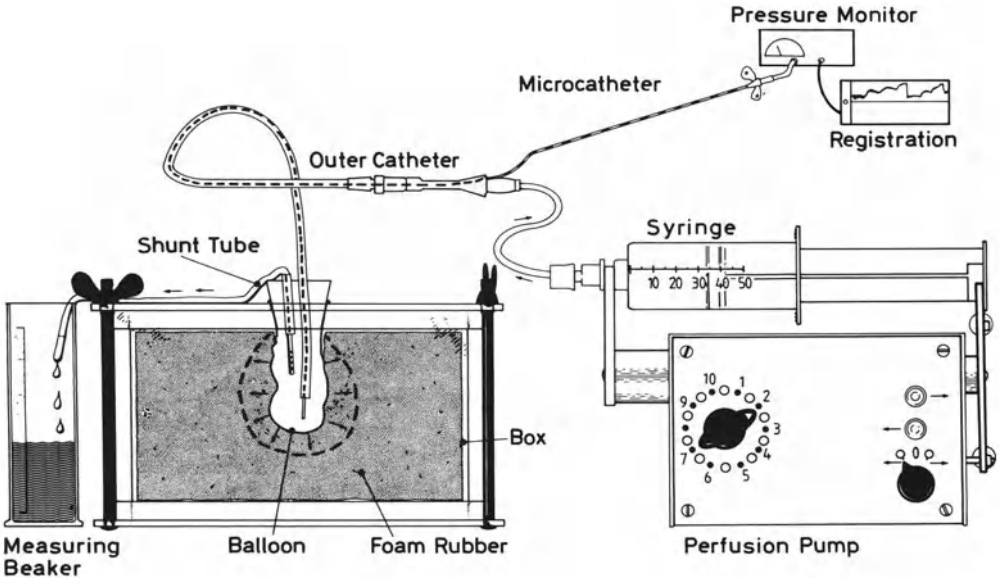

Fig. 2. Influence of *VF-viscosity* of *VF-pressure*, examined with the aid of an experimental set-up, consisting of a perfusor, a *ventricle-brain-like-model*, and a pressure gauge

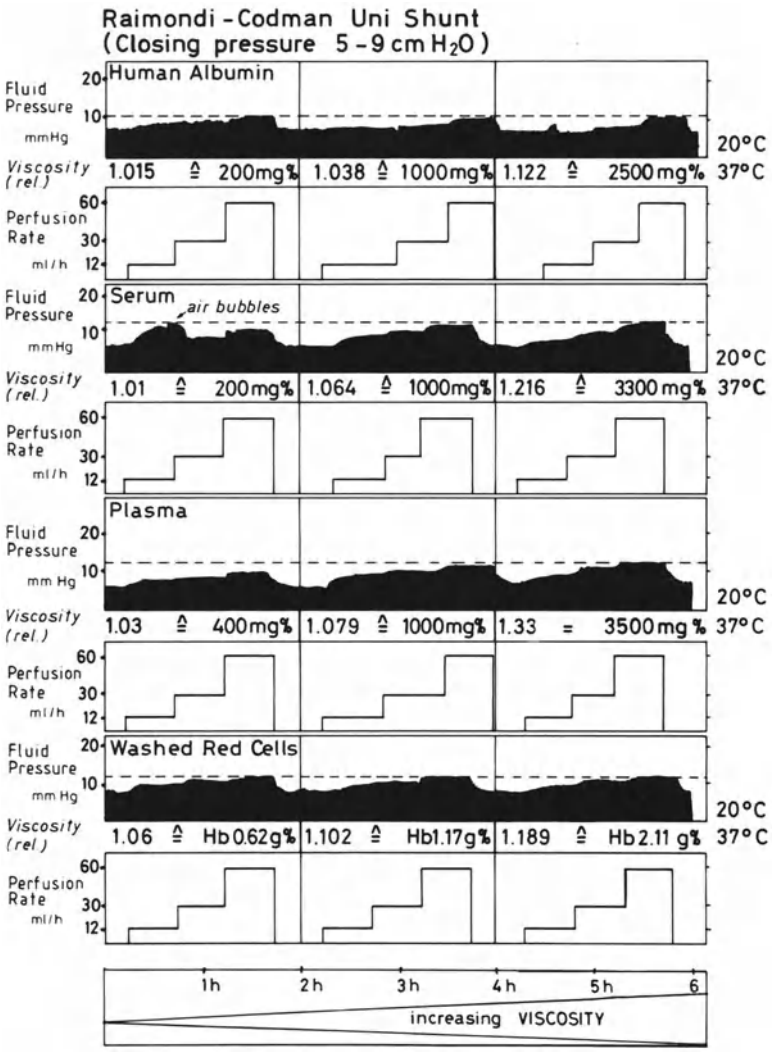

Fig. 3. Influence of *VF-viscosity* on *"ventricular" pressure* (balloon pressure) (see Fig. 2), vented by a RAIMONDI one-piece shunt with closing pressure of 5-9 cm H_2O. Increase of *VF-viscosity* by admixture of human albumin, serum, plasma, or washed red cells

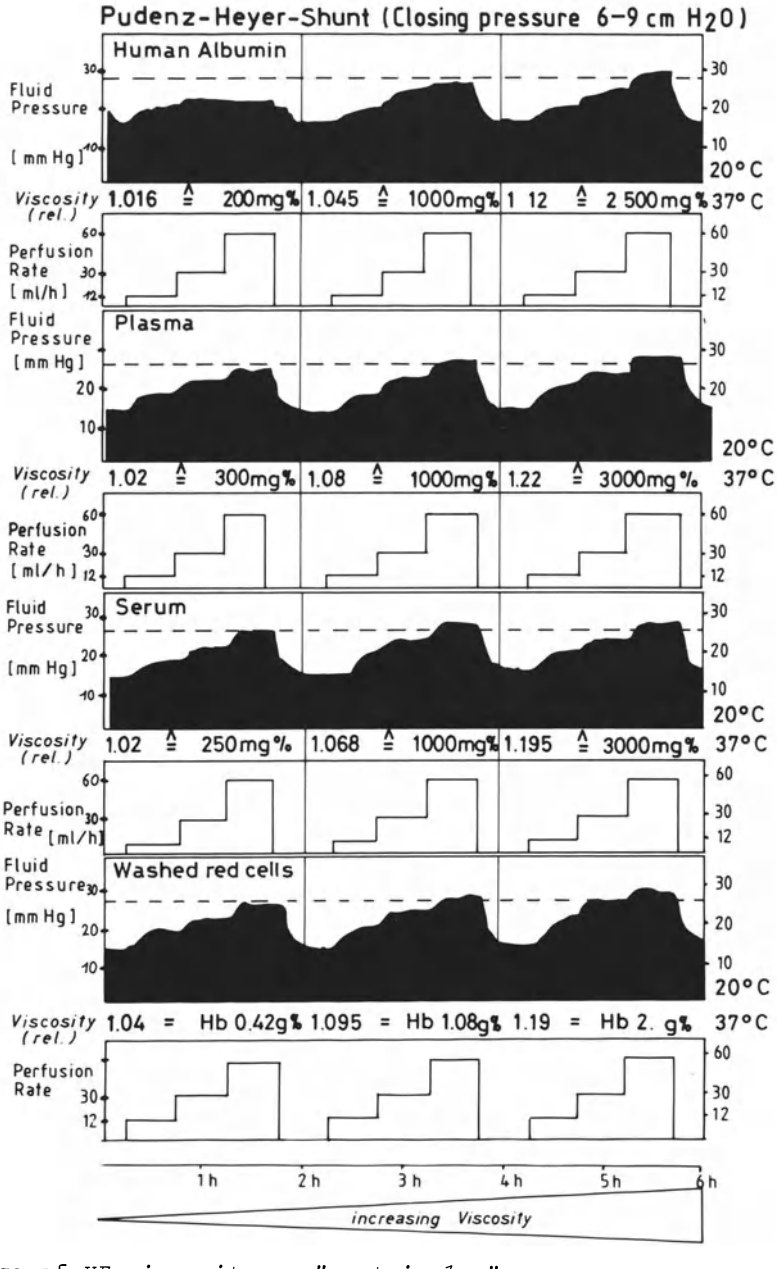

Fig. 4. Influence of *VF-viscosity* on *"ventricular" pressure* (balloon pressure) (see Fig. 2), vented by a PUDENZ-HEYER assembly with a closing pressure of 6-9 cm H_2O

Cystic Lesion of the Aqueduct and Obstructive Hydrocephalus

M. SCHÄFER, H. GRAU, and W. I. STEUDEL

Cystic, non-tumorous space-occupying lesions in the quadrigeminal region are rare, in contrast to those of the supratentorial cisterns. In literature we found only few similar cases, proven by operation or at autopsy (1, 3, 8, 9). Most were arachnoid cysts of the tentorial notch causing obstructive hydrocephalus in children and young individuals (1, 7, 9). In the case reported here, there was a communication between the collicular cyst and the aqueduct. This fact could be clearly demonstrated by Metrizamide Ventriculography[1]. Only one other similar case, also without verification, was reported by FREDERICKS and VAN NUIS (2) (Table 1).

Case Report

A 52-year-old woman was admitted to the University Medical Center on May 10, 1979 in a comatose state with suspicion of an intoxication. Previous history could not be obtained. Neurological examination revealed chronic bilateral papilledema, neck stiffness and no focal neurological signs. Computer-tomography (CT) showed an obstructive hydrocephalus with excessive dilation of the lateral ventricles and the third ventricle, as well as a cystic lesion of low density dorsal to the third ventricle. In this examination the fourth ventricle could not be identified (Fig. 1).

Because of severe intracranial hypertension (IHT), ventriculo-atrial shunting using a HOLTER Medium-pressure-system was immediately performed. The next day the patients was alert and reported a history of intermittent headaches of many years duration and bilateral loss of vision since about two years.

Examination

Now neurological examination of the cooperative patient showed paralysis of upward gaze (PARINAUD-Syndrome), poor pupillary reaction to light and diplopia, indicating local compression of the quadrigeminal plate.

Metrizamide ventriculography revealed a cystic lesion, communicating with the aqueduct (Fig. 2a and 3a). The fourth ventricle could not be filled with contrast medium. In addition, the floor of the third ventricle seemed to be compressed from below (Fig. 2a, b and Fig. 3a, b). For clarification of these findings pneumencephalotomography (PEG) was performed, showing a fourth ventricle of normal size and position.

1 Amipaque by Schering AG, Berlin, FRG.

Table 1. Case reported as cysts in the quadrigeminal area

Authors	Case	Sex	Age	Clinical findings	Neuroradiological examination	Therapy
HAMBY and GARDNER (1935)	1	F	16 years	IHT, deafness	PEG	Operation
ALEXANDER (1953)	1	M	18 months	IHT, spasticity	PEG	Operation
KATAGIRI (1960)	2	F	37 years	IHT, pupillary dysfunction	PEG, ventriculography	Shunt
		M	20 years	IHT	PEG, ventriculography	Shunt
LOURIE and BERNE (1961)	1	M	13 months	Papilledema, spasticity	PEG, ventriculography	Operation
KRUYFF (1965)	6	F	2 months	IHT	Ventriculography	-
		F	10 months	IHT	PEG, ventriculography	Operation
		F	3 weeks	IHT	Ventriculography	Operation
		M	11 months	IHT	PEG, ventriculography	Operation
		M	5 weeks	IHT	Ventriculography	Operation
		M	13 months	IHT	PEG, ventriculography	Operation
FREDERICKS and VAN NUIS (1967)	1	M	41 years	Headache, pupillary dysfunction, Parinaud-syndrome	PEG	-
HUCKMAN et al. (1970)	1	F	9 years	Papilledema, ataxia	PEG, angiography	Shunt and operation
LITTLE et al. (1973)	2	F	49 years	IHT	Ventriculography	Operation
		F	41 years	IHT	PEG, ventriculography	Operation
SCHÄFER et al. (1980)	1	F	52 years	IHT, pupillary dysfunction, Parinaud-syndrome	CT, ventriculography PEG, angiography	Shunt and operation

The "impressions" in the floor of the third ventricle now appeared as cysts or dilated cisterns ventral to the upper brain stem (Fig. 2b and 3b). The aqueduct and the communicating cyst also filled with air.

Operation

On July 3rd, 1979, a right occipital craniotomy revealed a cherry-sized cystic lesion containing clear fluid, dorsal to the quadrigeminal plate. The wall of the cyst gave the impression to consist of arachnoid, but there was not tissue enough available for histopathological examination. All membranous tissue was removed microsurgically. Thereafter the quadrigeminal plate and the large vein of GALEN were clearly identified.

At this point the advantages of the right occipital supratentorial or transtentorial approach (10, 11) to the quadrigeminal plate or pineal region should be emphasized:

1. Excellent visibility of the deep seated structures and, therefore, safe identification of vessels of particular importance.
2. Sufficient space for dissection and excision of the lesion.
3. No operative brain damage and consecutive functional deficit.

The postoperative course was uneventful (Fig. 4).

CT-control three weeks after surgery showed normal size and configuration of the ambient and quadrigeminal cisterns and of the upper brain stem.

The patient was seen 8 months later in our unit. Preoperative local signs caused by the cyst such as PARINAUD-syndrome and pupillary dysfunction had disappeared. There was a moderate bilateral deficit of vision in consequence of atrophy of the optic nerve. Nevertheless, the patient is working fulltime in her former profession.

Discussion

The differential diagnosis of quadrigeminal plate cysts should include pinealoma, meningeoma, arteriovenous malformation of the vein of GALEN and glioma invading the quadrigeminal plate (4). Since the availability of CT, mass lesions can be detected easily after injection of contrast media. Arteriovenous malformations should have a distinct angiographic appearance. However, as shown in our case, CT alone did not reveal the exact topographical situation and the pathogenic correlations (5). Therefore, ventriculography and PEG are of particular importance in such cases.

As mentioned by LOURIE and BERNE (9) the etiology and mechanisms of cyst-formation in the subarachnoid pathways are not clearly understood. It is likely that they result from more than one cause.

LITTLE et al. (8) postulated that arachnoid cysts probably occur in both a congenital and an acquired form. Acquired cysts in general may develop secondary to adhesive arachnoiditis or trauma, or as a diverticulum of the third ventricle or of the aqueduct. FREDERICKS and VAN NUIS (2) reported the only case of a cyst communicating with the aqueduct, and, in their opinion, a persistent fetal mesocoelic recess was responsible for this lesion. Another possible etiology

would be a cyst, originating from ependymal cell rests, which has ruptured into the cerebral aqueduct. Since no history of previous trauma or inflammation was obtained, and since other cystic lesions existed in the interpeduncular space, a congenital origin seems most likely in our case.

In regard to the intermittent IHT, a symptomatology similar to that observed with colloid cysts in the third ventricle, a valve mechanism should be postulated. A narrowing of the neck of the cyst would be followed by enlargement and consequent compression of the aqueduct.

Treatment of arachnoid cysts in the quadrigeminal region should be by direct approach and excision. The operation is essentially curative, just as in the previously reported series of pineal tumors operated on directly (10, 11).

Summary

We report on a very rare, surgically confirmed case of a 52-year-old female who had a history of chronic intracranial hypertension (IHT), with intermittent crises.

Computer tomography alone did not allow the correct diagnosis. Only the combination of air-encephalography and Metrizamide-ventriculography, performed after shunting, demonstrated a cystic space-occupying lesion near to the quadrigeminal plate, communicating with the aqueduct.

The cyst was successfully removed by direct microsurgical approach.

We want to emphasize the advantages of the right occipital supratentorial or transtentorial approach to the quadrigeminal plate or pineal region.

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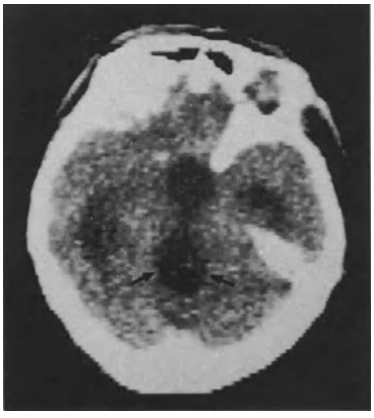


Fig. 1. CT shows marked ventricular dilatation and a cystic lesion dorsal to the third ventricle *(black arrows)*

Fig. 3. *Left:* ventriculography (a.-p.-projection) shows midline position of the cyst; *right:* PEG (a.-p.-projection) with air-filled cyst *(white arrows)*

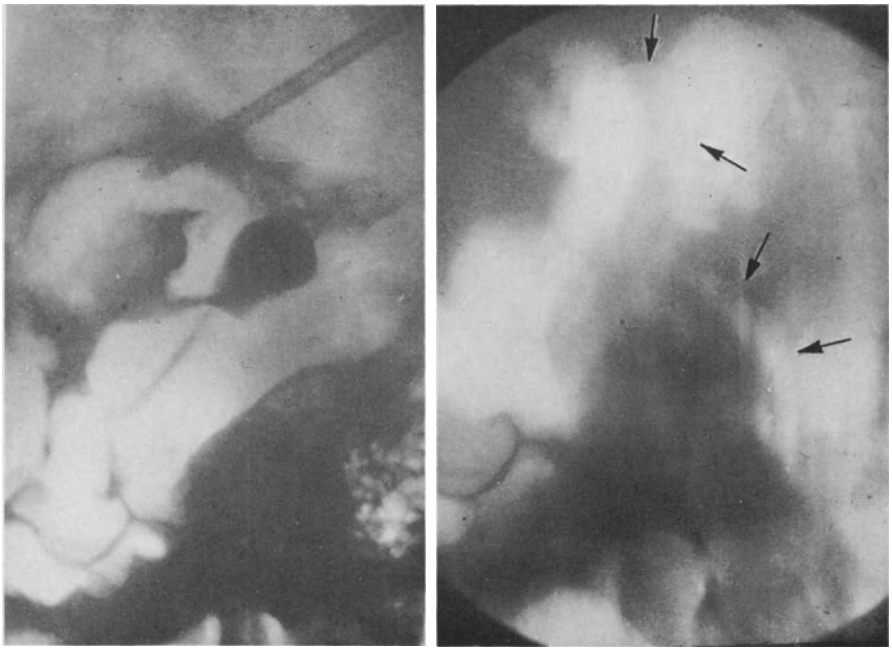
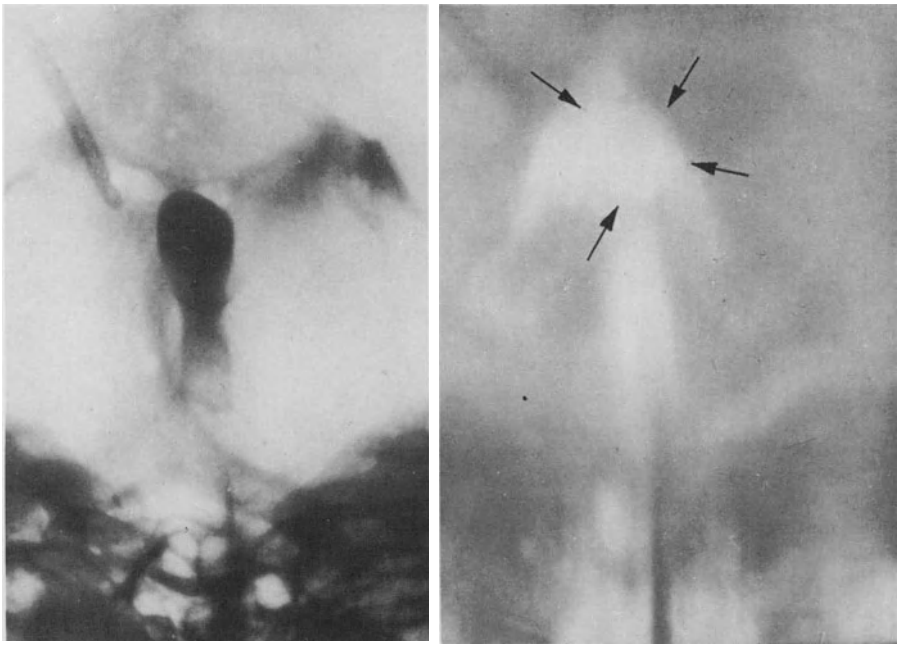


Fig. 2. *Left:* Metrizamide ventriculography (lateral view) reveals a cyst communicating with the aqueduct; *right:* pneumencephalotomography (lateral view) shows filling of fourth ventricle, aqueduct and the communicating cyst *(white arrows)*



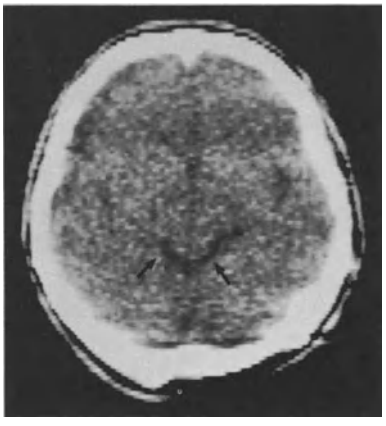


Fig. 4. CT image 3 weeks after surgery shows normal cisterns *(black arrows)* and upper brain stem

Reticulo-Histiocytic Granulomatous Encephalitis Producing the Clinical Picture of Encephalitis with Brain Tumor

A. BAROCKA, K. A. FLÜGEL, W. HUK, and T. THIERAUF

The reticulo-histiocytic granulomatous encephalitis (CERVOS-NAVARRO, 1960) is disparately interpreted by authors to be of more inflammatory or more tumoral origin. STAMMLER and CERVOS-NAVARRO, 1965, emphasize the inflammatory nature of the disease. Others see the close relation to reticulosarcomas and the so-called "microgliomatosis" of the brain. (MILLER and RAMSDEN, 1963, RUBINSTEIN, 1964, JÄNISCH et al., 1973).

A 58-year-old man was admitted to our hospital because of caudal cranial nerve disturbances. Five months earlier he had developed vertigo, hypacusis on the right, and headache. There were dysarthria, unsteady staggering gait, and mental detoriation. A few days after admission, fever of about 39° C and a severe impairment of consciousness appeared. CAT and angiography revealed no pathological findings. The CSF cell-count was 30/3, mainly lymphocytes, 60 mg/dl of protein, and normomastix precipitation at 3/VIII. During the course of the illness the EEG showed severe slow diffuse activity. Encephalitis was diagnosed. CAT controls, the last performed on May 13, 1979, showed nothing but cerebral atrophy (Fig. 1). In August the clinical picture changed to left-sided focal epileptic seizures, papilledema, and mydriasis on the right. Now CAT showed a large ring-shaped structure in the right hemisphere (Fig. 2).

CAT-guided stereotactic brain biopsy revealed polymorphous tumor cells, an inflammatory process not being definitely excluded. After six months of hospitalization the patient died of central heart failure. Only the microscopic examination of the brain allowed the diagnosis of reticulohistiocytic granulomatous encephalitis (Fig. 3, 4).

Reticulosarcomas and microgliomas together amount to about 0,5% of intracranial tumors (HUBERT 1967). According to VUIA and MEHRAEIN 1971 we distinguish three forms of CNS reticulosis:

1. Inflammatory - the encephalitis of CERVOS-NAVARRO with diffuse perivascular infiltrates, in particular of the basal ganglia and periventricular areas.
2. Proliferative - periventricular tumor formation by reticulocytes, histiocytes and other RHS cell elements.
3. Cerebral reticulosarcomas.

The case presented in this paper allowed following the transition from the diffuse inflammatory from to tumor formation in one patient by means of clinical and radiological observations. The assumption of a close relationship between these forms of primary CNS reticulosis is hereby supported.

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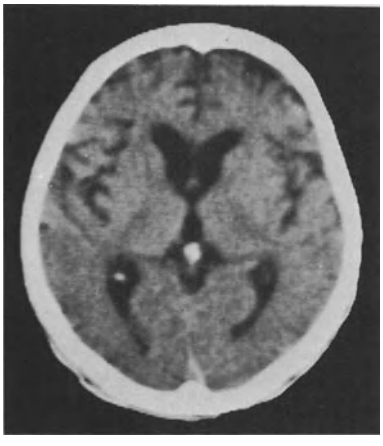

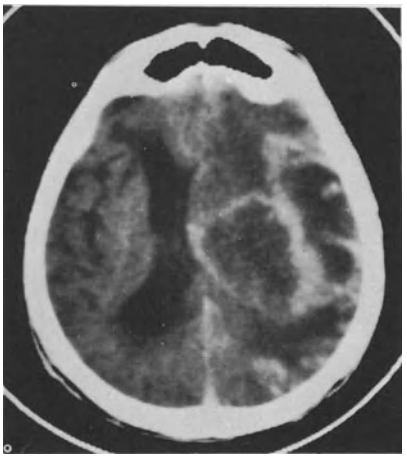

Fig. 1 *(left)*. Absence of focal CAT changes six weeks after admission to hospital and seven months after the first symptom

Fig. 2 *(right)*. CAT control six weeks later, showing a large ring-shaped structure in the right hemisphere

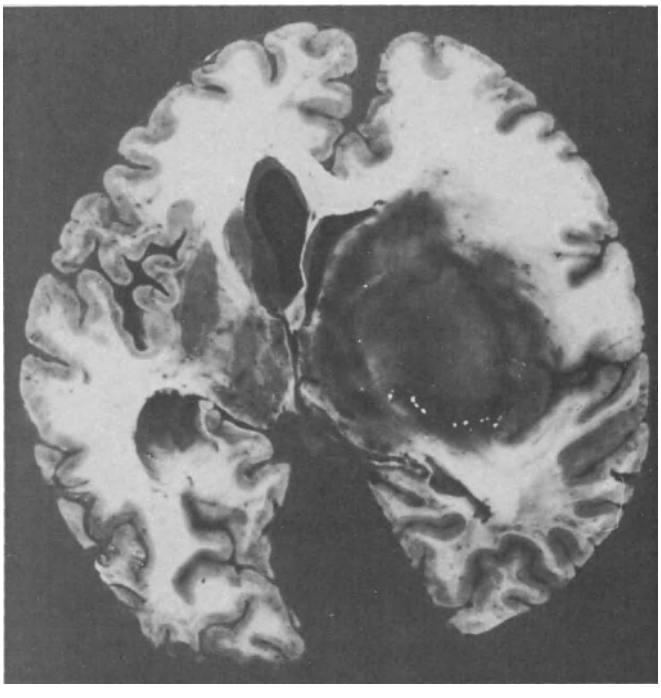

Fig. 3. Gross examination of the brain showing a mass in the right hemisphere

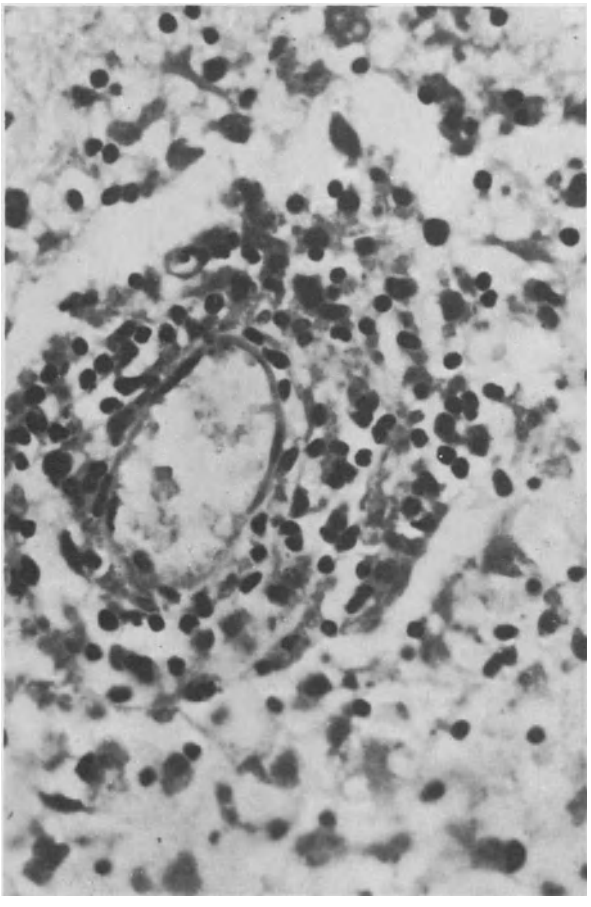

Fig. 4. Typical perivascular infiltrates containing lymphocytes, plasma cells, and reticulohistiocytes

The Restriction in Cranial Migration of the Spinal Cord

G. SCHACKERT, R. OTTO, F. ALBERT, H. WALDBAUR, and W. HUK

The problems associated with the restriction in cranial migration of the spinal cord are illustrated by means of a case report.

An 11-year-old Turkish boy had trouble with his urinary bladder for the first time at the age of ten years. First he had nocturnal enuresis, then a permanent bladder incontinence. Also, he had a paresis of the anal sphincter. A pendulous soft tumour in the paramedian lumbosacral region on the left had been present from birth (Fig. 1). The diagnosis of restriction in cranial migration of the spinal cord was made by X-ray and myelography. X-ray showed clefts in the sacral vertebral arches (Fig. 2). In the myelogram, the spinal cord could be followed as far as the second and third sacral vertebrae (Fig. 3). At operation we saw a subcutaneous lipoma which extended into the intradural space and into the conus medullaris. This explains why the spinal cord was fixed to the second and third vertebrae. Some roots had a horizontal direction, some showed an acute upwards angle. The lipoma was removed. The fibrous filum terminale was resected. The postoperative course was unremarkable. The neurological status improved.

We speak of a restriction in cranial migration of the spinal cord whenever the conus medullaris is found below the level of the second lumbar vertebra or when the thickness of the filum terminale is more than 2 mm (MATTHIAS and LAUSBERG 1972). In the 60 mm embryo the end of the spinal cord is at the level of the third sacral vertebra, in the newborn child at the third lumbar vertebra (GERLACH and JENSEN 1969). At the age of five years the cranial migration of the spinal cord is completed. The conus medullaris ends at the level of the first lumbar vertebra REIMANN and ANSON 1944). In 1886 a lipoma causing restriction in cranial migration of the spinal cord was described for the first time by v. RECKLINGHAUSEN. A subcutaneous lipoma was found, which extended into the intradural space and fixed the conus medullaris of the non-ascended spinal cord at the level of the second sacral vertebra (von RECKLINGHAUSEN 1886). This case is nearly identical with the one here described. In literature the most common cause of the restriction in the cranial migration of the spinal cord is thought to be spinal dysraphisms such as the meningomyeloceles, the pilonidal sinus or diastematomyelia (ANDERSON, 1968; GERLACH, 1969; JAMES and LASSMANN, 1972). Intraspinal lipomas and other tumors of the spinal canal are also well known causes (MATTHIAS and LAUSBERG, 1969; HEYER and MARKAKIS, 1977). The restriction in the development of the filum terminale, aberrations of nerve roots, atresias and stenoses of the spinal canal are also felt to be responsible (JONES and LOVE, 1956; JAMES and LASSMANN, 1962). The clinical symptoms are abnormalities of the skin in the dorsal midline, such as hypertrichosis or abnormal pigmentation. Some authors find these abnormalities in 65-100%. Incontinence of the urinary bladder is observed in

24-65%, whereas the dysfunction of the rectum is much less common. Malformations of the feet are described in 18-65%. These include the hollow foot or the clubfoot. Dysfunction of sensitivity and paresis of the lower limbs have also been reported (HJÄLMAS and WESSNER, 1974; MATTHIAS and LAUSBERG, 1972; VOGELSANG, 1969). The clinical deficits become manifest at developmental growth phases. They are due to different growth rates of the bony spinal canal and the spinal cord. This results in a damage by traction (GERLACH, 1969).

Diagnosis is confirmed by the radiological findings. X-rays reveal the cleft in the vertebral arch and the enlargement of the spinal canal, formation of block vertebrae and half-vertebrae, the well-known effect of pressure by a tumor with deformation of the vertebrae and enlargement of the spinal canal as well as formation of spurs in cases of diastematomyelia. At myelography the medial and dorsal filling defect of the contrast medium column due to the non-ascended spinal cord is typical for the restriction in cranial migration. Very often the caudal part is enlarged (megacauda) (VOGELSANG, 1969). We prefer to use a hydrosoluble contrast medium such as Dimer X, which provides good resolution in the lumbosacral region.

Early operation is indicated to prevent progressive neurological deficits.

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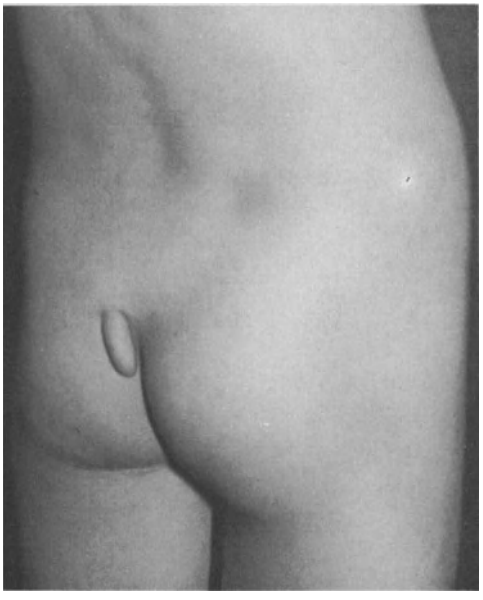

Fig. 1. This pendulous soft tumour in the paramedian lumbo-sacral region had been present from birth

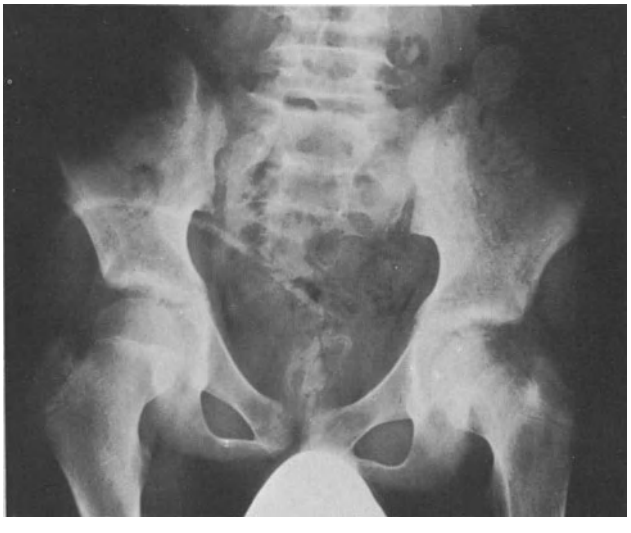

Fig. 2. The X-ray shows clefts in the sacral vertebral arches

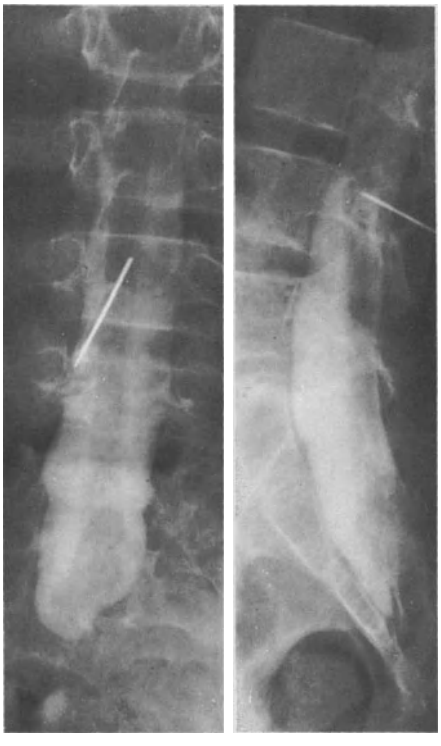

Fig. 3. In the myelogram the spinal cord can be followed as far as the second and third vertebrae

Unusual Vascular Formations Within the Orbit

U. MAYER, F. EMMERICH, and W. HUK

Differential diagnosis of non-inflammatory unilateral exophthalmos has progressed remarkably through the interdisciplinary co-operation between ophthalmologists and neurosurgeons on one hand, and through the modern methods of investigation, on the other. This has led to a significant therapeutic improvement.

The usual examination through the ophthalmologist consists of inspection, exophthalmometry according to HERTEL, motility tests, study of displaceability of the bulb using the piezometer according to W. JAEGER, as well as of routine X-rays of the orbit according to RHESE-GOALWIN (42), especially for the demonstration of the bony boundaries, the fissures (26) and the optic canals. ENT-findings are also taken into consideration. According to BOETTE (6) similar points of view play a role for the detection of angiomas (3, 14). TELEGINA and KESSAEV (44) state that diplosonography may be a help for the diagnosis as well. OSSOINIG (31), COLEMAN (11), and POUJOL (33), as well as many others, emphasize the importance of B-scan ultrasound investigations. With improvement in the resolution of computerized tomography, this method is assuming a most important position among the diagnostic methods (5, 31, 45 and many others). In some cases, especially of arteriovenous fistulas, angiography is necessary in order to establish the diagnosis (19, 43, 46). LOMBARDI and PASSERINI (25) published details on the technique of visualizing the normal course of the ophthalmic artery and its branches. OSMERS et al. (29) described the technique of retrograde orbital phlebography with its side-effects and complications. In a recent paper, ARTMANN (3) published a survey on the effect of computerized tomography and angiography which make scintigraphy (expected the P_{32} test) and orbitography with air or other contrast media superfluous.

Clinical cases will serve to demonstrate this:

Case 1: A 12-year-old boy was operated on for a cavernoma of the left orbit at the age of 1 1/2. Histological diagnosis at that time was: partly hemorrhagic lymphangioma with dilated veins and remarkable endothelial proliferation[1]. He now had a cherry-sized, blue, soft subcutaneous nodule in the nasal third of the left upper lid, suggesting a hemangioma. Ophthalmoscopic findings were unremarkable. X-rays showed nothing pathological within the orbit or the nasal sinuses. Only on the computerized tomogram (Fig. 1) did an area of increased density become visible, indicating a medial tumor of the orbit with dilated blood vessels extending as far as the optic foramen. Since visual acuity was only 1/20, the hemangioma of the lid was treated by diathermic puncture, which led to the desired cosmetic effect without influencing the exophthalmos.

1 The authors thank Prof. Münich, Würzburg, for the histological diagnosis.

Case 2: A 45-year-old woman complained of unilateral, axial exophthalmos on the right, 5 months after a flu. The mobility of the eyeball was free, function normal, but the backward displaceability of the eyeball was decreased. Further findings: papilledema of 2,5 dpt, unusual engorgement of the retinal veins. X-rays unremarkable. Computerized tomography showed a retrobulbar tumor measuring 2 cm in diameter, which could not be clearly delineated from the optic nerve (Fig. 2). Transfrontal craniotomy of the orbit by the neurosurgeon made it possible to remove the tumor completely and to relive pressure on the optic nerve without any alteration of visual functions. This patient did not suffer the same fate of the old man shown in Fig. 3 (*Case 3*), who was not treated in time. Only after he was blind on the left eye due to optic atrophy with an 18 mm protrusion of the bulb did he come to our department. Following enucleation of this eye, the hemangioma could be removed by frontal approach.

Case 4: 8-years-old boy, who was found to have intermittent exophthalmos of 2-3 mm on the left without further disturbances of function. In a bent over posture, the prominence of the exophthalmos increased by 1-2 mm, at which time engorgement of the retinal veins could be seen. Detailed questioning of the parents revealed that the child had had a concussion at the age of 7 years. Auscultation and X-ray findings were negative, as was the computerized tomogram and the exophthalmos-producing factor (EPF). By means of a scintigram, enlargement or overfunction of the thyroid gland could be excluded, the scintigram of the cranial vault with 99 technetium was also unremarkable[2]. The angiogram of the left external carotid artery (Fig. 4) revealed a dilatation of the ascending branch of the maxillary artery with typical dilatation and direct connection to a massively enlarged superior orbital vein. Tangential enlargements were able to exclude the involvement of the superficial temporal artery and the middle meningeal artery. Prior to a possible therapeutic embolisation, regular check-ups were planned with the parents.

In summary, all patients had cavernomas of the orbit, which HARRIS and JACOBIECS (18) strictly distinguish from the capillary hemangiomas of childhood. According to SCHRECK (38), they amount to 17%, HENDERSON (20) quotes 41%, GOTTSCHALDT and WALTER (16) 1/4 to 1/3 and ARON-ROSA and DOYON (1) 24% of all tumors of the orbit. As the above examples show, the exact topographic localization was only possible with the help of computerized tomography, a fact which ASREGADOO (4) already emphasized. Only in the case of the arteriovenous fistula was angiography the first investigation to reveal the pathology of the vascular system, as WRIGHT (47) and DILENGE (15) have pointed out. Endothelial proliferation in a hemangioma, as seen in the first patient, was described by CANAVAN and LOGAN (9) who mention a benign hemangioendothelioma in the differential diagnosis similar to HENDERSON (20). The localization of the cavernous hemangioma at the exit of the optic canal as well as its total removal and subsequent normalisation of vision are definitely rare observations. Similar cases in literature concern the bony orbit (10, 17), the retina (23), retina and optic disc (24) and the optic disc (37). Alternative forms of treatment are cryocoagulation (20), radiation (27), and cortisone (40). However, the last patient mentioned was a child possibly with a capillary hemangioma, which is said to disappear spontaneously until the age of six in the majority of cases (22).

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2 Laboratory of Prof. F. WOLF, Institut und Poliklinik für Nuklearmedizin der Universität Erlangen-Nürnberg.

The possible correlation between cavernous hemangioma and arteriovenous fistulae was discussed by SAVIR and MANOR (35), who present a case of anomalous blood vessels of the iris with ipsilateral cavernous hemangioma of the orbit leading to spontaneous hyphaema. According to HARRIS and JAKOBIEC (18), local hemodynamic disturbances lead to proliferation of vascular channels. SCHIEFER and WOLLENSACK (36), and CONELLEY (12), reported on posttraumatic arteriovenous fistulae, HAYE et al. (19) mention the involvement of the ophthalmic vein. A peripheral fistula between the maxillary artery and the orbital vein is relatively rare. A paper by STROOBANDT et al. (41) deals with the drainage of a carotid-cavernous fistulae via the superior ophthalmic vein following a perforating trauma to the orbit, and even via the contralateral vein. SERBINENKO (39) described two patients with arteriovenous anastomoses of the branches of the internal maxillary artery and the inferior orbital vein. In one of these cases the fistulae also contained blood from the branches of the ophthalmic artery. The patient in case 4 is also somewhat atypical, since a pulsating noise was never heard even on very careful examination. In this case it is hard to say what role the head injury plays and which role is played by embryonal malformations (36). Since spontaneous healing has been observed by several authors, further development may be awaited in view of the intermittent course.

All in all it is our purpose ot show how the new method of computerized tomography serves the diagnosis and treatment of these patients, particularly in the field of surgical indication, as for the transfrontal approach to the orbit. This development does not lead to an isolated specialty, but rather to new paths of interdisciplinary co-operation.

Summary

Communication concerning the diagnosis and therapy of non-inflammatory, vascular exophthalmus:

1. 12-year-old boy suffering from proptosis of 4 mm on the left, and of a hemangioma of the left upper-lid. Computerized tomography showed an orbital tumor extending its dilated vessels until the foramen opticum. Because of poor vision, the treatment was merely cosmetic, consisting in diathermic puncture of the lid hemangioma.

2. 45-year-old woman complaining of axial proptosis on the right. Computerized tomogram showed a retrobulbar tumor compressing the optic nerve. Operative removal of a cavernous hemangioma by the neurosurgeon led to *restitutio ad integrum*.

3. 8-year-old boy showing intermittent exophthalmos on the left. No tumor detectable in common examinations. External carotid angiography finally revealed an arteriovenous shunt between the A. maxillaris and the V. orbitalis superior.

These 3 descriptions of patients suffering from exophthalmus point out the actual diagnostic and therapeutic means for an ophthalmologic and neurosurgical collaboration.

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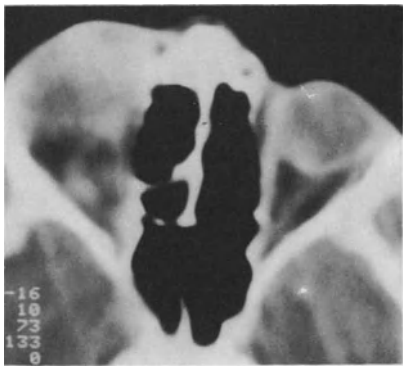

Fig. 1. Computerized tomogram made visible an area of increased density indicating a tumor of the orbit which extended blood vessels as far as the optic foramen

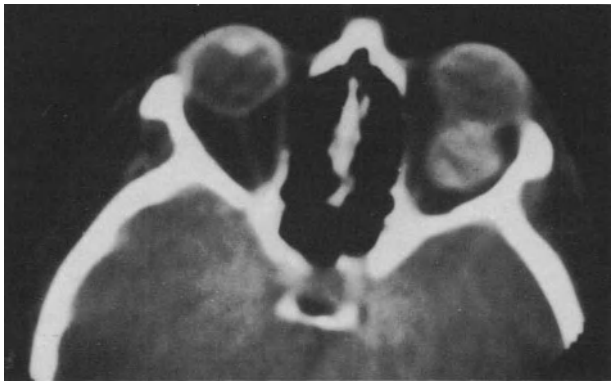

Fig. 2. Computerized tomography showed a retrobulbar tumor measuring 2 cm in diameter which could not be clearly delineated from the optic nerve

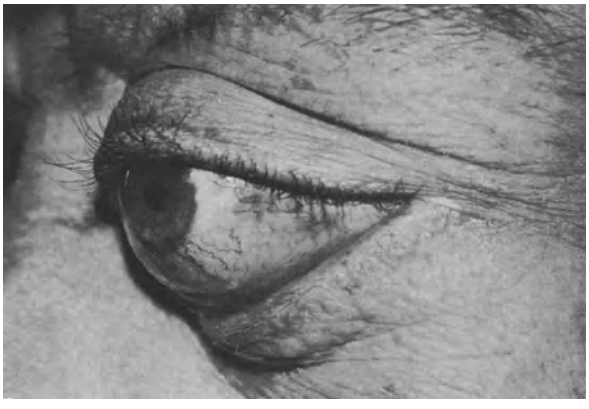

Fig. 3. Bulbar protrusion by 18 mm according to HERTEL. Blindness caused by optic atrophy due to a retrobulbar hemangioma not treated in time

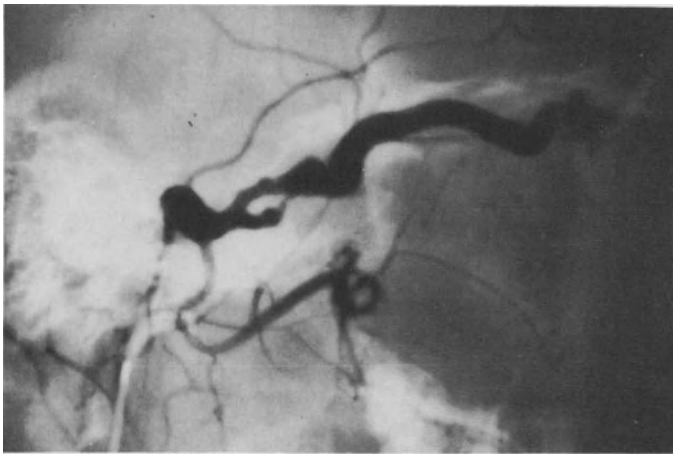

Fig. 4. Angiogram of the left external carotid artery: Dilatation of the ascending branch of the maxillary artery and direct connection to a massively enlarged superior orbital vein

Spinal Metastases of Gliomas

H. WALDBAUR, K. A. FLÜGEL, P. THIERAUF, and F. ALBERT

Whereas spinal metastases of medulloblastomas are often seen, this is much less frequent with intracranial gliomas. ZÜLCH (5), for instance, in the Handbook of Neurosurgery described one case of a primary cerebral glioblastoma with nodular metastases in the spinal canal. Further reports were given, among others, by CAIRNS and RUSSEL (1). We wish to call especial attention to two observations reported by THIERRY et al. (4); in both young patients an intracranial glioblastoma had become manifest primarily by compression of the spinal cord i.e. by metastases.

Our two patients had tumors of the astrocytoma type and, in both cases, an increase of malignity was found in the course of the disease. In the literature different data are reported as to this phenomenon. FINKEMEYER et al. (2) pointed out that the histological picture of recurring oligodendroglioma exhibited a significant increase of malignancy in a high percentage of cases. The same authors only sporadically observed similar changes in astrocytomas. However, GUILLOTTA et al. (3) found *no* increase in malignancy, as compared to the findings at the first operation, in only 6 of 50 recurring astrocytomas.

Case 1: In a 37-years-old patient an astrocytoma of the right temporal lobe was extirpated. Two-and-a-half years later an operation for recurrency was necessary. The findings of axial computerized tomography and brain scan had already indicated an increased tendency of growth. Histological findings revealed the typical signs of a glioblastoma.

Some weeks later pain and paresis of the right leg occurred. Lumbar myelography and CSF cell-count indicated a meningeal spreading of the tumor along the cauda equina. X-ray treatment of the lumbar region led to a transitory relief of pain. Thereafter, pareses of the other extremities developed as well as cachexia. The patient died 5 months after the second operation, following respiratory insufficiency. Autopsy revealed the tumor cavity to be filled with tumor tissue, which in some areas looked like a giganto-cellular astrocytoma and in others like a small-cell glioblastoma. Investigations of the spinal structures showed a meningeal gliomatosis with infiltration into the spinal cord of the upper cervical and lower thoracic region as well as a diffuse meningeal gliomatosis of the cauda equina.

Case 2: In a 37-years-old patient, a large right frontomedial space-occupying lesion was diagnosed. Computerized tomography was indicative of glioblastoma. Because of the growth in the region of corpus callosum surgery was not performed, and the patient was treated with dexamethasone. Furthermore, radiation therapy was applied in various series. Two years following the first hospital admission, an intra-

dural metastasis of the middle lumbar region (with the histological diagnosis of "astrocytoma") was extirpated and a 3 months later a further metastasis of the upper thoracic region, diagnosed to be a glioblastoma. During the last hospital stay there was an additional tumor of the right posterior horn in the computerized tomogram. Two months after the second operation the patient died at home, obviously due to increased intracranial pressure.

In this second patient it is striking that the comparison of both metastases, removed at an interval of only 3 months, shows a significant increase in malignancy. Since the frontal tumor was not treated surgically, and autopsy was not performed, we cannot decide about the histological structure and the development of the primary cerebral neoplasm. It is, however, not probable that this tumor should have experienced an increase of malignancy within three months. It appears more probable that it contained parts with different growth-tendency, and that different parts had caused metastases. An inhomogeneous structure of neoplasms can be seen relatively often and was also found at the autopsy of our first patient.

The question as to whether operation of spinal metastases of malignant intracranial gliomas is reasonable or not, cannot be answered generally. The decision will be made in the individual case depending on the speed of the neoplastic growth as such and on the general condition of the patient. In our second patient, who was able to walk around after both laminectomies and until shortly before death, we considered surgery to be indicated. However, in the patient who had findings indicative of diffuse spreading of the tumor, and who experienced rapid decline, spinal surgery was not performed.

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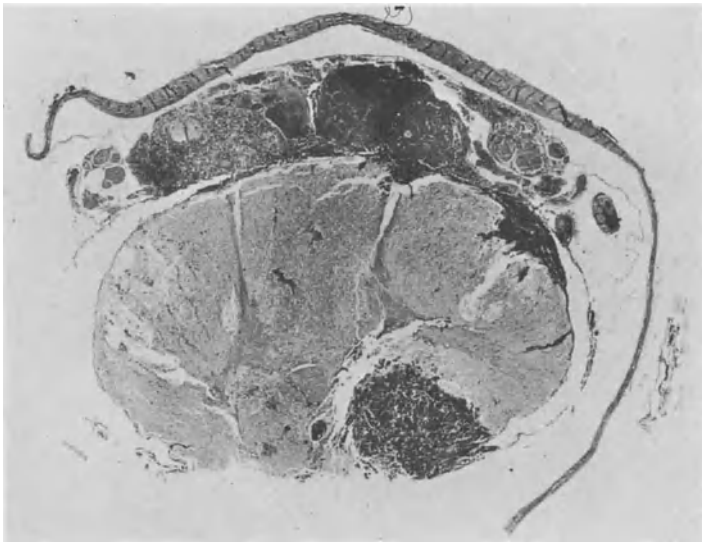

Fig. 1. Infiltration of the spinal cord in the case of a spinal metastasis (case 1)

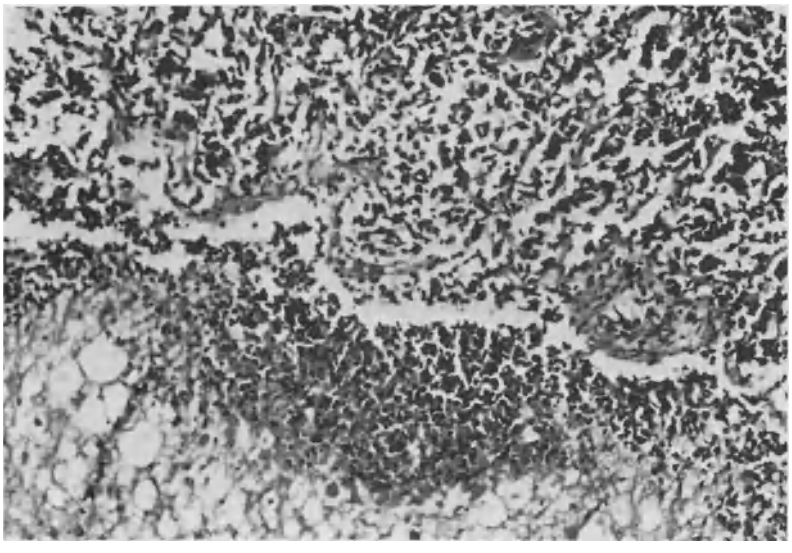

Fig. 2. Histological picture of case 1, showing a small-cell glioblastoma

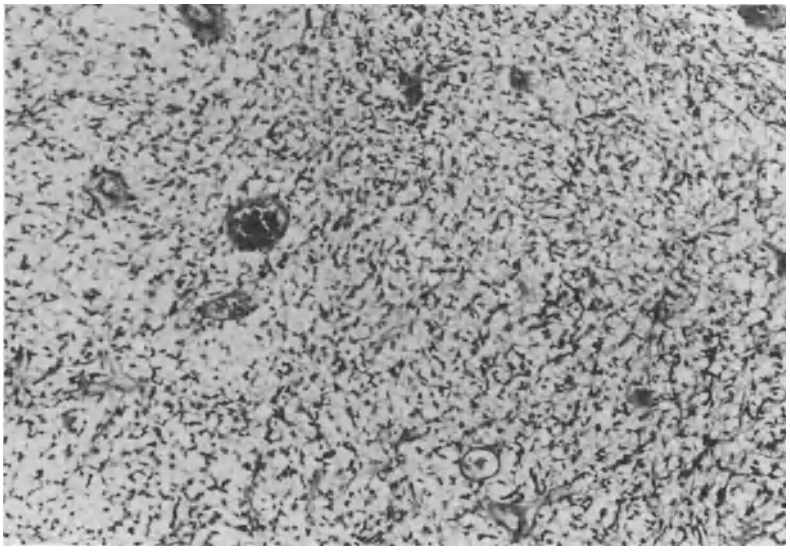

Fig. 3. Spinal metastasis of a frontal tumor (case 2) with the aspect of an astrocytoma

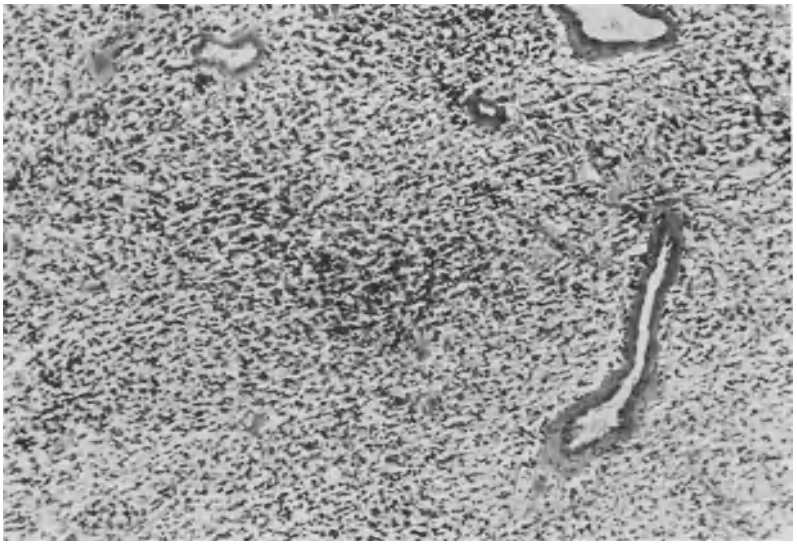

Fig. 4. Further spinal metastasis of the frontal tumor (case 2) having the aspect of a glioblastoma

Computed Tomography in Tumors of the Spinal Region

D.-K. BÖKER and K. SARTOR

Introduction

Tumors of the spinal region, i.e. neoplastic processes involving the intraspinal soft tissues, the spinal column or the paraspinal structures, are usually diagnosed by radiological means. In most cases more than one method has to be applied, ranging from plain radiography and conventional tomography to the various invasive contrast studies. Among the latter, angiography has importance only in selected situations (8, 9, 10), the major method being myelography. Myelography, on the other hand, is limited to the evaluation of tumors having some kind of effect on the spinal canal and its content. Also, it fails to visualize the lesion in the third (axial) plane. Performed with metrizamide, as increasingly preferred, it shows excellent detail (11, 12), but is not without hazard (6), even when comparatively low total amounts of the contrast material are administered (7). Therefore, several authors have investigated the diagnostic capability of computed tomography (CT) in tumors of the spinal region (1, 2, 3, 4, 5, 13, 14). Since reports on CT in larger series of such tumors are still few, the present communication appears justified. About half of the case material has been subject of a previous paper published by the senior author (14).

Material and Approach

During a period of 28 months, CT was performed on 77 patients, almost all of them adults, with neoplastic disease in the spinal region (Table 1). In most cases CT was an additional examination, either preceding or following conventional studies. Therefore, correlation of CT with these studies and evaluation of the relative merits of the various methods was almost always possible. Since 19 patients had more than one CT study, usually 2, maximally 5, and the majority of them was performed postoperatively, the total number of spinal CT procedures amounted to 105. In 34% of these examinations no contrast material was given. In 44% intravenous and in 22% intrathecal enhancement (metrizamide) was used. Intrathecal enhancement studies were performed either primarily or in conjunction with conventional myelography (primary and secondary CT myelography). Our examination technique (modes of contrast administration, positioning, scanning, level localization etc.) has been dealt with in previous reports (13, 14). Intravenous bolus enhancement has been used more frequently in recent CT examinations, though.

Results

Sixty-seven (87%) of all patients had CT findings of considerable informative value. In the great majority findings were of a kind that

Table 1. Location of tumors with positive and with equivocal CT findings

Predominant tumor location	Cervical	Thoracic	Lumbar	Sacral	No. of patients
Intramedullary	5	2	2	0	9
Extramedullary[a]	8 (2)	3 (3)	0 (2)	0	11 (7)
Extradural[b]	11 (3)	8	5	0	24 (3)
Paravertebral	6	14	2	1	23
Total	30 (5)	27 (3)	9 (2)	1	67 (10)

[a] Intradural; [b] Including intravertebral.

would have made at least a qualitative tumor diagnosis possible, being much more specific and detailed in many (Table 1). Ten patients (13%) had findings insufficient to allow a tumor diagnosis on the basis of CT alone and too insignificant to be of any complementary diagnostic value (Table 1).

There were 9 patients with tumors of (predominantly) intramedullary location. In the cervical region CT permitted the differential diagnosis "tumor vs. syringo(hydro)myelia", showing either no contrast filling of the central canal at CT myelography or no multisegmental cord cavities at non-invasive CT studies. Small cysts were found in 2 tumors, one cervical pilocytic astrocytoma and one (thoraco-)lumbar ependymoma (Fig. 1). CT with intravenous enhancement demonstrated one thoracic hemangioblastoma in a patient with v. HIPPEL-LINDAU's syndrome. A CT myelogram was the only study that showed the extramedullary (intradural) extension of a dysontogenetic, primarily lipomatous tumor in the thoracic region.

There were 18 patients with tumors of (predominantly) extramedullary-intradural location. In 11 cases CT demonstrated the lesion very well. This was particularly true of two calcified meningiomas, one cervical and one thoracic, which could be shown without contrast enhancement. It was also tru of most highly vascularized masses, particularly neurinomas, which could be demonstrated best after intravenous (bolus) enhancement (Fig. 2). Among the neurinomas 2 were of the hourglass-type. Extradural and paravertebral extension was considerable in both, but could be shown in only one. In 7 cases CT findings were equivocal or non-contributory: of the 2 cervical lesions one (metastasis) was very small, the other (neurinoma) suboptimally demonstrated due to patient motion and scanner malfunction. Of the 3 thoracic lesions one (meningioma) was more or less masked by contrast material 24 h after conventional metrizamide myelography. Two others, one neurinoma and one meningioma, were suboptimally visualized due to patient motion and scanner malfunction respectively. Of the 2 lumbar lesions (multiple neurinomas and multiple metastases respectively) both could only be suspected due to considerable picture noise inside the dural sac and insufficient (non-bolus) intravenous contrast enhancement.

There were 27 patients with tumors of (predominantly) extradural and intravertebral location, mostly metastases. In 24 cases CT demonstrated the main features of the mass in sufficient detail. Particularly well depicted were narrowing of the spinal canal secondary to osteoblastic changes, bone destruction, and intra- and paraspinal soft tissue involvement. In 3 patients with multiple vertebral metastases, involve-

ment of the segments studied by CT remained equivocal since the lesions seen were very small and difficult to differentiate from structural changes common in the ageing spine.

There were 23 patients with tumors of (predominantly) paravertebral location. CT was of great value in all of them. As a matter of fact, it was superior to all other radiographic methods: It demonstrated the exact topography, showed the kind and degree of bone involvement and gave some information on type and biological behavior of the lesion. In the thoracic region CT studies without contrast enhancement were sufficient in almost all cases. In the lumbosacral and cervical regions intravenous enhancement, preferably by bolus injections immediately before the scan was frequently found necessary. In this way neighboring major blood vessels could be better localized. Also, the overall size of the tumor, including its possible intraspinal extension, could be far better assessed (Fig. 3).

Discussion

CT is a method of axial radiography. It has, therefore, a distinct advantage over the conventional radiological methods commonly used to diagnose tumors of the spinal region: Topographic relationships between the lesion and neighboring structures are excellently shown. This is of particular importance in paravertebral and intraspinal masses. Tumors with predominantly paravertebral or intravertebral location can frequently be evaluated without any contrast enhancement. Intravenous enhancement may be used to better demonstrate extra- and intraspinal soft tissue involvement in well vascularized tumors. When intraspinal masses are small, not well vascularized, or located in the thoracic/lumbar region, intrathecal contrast enhancement may still be mandatory in order to visualize the lesion. However, in primary CT-myelography the total amount of contrast material necessary to enhance the subarachnoid space is very low as compared to conventional (metrizamide) myelography (2, 13, 14).

CT in conjunction with conventional myelography, secondary CT myelography, demonstrates the tumor in the third plane, and again provides information on topographical relationships which might be otherwise difficult to obtain; it is an ancillary procedure.

Certainly, calcified intraspinal tumors or lipomas of sufficient size need not to be enhanced to be visible on CT (14). Improvement of the quality of non-invasive intraspinal soft tissue demonstration can be awaited from new CT technology, offering shorter scanning-times (elimination of the effect of biological motion) and better contrast resolution within the spinal canal. Also, with new scanners level localization of spinal tumors will be much easier than with older machines (as the one used in our study). CT depicts soft tissue as well as bone, and allows slice-by-slice study of the object. Therefore, it could well be used to reduce the number of non-invasive radiographic procedures in patients with tumors of the spinal region, particularly (conventional) tomography.

Conclusion

CT is a promising radiodiagnostic method in the evaluation of tumors located in the spinal region: It provides information otherwise not obtainable, particularly as regards topography in the axial plane. It also reduces the number of invasive studies, and will probably have a similar effect on conventional tomography.

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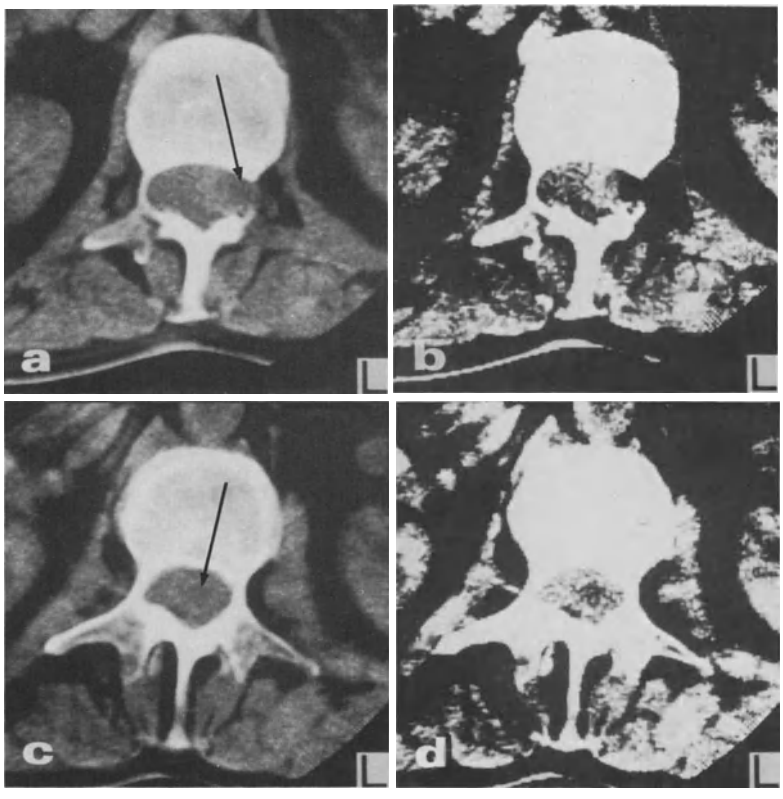

Fig. 1 a-d. Intramedullary tumor location: Ependymoma of conus medullaris (CT scans without contrast enhancement). a, b Scan at the level of L 1, at low and high contrast window setting respectively, showing widened spinal canal with excavation of vertebral body and marked thinning of pedicles; inhomogeneous appearance of intraspinal soft tissues, area of low density medial to extremely thin left pedicle (a, *arrow*) probably representing tumor cyst. c, d Scan at level of L 2, at low and high contrast window setting respectively, showing less thinning of pedicles and less widening of spinal canal; area of low density in center of intraspinal soft tissues (c, *arrow*) probably representing additional tumor cyst

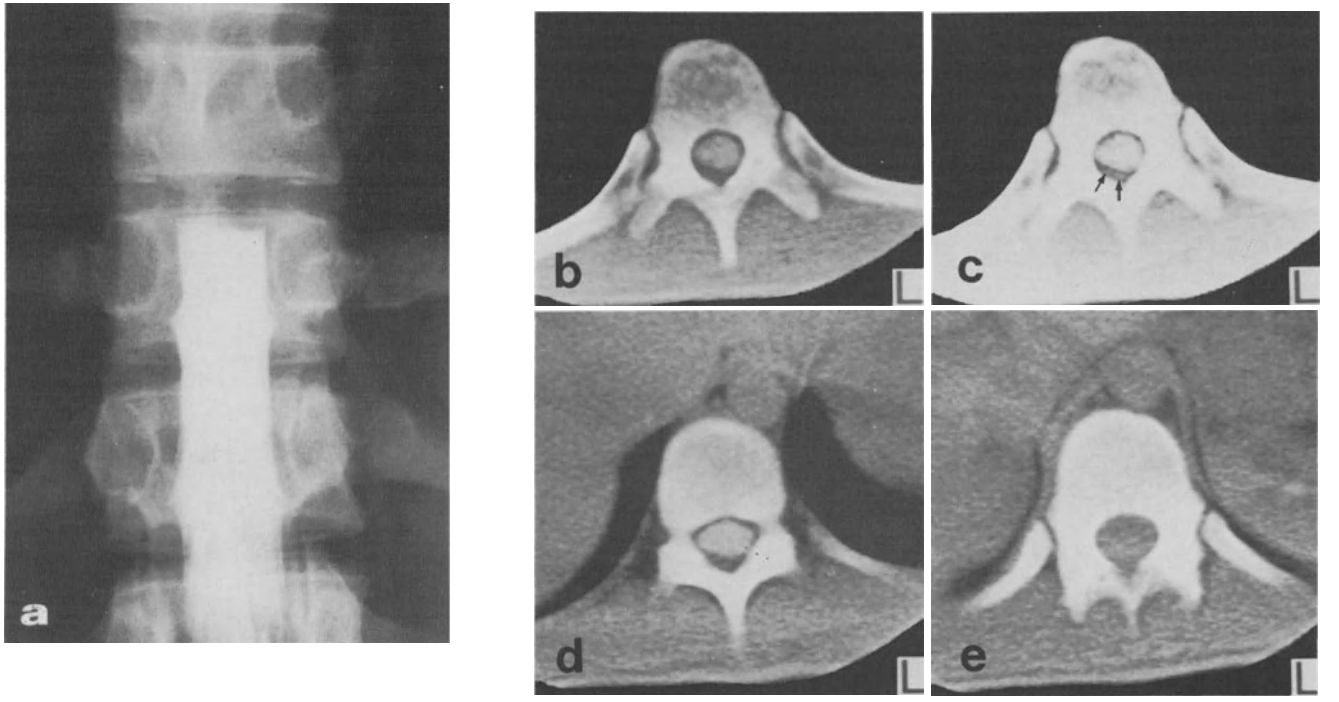

Fig. 2 a-e. Extramedullary (intradural) tumor location: Two adjacent thoracic neurinomas. a Ascending metrizamide myelogram showing total block at upper of D 11; exact position of spinal cord relative to space occupying lesion difficult to evaluate. b, c CT scan at the level of the upper portion of D 10 after intravenous bolus enhancement (two different window settings, scan performed during deep inspiration) showing upper neurinoma; spinal cord extremely flattened and posteriorly displaced (c, *arrow*). d Scan at the level of the lower portion of D 10 after intravenous bolus enhancement (performed during almost exspiration) showing lower neurinoma. e Scan at level of D 12 with normal appearance of intraspinal soft tissues

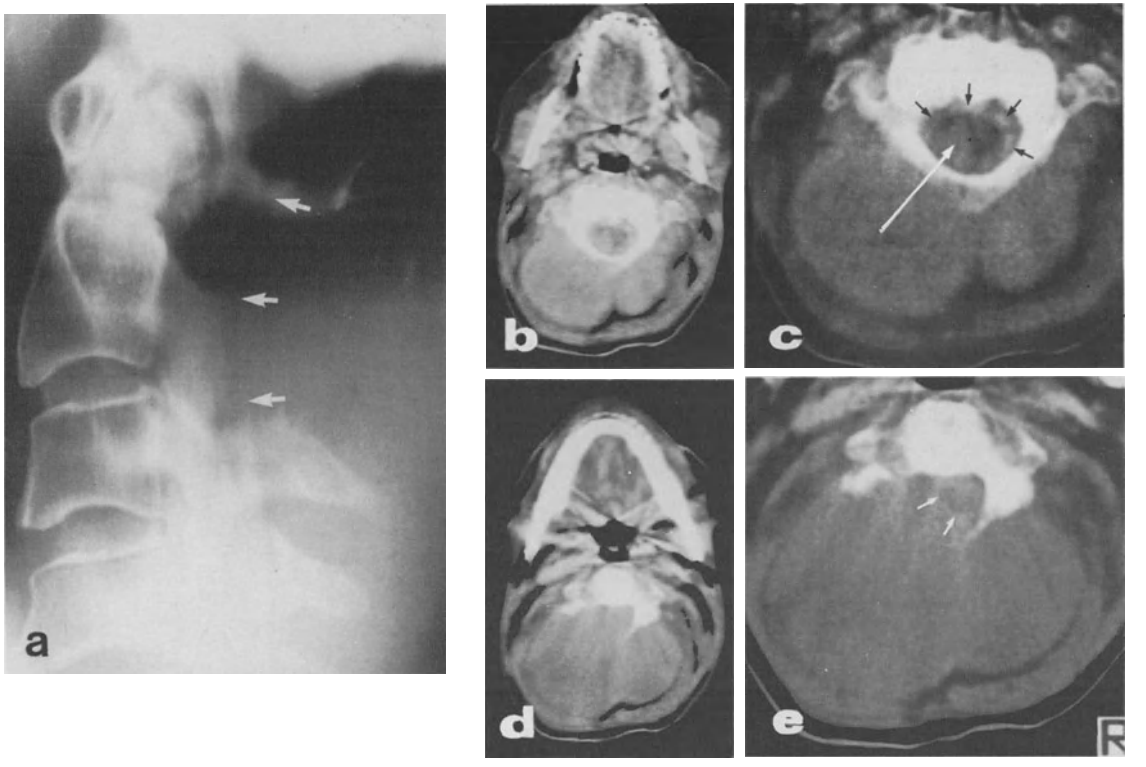

Fig. 3 a-e. Extradural, intravertebral and paravertebral tumor location: High cervical metastasis of an undifferentiated carcinoma. a Midline metrizamide myelotomogram showing marked compression of dural sac at level of C 1 and C 2 *(arrows)*; extensive destruction of neural arch of axis. b, c CT scan at level of C 1 after intravenous bolus enhancement (full picture and quadrant enlargement) showing a mass encircling (c, *small black arrows*) and compressing dural sac from left (c, *long white arrow)*; tumor invasion of posterior arch of atlas, extensive involvement of paravertebral (neck) musculature, particularly on left. d, e Scan at the level of C 2 after intravenous bolus enhancement (full picture and quadrant enlargement) showing marked compression of the dural sac (e, *arrows*), destruction of the neural arch of the axis and very extensive paravertebral soft tissue infiltration with central necrosis

Preliminary Results with the Microsurgical Lumbar Discectomy

U. EBELING and H. J. REULEN

Since October 1977 microsurgical lumbar discectomy according to the technique of CASPAR (1) was performed in about 700 patients. 150 consecutive patients were evaluated 3-12 months postoperatively concerning the outcome of surgery, complications and recurrent herniations. CASPAR advocates the advantages of the microsurgical approach because of minimum alteration of the anatomy, the lower risk of complications and the optimum visualization of the operative field. We have therefore tried to compare our results with those treated with the conventional technique. For that purpose the result of the BERLIN-JOINT follow-up study (1977) (8), consisting of 3238 cases from 15 neurosurgical clinics in Germany (FRG) and Austria, as well as the result of the study of MATTMANN (3784 cases) (5) were used for comparison.

Results and Conclusions

With the help of an adequate praeoperative myelogram and neurological examination, a selective monosegmental approach (interlaminar fenestration at one level) was performed in 84% of our patients. Furthermore, an attempt was made to preserve the integrity of the facet joint. In 86% the discectomy could be restricted to one level; discectomy at two levels was done only in 4%. Hemilaminectomy becomes necessary in 1,3% of the patients. In comparison, the conventional technique of fenestration of the interlaminar space at two levels was performed in 43%, discectomy at two levels in 17,2% and hemilaminectomy was necessary in 27,3%. It may be concluded that the surgical trauma to muscles, the lumbar spine and the facet is less with the microsurgical approach (Table 1).

The refined instruments (devised by CASPAR) and the surgical microscope with its optimum visualization of the operative field allowed a careful handling of the nerve root and dura and an easier identification and removal of the protruded disc material. This reduced the trauma to the neural structures. As a result there is less postoperative pain and particularly elderly patients may be mobilized earlier. As shown in Table 2, the incidence of increased neurological deficit, small dura opening (CSF-leak) and catheterisation of the bladder was reduced as compared to the conventional technique. The incidence of wound infections was also significantly lower.

The incidence of repeat surgery following the microtechnique, i.e. true repeated herniations at the same level, adhaesions of the root or entraptment of the root by scar tissue did not essentially differ from the data reported from the conventional technique. In our small series we observed 4% recurrent herniations at the same level (Table 3).

Table 1

Extent of surgery	Microsurgical technique (%) EBELING (n = 150)	Conventional technique (%) OPPEL et al. (n = 3232 (8))
Interlaminar fenestration at one level	83,7	50,0
Interlaminar fenestration at two levels	16,7	43,0
Laminectomy	0,0	4,5
Hemilaminectomy	1,3	27,3
Discectomy at one level	95,3	77,5
Discectomy at two levels	4,0	17,2
Discectomy at three levels	0,0	0,9

Table 2. Complications

	Microsurgical technique (%) EBELING (n = 150)	Conventional technique (%) Average was calculated from the data of following authors (6, 8, 9, 10, 11)
Discitis	2,5	1,5
Wound infection	2,7	8,1
Dura opening	2,7	3,7
Perforation	0,0	-
Increased neurological deficit	8,0	15,8
Cystitis	4,0	10,3
Mortality	0,0	0,27

Comparison of the results of the outcome of surgery with those of most other authors is difficult, since the criteria used for the assessment of the results differ considerably. We used the criteria of LA MONT (3) who considered relief of radicular pain and restoration of professional capacity as equally important for the assessment of the result of surgery. Consideration of only one of the two factors tends to favour overestimation. In our series, for instance, 92% of the patients at demission from the hospital reported a complete or essential relief of sciatic pain, 5% were unchanged (in 3% the question remained unanswered). Thus, under the exclusive aspect of pain relief, 92% of the patients considered the result of surgery as successful.

The result of the outcome of surgery 3-12 months postoperatively based on the records, a questionnaire (returned by 93,3% of the patients) and a subjective self-assessment by the patients, is shown in Table 4.

Table 3. Repeat operations

Technique	No. of patients	Repeat surgery Total (%)	True repeat herniation (%)	Repeat herniation at another level (%)	Adhasesions and scars (%)
Microsurgical technique					
EBELING	150	7,4	4,7	2,0	0,7
Average[a]	827	6,6	3,5	2,0	0,9
Conventional technique					
Average[b]	24.745	7,4	4,5	3,2	1,1

[a] Average is calculated from data of following authors: 2, 14, EBELING
[b] Average is calculated from data of following authors: 3, 4, 5, 8, 12, 13

Table 4. Outcome of surgery

Technique	Satisfactory (%)	Slight improvement (%)	Unsatisfactory (%)
Microsurgical technique			
EBELING	82,0	-	18,0
Average[a]	89,0	-	8,0
Conventional technique			
Average[b]	67,5	26,1	17,4

[a] Average was calculated from data of following authors: 2, 14, EBELING.
[b] Average was calculated from data of following authors: 3, 4, 7, 8, 9, 11, 12.

In 70% the result may be considered as excellent and good, which means full professional capacity in previous employment *and* complete relief of sciatic pain with occassional mild discomfort, needing no analgesic medication. In a further 12%, the result was satisfactory, i.e. the patients returned to economic productivity and had a distinct improvement of the sciatica, but needed analgesic medication. Thus 82% of the patients achieved an excellent, good or fair result following one procedure. In 18% the result of surgery was unsatifactory either concerning the pain, the professional capacity or both. Of this group, 9% had some improvement of pain, but were not able to work 3-12 months postoperatively, the other 9% considered themselves as unchanged or worse.

In addition to our results, Table 4 contains recently published data of GOALD (2) and WILLIAMS (14), both using a microsurgical technique of disc surgery. The pooled data of the microtechnique may be compared with those of the conventional technique.

Summary

With the microsurgical lumbar discectomy the surgical trauma to muscles, the lumbar spine and the facet joint is smaller than compared to the conventional technique of lumbar disc surgery. The incidence of wound infections, CSF-leaks and surgical neurological deficit also is lower. However, the incidence of recurrent herniation remained unchanged. It seems, that the outcome after surgery is somewhat more favourable following microsurgical lumbar discectomy. It must be stressed, however, that the number of patients is too small and the time interval after surgery too short to make a definite conclusion.

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Internal Fixation of Cervical Spine Injuries

A. KARIMI-NEJAD

Early surgical reposition of cervical spine injuries in anatomical position with concurrent relief of the neurogenic parts or the spinal cord should be firm enough to replace in full any external fixation, as the latter involves nursing handicaps and complications. The difficult treatment in an acute stage as well as rehabilitation of patients with severe neurological deficit, even with irreversible paraplegia, will show much better results, if early mobilisation is achieved by sufficient fixation. Late deficits or additional handicaps which may result if the vertebral column heals in a false position can be avoided.

Despite relatively favourable results achieved by the surgical treatment of cervical spine injuries, there are frequent objections. These claim that

1. surgical treatment cannot fully replace external fixation and, thus, does not offer any real advantage for patients with severe neurological deficit, when compared to the good results of conservative treatment;
2. quite frequently dislocation or false position recurs, especially with dislocation or compression fractures (4, 5).

After the encouraging initial results achieved through early surgical treatment of cervical spine injuries (13, 1, 3, 10, 8, 7), we have tried in recent years to fix the injured segments of the cervical spine to such an extent that additional external fixation, which makes nursing difficult, is lo longer necessary. The reappearance of dislocation or angulation can no longer occur.

For surgical treatment, cervical spine injuries have to be subdivided in 2 groups due to the pathomorphological changes through trauma and the given anatomical situation.

1. Injuries of the upper cervical spine, i.e., higher than C3 and
2. injuries of the lower cervical spine, i.e. at the level of C3 and below.

Injuries of the upper cervical spine are:

1.1 the typical Hangman's fracture with or without an additional fracture of the axis body,

1.2 fractures of the odontoid process.

Most injuries of the upper cervical spine - if survived - are hardly, if at all, accompanied by neurological deficits. Such patients are,

however, highly endangered because of the considerable instability of their cervical spine. According to our own observations in recent years, neurological deficit, even leading to tetraplegia and death may occur as a result of incorrect movement of the patient on first admission or during transport.

The typical Hangman's fractures with a fracture of transversal arch of the 2nd cervical vertebra and - very often - slight angulation of the 2nd vertebra to the third, do not, as a rule, require surgical treatment. With cooperative patients a relatively good position can be achieved by a removable plaster. But, despite prolonged external fixation, an increasing angulation of the fractured segments, i.e., a dislocation of the 2nd to the 3rd vertebral body may occur.

With severe primary dislocation, especially with increasing angulation - despite immobilisation - we consider surgical treatment to be indicated even more, since, the patient is then no longer handicapped by the very unpleasant external fixation.

Contrary to the typical Hangman's fractures, concurrent fracture of the axis body necessitates surgical treatment. According to our experience, the fracture of the axis body very often leads to an increasing angulation despite external fixation. Healing in false position may lead to severe neurological deficit with subsequent exitus - even after 10, 20 and up to 30 years - (6).

Hangman's fractures accompanied by an additional fracture of the axis body lead to a tilting forward of the odontoid process and the atlas and, subsequently, of the skull. As a rule the dislocation of the 2nd vertebra to the 3rd is not very considerable or course-determining, since the spinal canal is widest at this level. In the acute stage, cord lesions occur either through scissor movement of the injured segment or, due to false healing through compression of the spinal canal in the subsequent course. Since instability is due to a fracture of transversal arch and/or fracture of the axis body, the results of anterior fusion at this level are not very satisfactory either. The purpose of surgical treatment can only be to ensure that the fractured axis body or odontoid process and, subsequently, the atlas and skull are restored and fixed in the anatomical position. Posterior fusion of the upper cervical spine with the occiput as recommended by CONE and TURNER (2) (1937), and later on by ROBINSON, SOUTHWICK (9) (1960) and by SCHÜRMANN (11) (1979) for rheumatic atlanto-axial deviations, is mainly done in order to fix the atlanto-occipital segment. However, all kinds of the so-called Hangman's fractures or fractures of the odontoid process are accompanied by instability, i.e., anatomic deformation at C 1/2. Since the atlanto-occipital segment is not injured, fixation of this segment is superfluous, as this would only lead to an unnecessary restriction of movement. For this reason, we carried out a bilateral posterior fixation, as is shown in Fig. 1. With the patient in a resting position and under a traction of 10-12 kg, a posterior approach of the upper cervical spine is made and - under sight as well as radiographic control - a wire having a diameter of 0.6-0.8 mms is introduced on both sides and passed under the transversel arches of the 1st to the 3rd cervical vertebrae. By subsequent traction on both sides of the posterior arches of the atlas, both axis body and odontoid process and, in this way, the skull, can be brought back into the anatomical position. This position is then fixed by two bone grafts taken from the tibia, which serve as supporting beams, and which are connected to the wires by bore-holes, as shown in Fig. 1. This position is now maintained by the bone grafts, so that there is no tension on the vertebral arches, which would otherwise bring about the risk of a later fracture of the transversel arch.

In order to avoid osteosynthesis which would result in a lasting restriction of movement of the injured segments and, especially, those not injured, the bone grafts are fixed with their cortical side resting on the vertebral arches. As shown in Figs. 3 and 6, in the advantage of this position is the fact that a complete absorption of the bone grafts resting in the soft parts takes place over a period of time that is individually different, but, generally ranges between 6-18 months. In this period of time, the fracture will be fully consolidated and, due to the absorption of the bone grafts, there will be no more reduction of movement.

Typical Hangman's fractures without fracture of axis body are treated similarly, as shown in Fig. 1, but just by *posterior fusion* of the *1st and 3rd vertebra*. The fractured segments are pressed together (6). With dislocation fractures, however, bilateral *posterior fixation* of the *1st and 2nd vertebra* will be sufficient. In order to achieve a lasting fixation or osteosynthesis in cases of *pseudoarthrosis of odontoid process*, we decided to fix the *tibia bone grafts* with their *spongiosa side resting* on the *transversel arches* (6).

2. According to the results obtained so far, surgical treatment of injuries of the lower cervical spine is indicated in the following cases:

2.1 axial deviation,
2.2 simple dislocation,
2.3 fracture dislocation,
2.4 compression fractures,
2.5 severe compression fractures.

As the clinical course of lasting complete transsections at C4 and higher always leads to exitus, we decide on surgical treatment only in such cases, where conservative treatment with traction results in a decrease of neurological deficit indicating that the transsection lies below C4.

Severe neurological deficits after cervical spinal cord injury *without recognizable further anatomical or radiological impairment* are seldom. If they occur at all, the are caused by an isolated disc prolapse. They are, however, the result of a spinal contusion. We shall not discuss the question of how often a spinal cord injury of either a normal or a pre-damaged cervical spine may lead to an isolated disc prolapse. Contrary to injuries of the upper cervical spine, all injuries of the lower cervical spine are accompanied by a traumatic disc lesion with course-determining compression prolapse of the soft parts into the narrow spinal canal. For this reason, a ventral approach is indicated in all cases of lower cervical spine injury to relieve the very narrow spinal canal and the epidural space of compressing soft parts. Axial deviations and simple dislocation following *intraoperative reposition* generally require a typical anterior fusion with subsequent external fixation by means of a removable jacket for a period of 6-8 weeks, provided the patients are cooperative and able to walk.

In patients *with severe neurological deficit*, external fixation by a thorax jacket may lead to serious decubital ulcers. *Restless patients* may damage their jackets which, in turn, may lead to additional *axial deviations* or *dislocation* and a *reappearance of dislocation* or *increasing angulation*. Despite external fixation, there is always a danger of a *recurrence of the dislocation* or *angulation*, especially with *dislocation fractures*. That is why we carry out an *internal*

fixation in all *dislocation fractures* but also in *restless* or *paraplegic* patients with *axial deviation* or *dislocation*. After intra-operative reposition and clearing of the intravertebral and epidural space, two wires with a diameter of 0.5-0.7 mms are introduced deep into the neighbouring dislocated vertebral bodies and passed through. In such cases, too, autogenic bone grafts are used for fixation. At the same time, a wire is passed through the bone graft to fix its position. After that, both the wires going through the bone graft and through the vertebral bodies are fixed to a tibia bone graft, which serves as a supporting beam and is fixed in anterior position over both vertebral bodies (see Fig. 4).

In recent years, this wire fixation has become a routine procedure for us in all cases of injuries of the lower cervical spine at all the above mentioned levels (6). This internal fixation guarantees full mobilisation of the patient. Patients feel that an additional collar, which does not handicap nursing, is quite helpful.

Generally, compression fractures with transversal dislocation of fractured vertebral body into the spinal canal are accompanied by severe neurological deficit. In most cases, the vertebral body is fractured at the root of the transversal arch and dislocated posteriorly into the spinal canal. This leads to a complete destruction of the neighbouring discs. From their - partly - own experience, VERBIEST (13, 14) or SCHÜRMANN et al. (12) recommend a vertebral body replacement by an autogenic bone transplantation taken from the iliac crest or from tibia. What we did was to bring back by a wire fixation going around the vertebral body (see Fig. 6) into the anatomical position the dislocated fractured vertebral body. To do this, the neighbouring intervertebral spaces are cleared and the epidural space, too, is cleared from soft parts. After reposition of the vertebral body into the anatomic position under the microscope and X-ray control, two wires are passed around the fractured vertebral body epidurally. This is done by technical means and without any risk or damage to the epidural space or the cord. After fusion of the neighbouring intervertebral spaces with autogenic tibia bone grafts, the vertebral body is fixed to a tibia bone graft reaching over the proximal and distal uninjured disc which serves as a beam due to the epidural wires. We have done this wiring of compression fractures at all levels of the lower cervical spine with similarly good results (see Fig. 6).

With *severe compression fractures* the vertebral body is splintered and the bony fragments are dislocated into the spinal canal in an anterior and/or posterior position. In most cases, however, part of the posterior border of the vertebral body is still existent, and it is only in such cases that we carried out a partial replacement of the vertebral body followed by internal fixation through wiring of this partly replaced vertebral body, as is done with compression fractures (see Fig. 6d).

Table 1 shows the surgical management and respective fixation procedures of cervical spine injuries. According to our experience, all injuries higher than C3, i.e., with isolated fractures of the odontoid process and different kinds of Hangman's fractures, varied internal posterior fusion is recommendable. With injuries of the lower cervical spine, however, the anterior approach is generally indicated. With axial deviations and dislocations, anterior fusion with external fixation will do, provided the patient is cooperative and able to walk. If, however, the patient is restless or paraplegic, or, with dislocation fractures or compression fractures, additional internal fixation is indispensable. Vertebral body replacement is necessary only in cases of severe compression fractures.

Table 1. Surgical management of cervical spine injuries

	Nature of injuries	Surgical procedure
Upper cervical spine ↑ C3	1.1 Hangman's fracture without or accompanied by axis fracture	Varied internal posterior fusion
	1.2 Fracture "dislocation" of the odontoid process	
Lower cervical spine ↓ C3	2.1 Axial deviation	Anterior fusion and external fixation
	2.2 Simple dislocation	
	2.3 Fracture dislocation	Anterior fusion and varied internal fixation
	2.4 Compression fracture	
	2.5 Severe compression fracture	Vertebral body replacement and internal fixation

Results of Surgical Treatment

Table 2 shows the cases of 80 patients with cervical spine injuries, who received surgical treatment, according to the nature and level of injury.

In order to facilitate the presentation of the results obtained according to the neurological deficit, the total of 80 patients was subdivided into 5 groups, just as we have done before (6):

1. Patients without neurological deficit,
2. patients with radicular deficit,
3. patients with incomplete transsection, but able to walk,
4. patients with incomplete transsection, but unable to walk, and
5. patients with total transsection.

Figure 7 shows the late results (horizontal column) depending on the preoperative neurological syndrome (symbols) and the level of neurologic deficit (vertical column). The high rate of mortality of 27% was mainly due to the preoperative complete transsection at or higher than C4. Apart from the relatively good results, it is remarkable that a total of 4 patients with primarily complete motor transsection managed to recover their ability to walk.

Table 2. Level and nature of cervical spine injuries (80 cases)

Upper cervical spine ↑ C3		Hangman's fracture without and with fracture of axis					8
		Fracture of the odontoid process					6
Lower cervical spine ↓ C3	**Level**	**Discs**	**Axial deviations**	**Dis-locations**	**Fracture dislocations**	**Compression fractures**	**Total**
	C3 3/4	2	1	1			4
	C4 4/5			5	3	3	11
	C5 5/6	4	1	7	7	6	25
	C6 6/7	1	1	10	10	1	23
	C7 7/Th1			2		1	3
	Total	7	3	25	20	11	80

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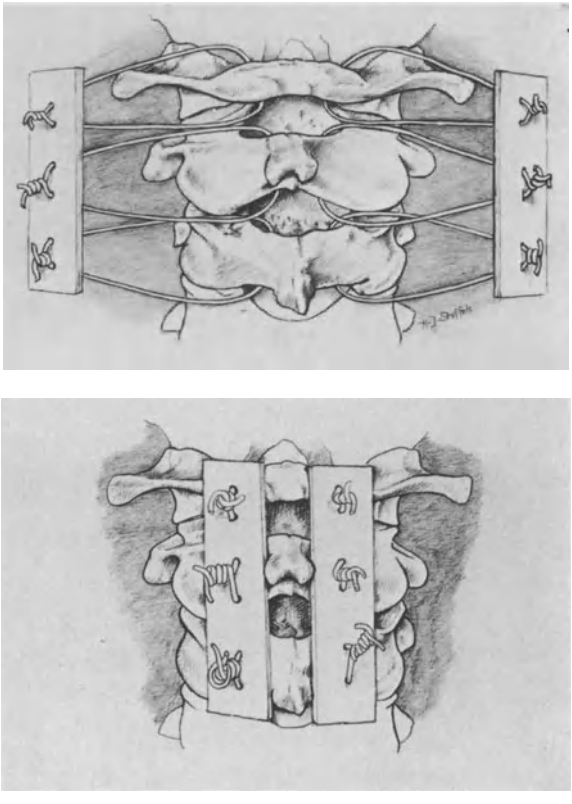

Fig. 1. Posterior fixation of upper cervical column; needs to be varied depending upon the level and type of injury (see text)

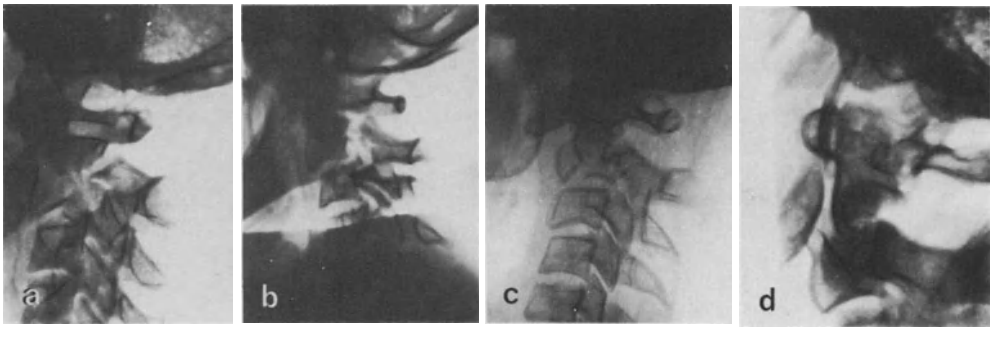

Fig. 2 a-d. Type of upper cervical column injuries; postoperative status, see Fig. 3. a Hangman's fracture accompanied by axis fracture; b Hangman's fracture; increasing angulation despite prolonged external fixation; c axis-body fracture; d fracture "dislocation" of the odontoid process

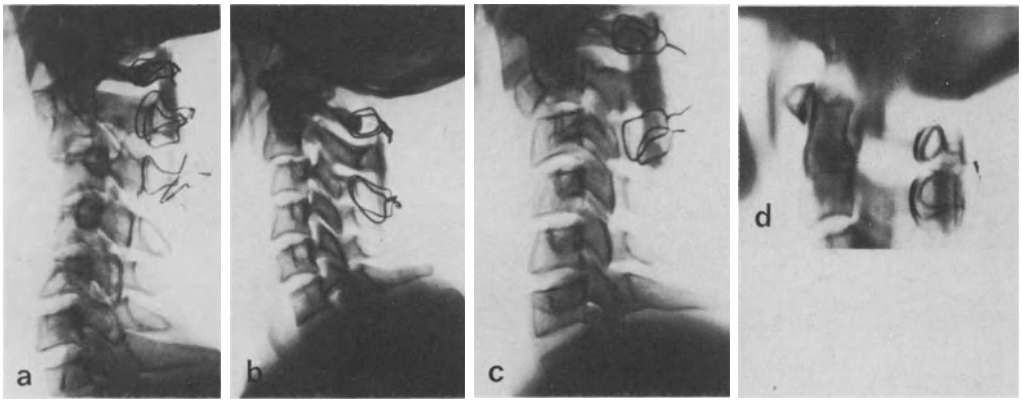

Fig. 3 a-d. Postoperative status of posterior fusion of upper cervical column; preoperative status, see Fig. 2. a 6 months after operation; b 12 months after operation; c 1 month after operation; d 4 months after operation

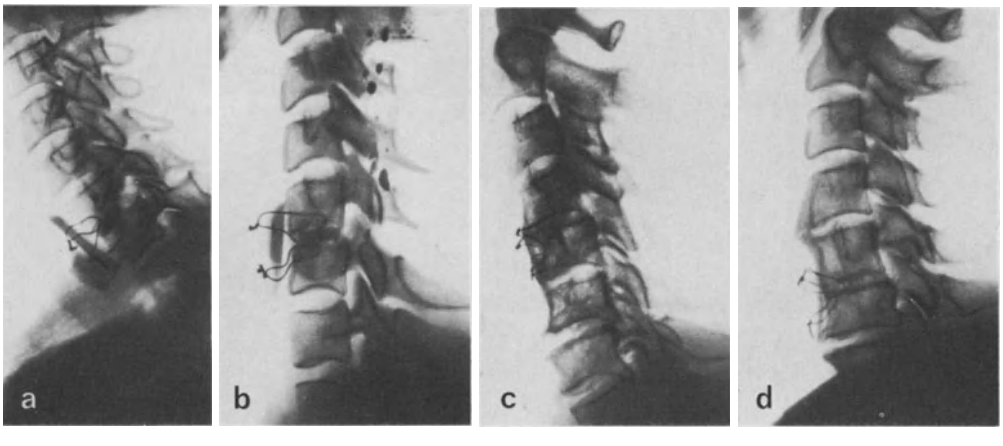

Fig. 4 a-d. Internal fixation of fracture dislocations at different levels of the lower cervical column. a 7 days after operation; b 7 months after operation; c 24 months after operation; d 30 months after operation

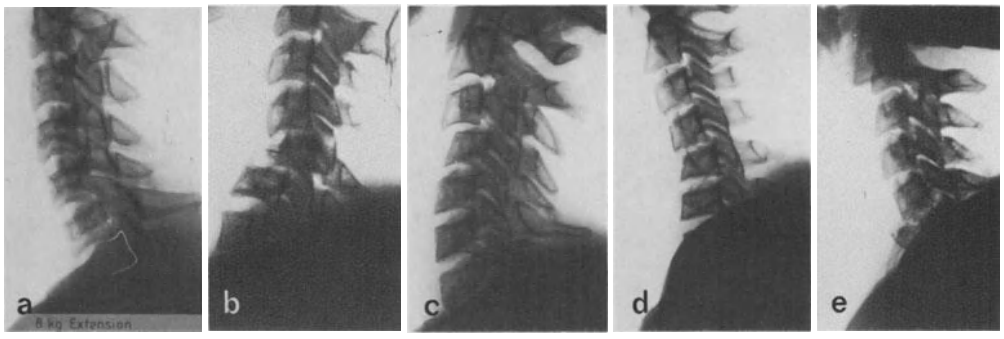

Fig. 5 a-e. Compression and severe compression fractures with slight or extreme transversal dislocation of fractured vertebral body; post-operative status (see Fig. 6). a Compression fracture of C7; extension 8 kg; b compression fracture of C5; c compression fracture of C4; d Compression fracture of C5; e severe compression fracture of C7

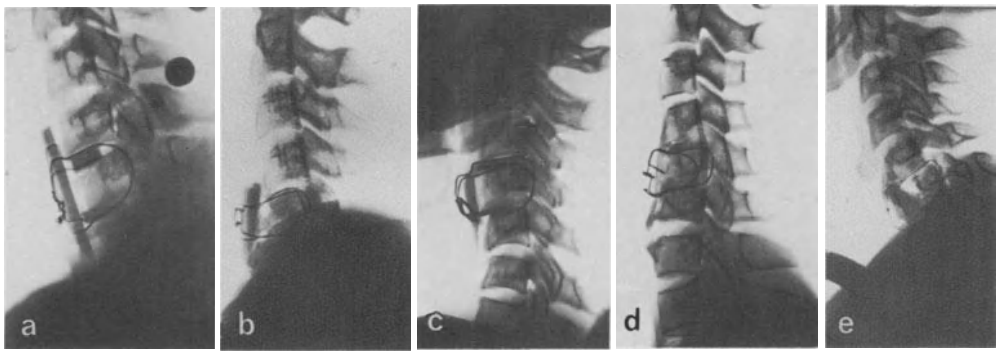

Fig. 6 a-d. The radiographs after internal fixation of compression fractures; preoperative status (see Fig. 5). a 2 days after operation; b 1 month after operation; c 12 months after operation; d 2,5 years after partial replacement of vertebral body + internal fixation. Note: The radiographs reveal depending upon the time after operation the partial or complete resorption of bone-grafts

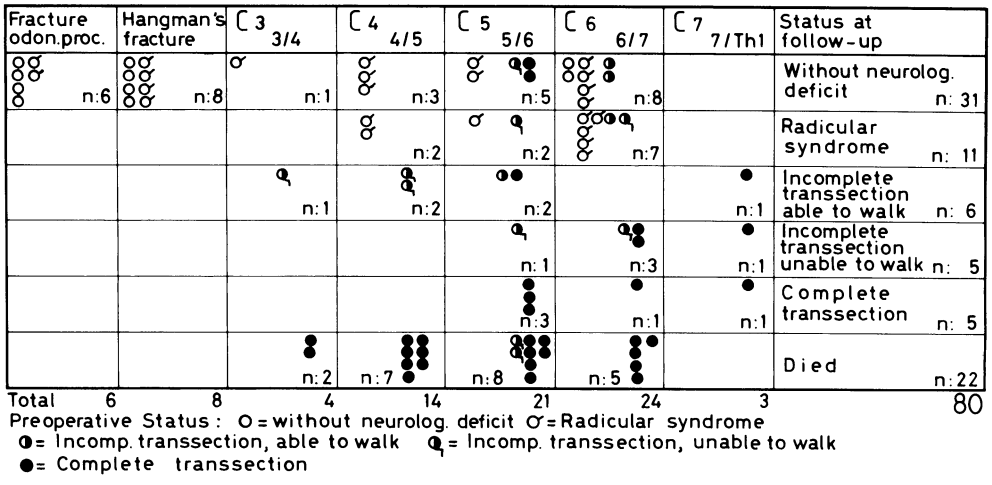

Fig. 7. Results of surgical treatment in relation to primary neurological syndrome and level

Prognosis and Therapy of Metastatic Tumors of the Spine

D. RINKER

Introduction

The consequent surgical treatment of all solitary epidural space-occupying lesions of the spine was proposed in 1975 at the 5th International Symposium of Neurology, Neuroradiology and Neurosurgery (5, 10). During the past years the number of voices has increased that proclaimed primary radiotherapy (4, 11) or asked for an assessment of this or that form of exclusive therapy (13).

As regards the obvious uncertainty about the therapy of choice, we analysed all pertinent cases treated by our unit.

Methods

Data of 77 cases treated for metastatic malignant spinal tumors in the Department of Neurosurgery of the University of Tübingen from 1959-1980 were evaluated. Results were assessed by comparing pre- and postoperative conditions as well as noting the preponderant prognostic factors.

Results

1. Mean age of our cases was about 47 years. Sex distribution of male to females was 3:1. In 48 cases a malignant disease was unknown on admission. In 23 of these a previously silent primary process could be detected.

2. Distribution of primary tumors was as follows: *44 metastases of carcinoma* (13 anaplastic, 11 hypernephroid, 9 bronchial 5 prostatic, 2 genital of ovarian and uterine origin, 2 mammal, 1 thyroid and 1 gastric)
   12 metastases of solid sarcoma
   4 malignant melanomas
   6 plasmocatomas
   3 Hodgkin's disease and lymphoid sarcoma
   8 tumors of different rare types (pleuromesothelioma, neuroblastoma, malignant phaechromocytoma, Wilms' tumor of the kidney, 4 unidentified tumors).

On admission we found that *more than 3/5 of the patients were already paraparetic, half of them evem paraplegic.* Mean duration of *symptom development* usually lasted *longer than 90 days,* while paraparetic lesions were present for more than 72 h in the majority. In single cases, signs of paraspasticity had existed for more than 5 months.

Clinical results were as follows: Neurological *improvement* was reported *in 13, no change in 52,* and *deterioration in 12* of the 77 cases. Six patients died of their disease within the immediate postoperative phase of 30 days. Previously incurable back and radicular pain was eliminated, or at least palliated, in 51 cases.

Level distribution showed a predominance of the thoracic spine with 45 cases. Tumor-growth appeared from the paravertebral to vertebral and intraspinal space in 29 cases, while in 16 the vertebral bone and the intraspinal space were afflicted. In 9 cases growth developed exclusively in the spinal epidural space.

Predominant therapy was the combination of laminectomy and consecutive radiotherapy in 52 cases. Only one patient in this series received no treatment at all on behalf of his extremely poor condition.

Mean survival time was about 1,95 years. In all 37 cases with the tumors of worst prognosis (anaplastic, hypernephroid and bronchial carcinomas as well as malignant melanomas) death occurred within less than 6 months following the treatment.

Discussion

The results of our series, with 17% of clinical improvement, are somewhat discouraging, even considering the fact that most of these unlucky patients were freed of their incurable pain. Other authors reported much more satisfying results. Using very straight criteria of success, and supervising a span of 6 months after operation, they mention 30% of improvement (1, 7).

The high rate of 2/3 of our patients being admitted only in the last phase of the disease, i.e. already in paraparetic state, as well as the large number of tumors with bad prognostic was of disadvantage in our series.

Since we found no publication of a successful series irradiated only and comparable to the neurosurgical series, the primary treatment and management of this malignant entity still seems to remain the field of the neurosurgeon (5, 10, 13). The oncologic emergency of impending or manifest paraparesis (3), with all individual and social implications, obviously has to be treated by the operative way in order to take advantage of the last minimal chance of improvement of life quality (at least for the last life span still left) (1, 5, 7, 8, 9, 10, 11).

Quick decompression of the spinal cord or cauda still seems to be the only appropriate way, not just on behalf of possible improvement of the patient's condition, but also with respect to the necessary urgent histopathological diagnosis. The necessity of appropriate case selection leads to the following practical conclusions.

Practical Conclusions

We still believe in the urgent exploration and decompression in every case of spinal extradural space-occupying lesion with the characteristic history, especially if a primary process is still unknown.

However, we believe one should no longer operate on paraparetic patients with only minor functions intact, if paraparesis has lasted longer than one week, or if continence of bladder and bowel have been missing for more than 12 h.

Cases of known bronchial carcinoma or with apoplectic paraparesis will no longer be operated on as well because we have never observed any improvement in such cases (6, 8).

Summary

Seventy-seven cases of metastatic spinal tumors are reported. Sex-relation was about 3:1 (58 males : 19 females). The mean age was 46,4 years. A known malignant disease was present in 48 cases. In 23 additional cases the primary tumor could be detected.

Forty-eight patients were already paraparetic on admission, half of them completely. An improvement was obtained in 13 cases, in 52 there was no change, 12 deteriorated, 6 died within one month after admission. The rate of tumors with a very bad prognosis (bronchial, anaplastic and hypernephroid carcinoma and malignant melanoma) was high (37 cases).

Comparing our own results with data from literature operative indication is assessed. Indication for a radical procedure depends on histological diagnosis.

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Radiological and Morphological Findings After Experimental, Simultaneous, Cervical Interbody Fusion Using Bone Cement and Autogenous Bone

K. ROOSEN, L. GERHARD, H.-H. SCHATTKE, and W. GROTE

Introduction

Studying the clinical long-term results following anterior cervical fusion with bone cement (polymethylmethacrylate = PMMA), the authors became aware of radiological phenomena, such as "halos" (25), i.e. annular areas of increased radiolucency and changes in the adjacent vertebral bone structures. Because we did not know the cause, an experimental study was designed in order to elucidate the clinical and pathogenetic relevance, and the morphological correlation of these findings (8).

Material and Method

In 21 female pure-bred, 2-years-old beagles, the cervical spine was exposed by the antero-medial approach (1, 3). Because of the very small topographical conditions (12, 23), a microsurgical technique had to be developed (Fig. 1a, b). After exstirpation of two cervical discs, mostly at C 2/3 and at C 4/5, stable spondylodesis was achieved by simultaneous implantation of autogenous hip bone in the one and viscous bone cement in the other intervertebral space. Based on the studies of WHITE and HIRSCH (1971), we preferred the ROBINSON-SMITH (1955) bone model in a slight modification (Fig. 1a, b). The technique of vertebral body fusion by alloplastic PMMA was first published by GROTE and RÖTTGEN in 1967. The two stabilized segments were always separated by one, sometimes two, intact intervertebral discs so as to examine the mechanical influences of cervical fusion upon adjacent structures.

The fixation of the implants in the central burr-holes and in the burred transverse sulcus (Fig. 1a, b) prevented the dowels from luxating. According to KUMMER (1969), mechanical forces on the disc replacing material are exerted in the direction of the upper and lower vertebral body; therefore, physical conditions are similar to those in upright walking vertebrates.

At regular monthly intervals, X-ray studies (sagittal and lateral projections, tomography and xeroradiography; 9, 22) were performed so as to investigate the correct position of the implants, and changes of the bony and discogenic elements of the cervical spine (Fig. 2a-c).

Postoperative survival-time varied from 3 weeks to 9 months or longer (four beagles are still alive for long-term observation); four periods were distinguished:

Phase	Postoperative survival time
I	< 3 weeks
II	> 3 weeks, < 3 months
III	4-9 months
IV	> 9 months

For micro- and macroscopic morphological investigations we used deep-frozen macro-sections, a technique derived from autoradiography (2, 27). The specimen of the cervical spine were embedded in methyl cellulose, deep-frozen and sectioned in an ap direction using the cyro-microtome (LKB 2258 (PMV, Stockholm)). Section thickness was 20 µm. The specimen were stained with HE or fixed to tape, dried and stained later (v. GIESON, SCHMORL, LADEWIG).

Results

During phase I (Fig. 2a, 3a) there are no morphological changes except those operatively induced, such as minimal osteonecrosis next to the burr-cavities. The height of the stabilized intervertebral spaces is nearly equal to that of normal discs; differences depend only on the manual preparation of the dowels.

The PMMA-implant is surrounded by a thin layer of necrotic tissue, caused by mechanic, toxic or thermic influence of the monomer-polymer mixture of methylmetharylate (4-6, 14, 18, 21, 25, 29-34).

During the periods II to IV the necrotic material is resorbed by phagocatosis and replaced by a ring of fibrous tissue (Fig. 3b). This connective tissue formation corresponds to the "halo" seen radiologically (Fig. 2b, c), the ring-structure of increased radiolucency surrounding the implant.

The bone implant is transformed (7, 13, 15), new bone is formed, and a perfect osseous fusion will be achieved 4-6 months after surgery (Fig. 2b, c and 3b), due to the great osteogenetic potency of the implant material and the bed of implantation.

Discussion

This process of bone transformation probably corresponds to a period of reduced stability, as demonstrated by the narrowing of the intervertebral space (Fig. 2b, c; 4a, b) observed in all X-ray plates and sections. Clinical symptoms, revealing a possible pathologic relevance of this morphological process did not occur.

During phase III and IV, cartilage is formed within the connective tissue, and later ossified in cases in which there is some movement in the segment, an essential prerequisit for bone formation.

In agreement with our clinical X-ray studies, the development of an "osseous sleeve" surrounding the alloplastic (17, 19) material will be concluded after two years or later.

Both implant materials are suitable for experimental intervertebral body-fusion after disc resection. Up to now we did not observe any inflammatory, circulatory, osteonecrotic or mechanical complications, neither sarcomas or pathological changes of the adjacent discs.

The transplants of autogenous bone are characterized by a better structural and biological integration, whereas the allografts permit a more solid, distracting, space preserving function.

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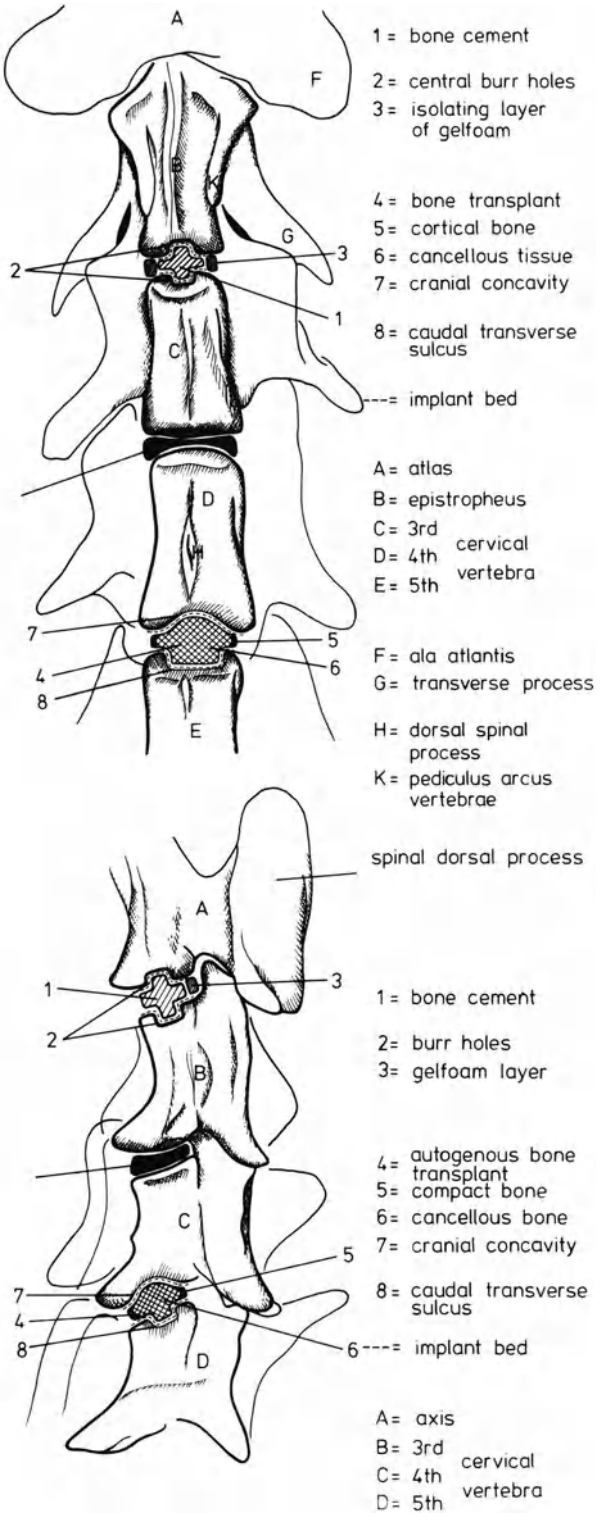
Fig. 1
Operative procedure for cervical interbody fusion using autogenous hip bone and PMMA simultaneously.
Above: sagittal diagram;
below: lateral view



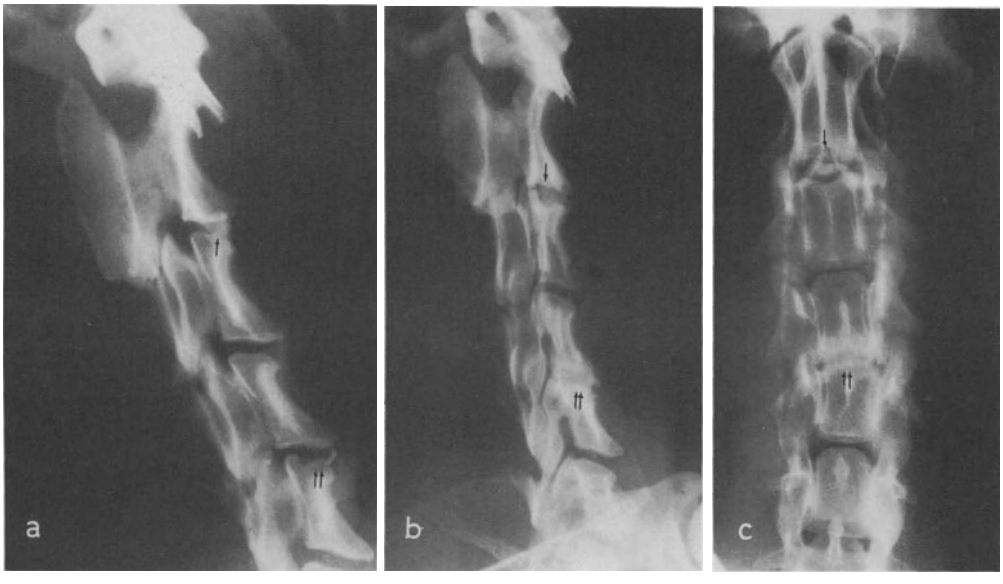


Fig. 2a-c. Lateral and sagittal X-ray projections of the cervical spine C 2/3 - PMMA ←, C 4/5 - autogenous bone ⇇. a Phase I - immediately after operation; b, c Phase III (217 days after surgery) halo at C 2/3; complete osseous fusion at C 4/5

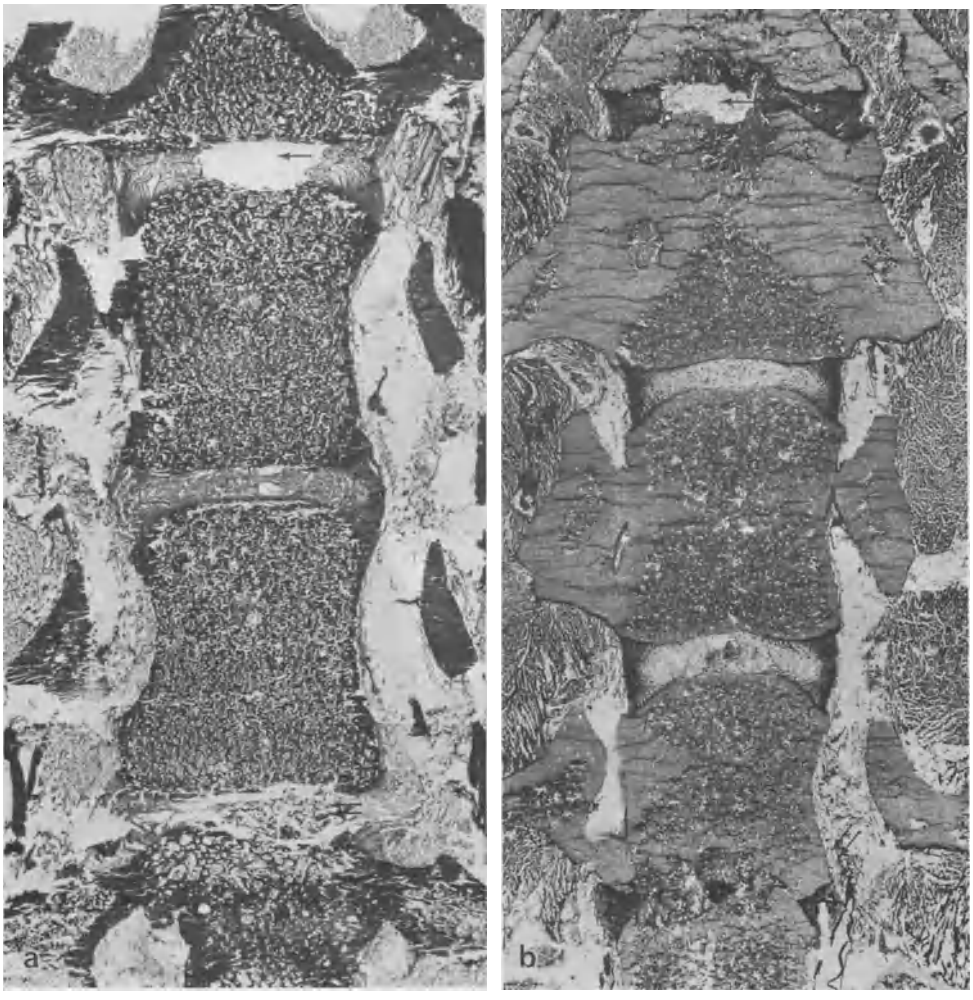


Fig. 3. a LADEWIG staining. Phase I - C 2/3 - PMMA ←, C 4/5 - bone transplant ⇇, C 3/4 - normal disc; b SCHMORL staining. Phase III C 2/3 - PMMA ←, C 3/4 + 4/5 - normal discs, C 5/6 - partially osseous fusion ⇇ (161 days after surgery)

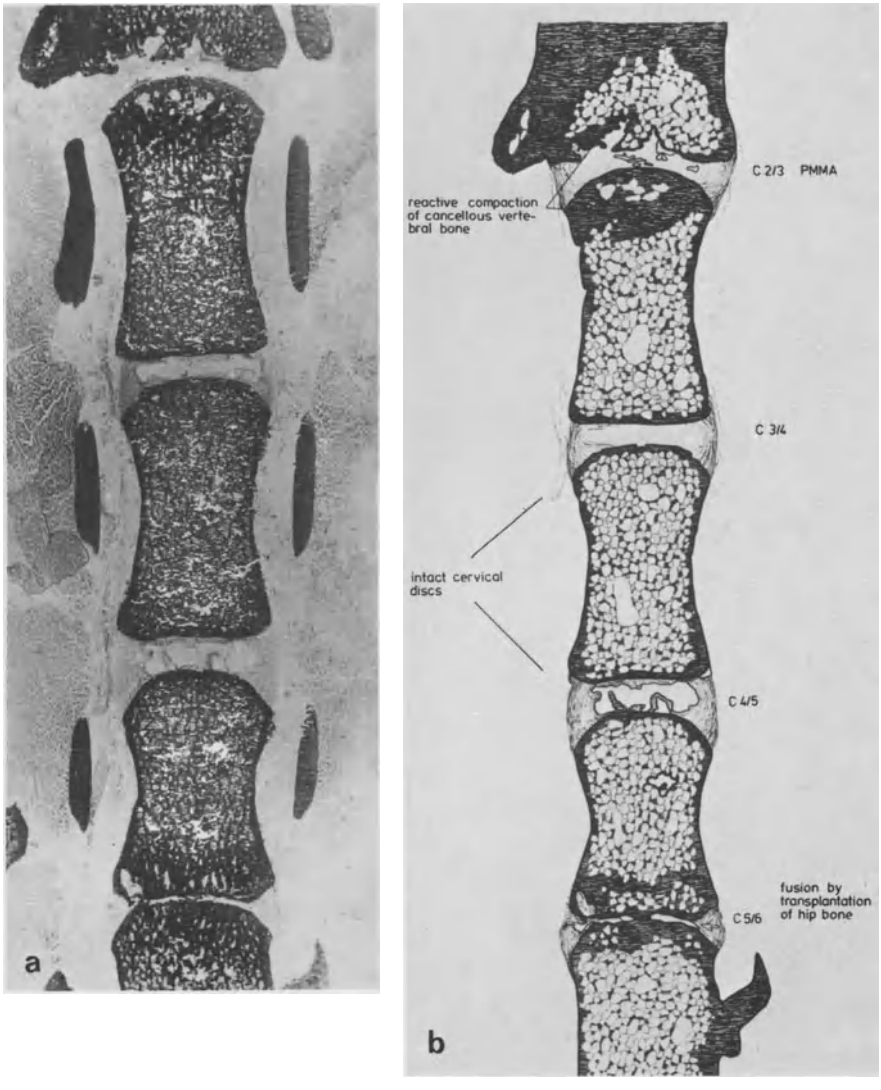


Fig. 4a, b. HE - section preparation (a) and corresponding graphic representation (b). Phase III section plane behind the implanted dowels; C 2/3 PMMA; C 5/6 osseous spondylodesis

X-Ray-Investigation in Cases of Intraspinal Space-Occupying Lesions: Synopsis of Conventional Diagnosis and CT

I. SCHÖTER

Introduction

Conventional X-ray investigation, including myelography, is sufficient for the localization and differentiation of many space-occupying spinal lesions. Under certain circumstances, however, CT may supply new valuable data which can not be provided by the conventional methods of radiographical exploration (7).

Selected from 120 CTs of various regions of the spine, some cases are presented to demonstrate that CT is apt to provide additional information.

Material and Approach

The examinations were performed with a Tomo-scan 200 (Philips), the gantry in position "0 degree". The circle of reconstruction was limited to a diameter of 25 cm in the cervical and 40 cm in the thoracal and lumbar region. Either a 10-mm or a 5-mm thick slice was obtained. The scanning-time was 64 sec, the X-ray generator was operated at 140 kV and 28 mA. All scans were taken with the patient in supine position to avoid artifacts of respiratory movement.

In 73 cases CT was performed without contrast medium, in 37 cases a previous Amipaque myelogram was demonstrated in the axial plane. Ten patients were given 50 ml Telebrix^{R} i.v.

The visualization and documentation of spinal CTs, including structures of extremely different density, is highly dependent on window-focussing. There is no possibility for exact and simultaneous delineation of bony structures and soft tissue with the present CT-generation. In order to obtain fine detail of the osseous spinal column it is necessary tu use a wide window of 1000 Hounsfield units or more (4).

To demonstrate structures of low density as paravertebral tissue, intraspinal calcification or vertebral discs the window must be reduced to 400 Hounsfield units or less. Therefore CTs revealing soft tissue lesions will be indistinct concerning the bony structures.

Case Reports

Native CT

Based on the higher sensibility of the equipment, native CT is superior to conventional X-ray investigation in many cases. Under certain circumstances native CT may be even superior to myelography:

- The plain films of a 35-year-old patient with cervical luxation at the level of C5/6 do not clarify the reason for the concomitant transverse lesion. CT demonstrates the dislocated vertebral disc, restricting the spinal lumen (Fig. 1).

- Conventional radiography of a 38-year-old patient with intercostal neuralgia demonstrate an angiomatous thoracal vertebra. CT proves the spinal canal to be unrestricted by osseous malformations (Fig. 2).

- The myelogram of a 22-year-old patient who had suffered a trauma visualizes the compression of the third lumbar vertebra, the contrast medium being restricted to the dorsal part of the spinal canal. CT delineates a fracture line crossing the vertebra in sagittal direction.

  On the following scans spongy substance emerges from the fracture and occupies the ventral part of the lumen (Fig. 3).

- The myelogram of a 59-year-old patient with progredient paraparesis of the legs delineates the outlines of a juxtamedullary tumor. CT visualizes the calcified meningeoma and its relationship to the adjacent structurs.

Computer-assisted Myelography (CAM)

In previous reports it has already been pointed out that computer-assisted myelography may be helpful in the differential diagnosis of space-occupying lesions (2, 3, 6, 8, 9, 10):

- The conventional myelogram of a 72-year-old patient with paraplegia of the lower limbs demonstrates a contrast block at the level of D10 without indicating the outlines of the lesion. CAM reveals the reduced CSF-space and the enlarged epidural cavity indicating an epidural process. A plasmocytoma was verified by blood-test and biopsy.

- The myelogram of a 63-year-old patient with weakness of the legs is pathognonomic for a space-occupying lesion at the level of D6. The medullary contour is not visible. CAM demonstrates the enlarged CSF space in the region of the lower tumor pole, adjacent to the insertion of a subarachnoid process. The operative finding of a juxtamedullary meningeoma proves the CAM to be correct (Fig. 4).

Results

In 40% of 73 investigations, native CT was apt to supply diagnostic data which could not be obtained by conventional methods of plain radiological exploration (calcified intraspinal tumors, paravertebral processes, traumatic lesions, malformations). In 5 cases, native CT was superior to conventional myelography.

CAM was valuable for confirmation of myelographic findings. In 37% of 37 cases new data were provided concerning the localization of intraspinal lesions and their relationship to adjacent structures. In one patient with multiple intramedullary metastases causing a myelographic block, the lesions could be localized by CAM. In another patient, in whom conventional myelogram led to the suspicion of intraspinal lesion, CAM permitted its exclusion.

Although reported in some papers (1, 5, 7), we did not see an enhancement after intravenous injection of contrast in our recent investigations.

Reviewing the literature and summarizing our experiences, it appears that spinal CT is valuable for diagnostic approach whenever conventional radiographic investigation has reached its technical limit. Advances in CT will probably provide comouter generations of further improvement.

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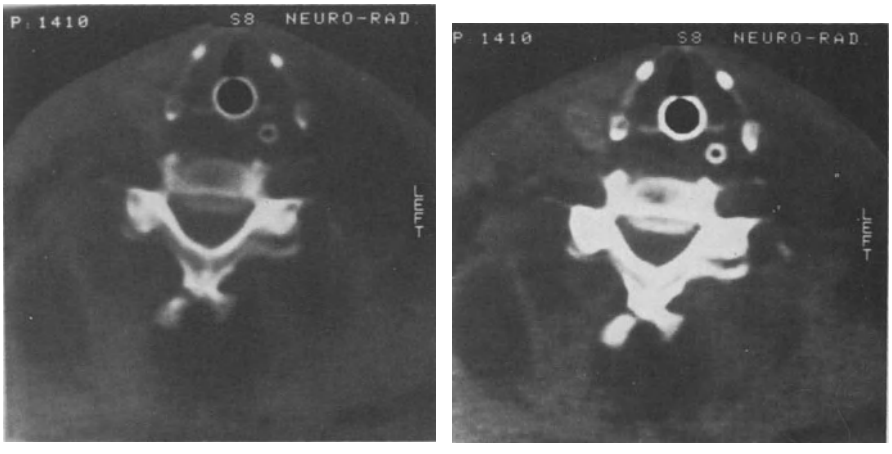

Fig. 1. Native scan: dislocated disc at the level of C5/6. *Left:* window-width 1000, window-level 227; *right:* window-width 400, window-level 88

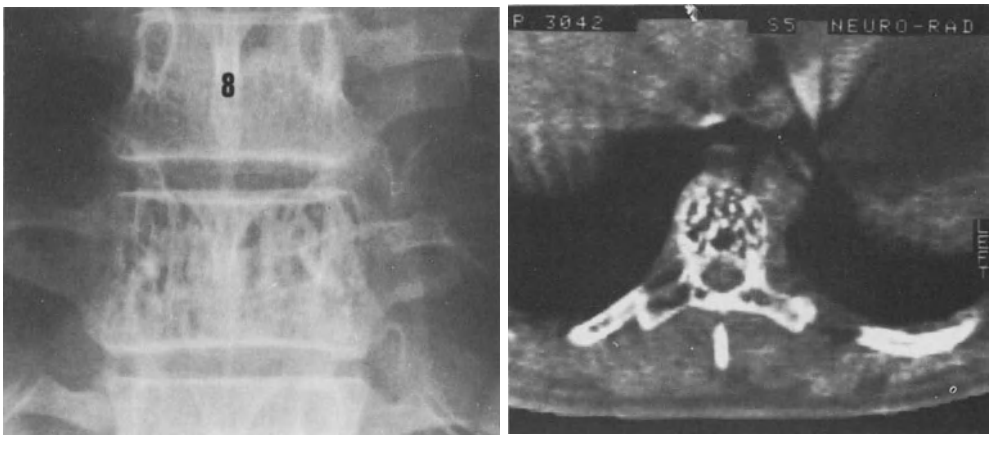

Fig. 2. Angiomatous vertebra (D9). *Left:* plain film; *right:* native scan

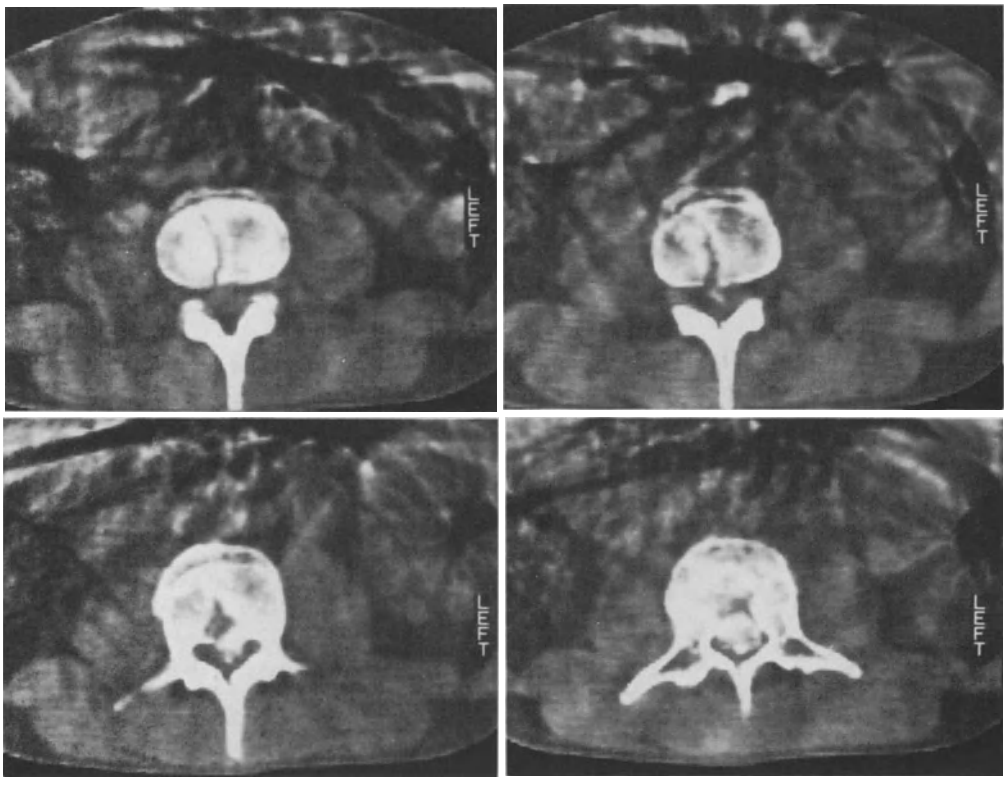

Fig. 3. Native scans: traumatic compression of L3. Consecutive slices. Spongy substance emerging from a gapping sagittal fracture

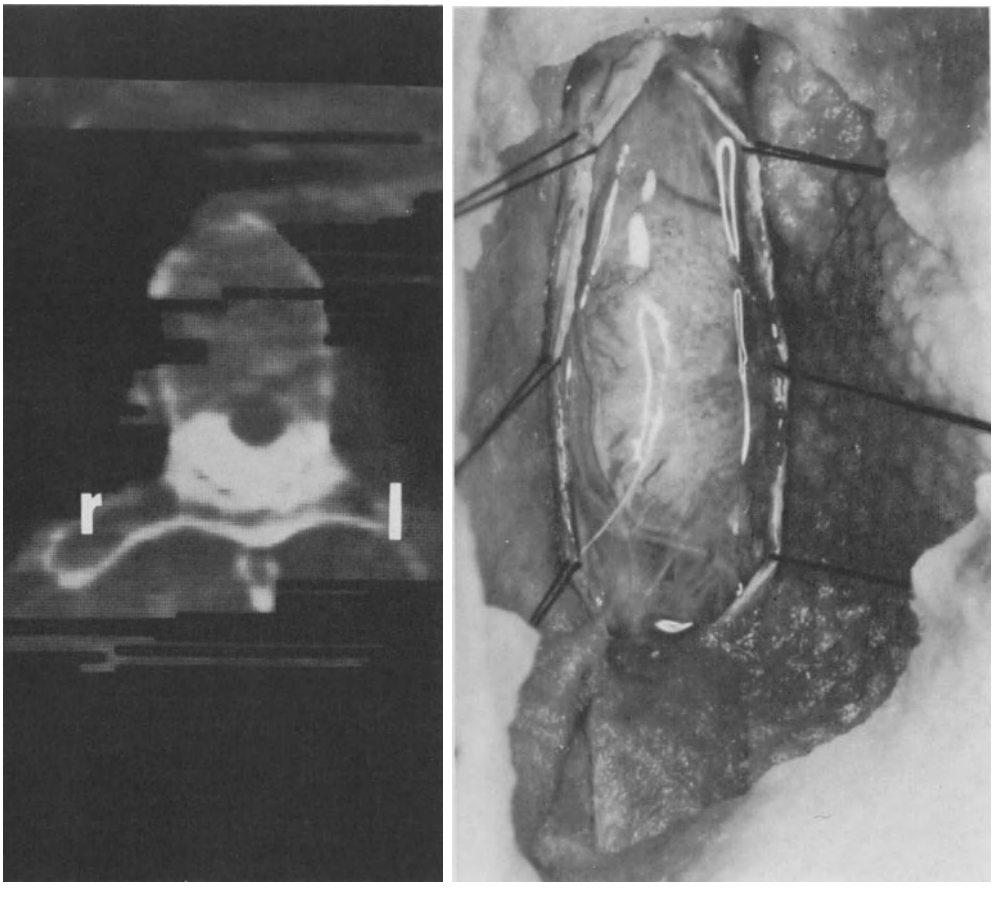

Fig. 4. Meningeoma at the level of D6. *Left:* CAM of the lower tumor pole. Enlarged CSF-space adjacent to the insertion-plane of the meningeoma. *Right:* site of the operation, arachnoid still closed, confirming CAM-findings

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