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Symptomatology of the Most Severe Form of Tuberculous Meningitis

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Summary. Seven cases of the most severe form of tuberculous meningitis, in which a midbrain syndrome developed, are reported. Three different types of progress were observed. Exudative inflammation and cerebral edema dominated in the first group, causing the rapid development of the acute midbrain syndrome, which may turn into a bulbar syndrome. In the second group the development of the midbrain syndrome was delayed and an apallic syndrome followed. The morphological examination disclosed local diencephalic and midbrain lesions caused by herniation and specific vasculitis and vascular compression. The third group showed disintegration of cortical function as a result of parenchymal lesions, apart from local midbrain symptoms which never fully intensified into the midbrain syndrome. Observation of the progress of the disease proved that late diagnosis and delayed therapy were decisive in cases of the most severe form of tuberculous meningitis.

Key words: Tuberculous meningitis – Midbrain syndrome – Bulbarbrain syndrome – Apallic syndrome – Specific vasculitis.

Zusammenfassung. Es wird über 7 Fälle einer schwersten Verlaufsform der Meningitis tuberculosa berichtet, bei denen sich ein Mittelhirnsyndrom entwickelt hat. Es ließen sich 2 bzw. 3 Verlaufsformen trennen. Bei der ersten Gruppe stand die exsudative Entzündung mit Hirnödem im Vordergrund und dadurch eine relativ rasche Entwicklung zum Vollbild des akuten Mittelhirnsyndroms, das in ein Bulbärhirnsyndrom übergehen kann. Bei

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der zweiten Gruppe zeigte sich eine protrahierte Entwicklung des Mittelhirnsyndroms mit Übergang in ein apallisches Syndrom und morphologisch eine lokale Zwischenhirn- und Mittelhirnschädigung durch Einklemmung und spezifische Vaskulitis bzw. Gefäßkompression. Die dritte Gruppe wies neben der lokalen Mittelhirnsymptomatik, die sich nie bis zum Vollbild verstärkte, eine diffuse Großhirnstörung in einem Desintegrationsverlauf auf. Aus den Verlaufsbeobachtungen ergibt sich, daß die spät einsetzende Diagnose mit verzögertem Therapiebeginn für die schwerste Verlaufsform der Meningitis tuberculosa von entscheidender Bedeutung ist.

Introduction

We distinguish a mild, a moderately severe, a severe, and a most severe form of tuberculous meningitis. Text books of internal medicine, pediatrics and neurology, as well as papers on the subject, mention the clinical symptoms of the most severe form of tuberculous meningitis only superficially and mostly summarize them as "decerebration" in tuberculous meningitis. Only a few authors analyze more closely the symptomatology, development, and progress of the most serious form of tuberculous meningitis accompanied by decerebration [3, 12]. The main problem of the most severe form is the late diagnostic verification of the disease and thus the delay of specific treatment. Moreover, rehabilitation of surviving patients, who usually show most severe brain lesions, is extremely difficult.

Having observed seven cases of the most severe form of tuberculous meningitis, we wish to analyse characteristic features of the progress of the disease and details of the development of its symptomatology. Special attention will be paid to the appearance of brainstem symptoms, in particular of midbrain or bulbar brain syndromes and of the apallic syndrome. Differential diagnosis between tuberculous meningitis and etiologically different severe brain lesions will be taken into consideration.

Case Reports

During the past decade seven cases of the most severe form of tuberculous meningitis as been examined and the progress of the disease has been observed. Six patients died; one lives suffering from very serious sequelae. The patients were three boys below the age of 14, two adolescents (a male patient of 19 and a female patient of 15), and two adults (a woman of 38 and a man of 48). Table 1 gives a summary of the clinical symptoms, while Table 2 presents the morphological findings.

Case 1. E.R., a boy of 13, had symptoms of influenza for a period of 10 days. After 3 weeks he was hospitalized for meningeal complaints. Cell count and sugar in the CSF were normal but protein was increased (91 mg%). Carotid angiography was normal. During the following days the meningeal signs increased. Results of a control lumbar puncture were: pleocytosis (cell count 531/3, 80% granulocytes), increased protein (115 mg%), normal CSF sugar. The patient was confused and in a state of maniacal agitation 5 days after the onset of meningeal symptoms. He was transferred to the Psychiatric University Hospital of Vienna. Upon admission he was in comatose, had marked meningeal signs, hyperreflexia without pyramidal signs, and fronto-

Table 1. Clinical course

Case No.	Initials	Age (years)	Sex	Demonstration of M. tuberculosis	Meningeal symptoms
1	E.R.	13	m	negative	+++
2	S.S.	38	f	negative	+++
3	L.K.	19	m	negative	+++
4	D.U.	15½	f	spinal fluid culture positive	++
5	E.K.	2⅔	m	spinal fluid culture positive	++
6	J.S.	48	m	negative	++
7	H.J.	3½	m	sputum stain positive	+

basal symptoms. CSF cell cout was 213/3 (40% granulocytes), protein 120 mg%, sugar 26 mg% (blood sugar was normal), Halberg stain was negative. The excitement declined within 12 h and consciousness improved. Three days later somnolence reappeared with signs of the initial stage of an acute midbrain syndrome with left side lateralisation. After 3 more days the third stage of midbrain syndrome appeared (coma, diminished pupillary reaction to light, divergent position of the eye balls with disconjugate movements, flexion of the upper and extension position of the lower extremities). After 24 h the midbrain syndrome was fully intensified: divergence of the eye balls, miosis, diminished reaction of the pupils to light, extension of all extremities, spontaneous extensor synergism intensified by pain stimulation, hyperreflexia including the mandibular reflex, bilateral positive pyramidal signs, spasticity of the limb and mandibular muscles, disinhibition of all vegetative functions (hyperthermia, tachycardia, hypertension, hyperventilation). The patient died 4 days later with an acute bulbarbrain syndrome: the extension synergism had disappeared, reflexes were abolished, flaccid posture, breakdown of all vegetative functions (respiratory arrest).

Morphological Report. Caseate primary lesion of the right upper pulmonary lobe, miliary tuberculosis of the lung, pleura, spleen and liver; tuberculous leptomeningitis with profuse exudation in the basal cisterns and in the area of the tuberal part of the pituitary gland, numerous miliary tubercles in the basal leptomeninges, diffuse increase of brain volume, marked signs of tentorial and cerebellar herniation.

Case 2. S.St., a woman aged 38, felt completely healthy, when suddenly meningeal symptoms appeared. Upon immediate hospitalization CSF was normal. Examinations and tests on the 12th day revealed a lesion of the right oculomotor nerve, bilateral positive pyramidal signs, CSF protein highly increased, cell count 112/3, CSF sugar 55 mg%. During the following 4 days symptoms of a beginning midbrain syndrome appeared, and during the next 4 days the third stage of midbrain syndrome with bilateral papilledema of 3 diopters developed. CSF contained 199 mg% protein, cell count 118/3, sugar 13 mg%. Tuberculostatic therapy was initiated. On the next day the acute midbrain syndrome had fully developed and 3 days later it changed to an

CSF sugar	Beginning of tuberculostatic therapy	Acute midbrain syndrome		Acute bulbar-brain syndrome	Apallic syndrome			Death
		initial stage	complete picture		transitional stage	complete picture	remission stage	
on the day after the onset of meningeal symptoms								
5th 26 mg%	—	8	12	16	—	—	—	16
20th 13 mg%	20	16	21 35	35	24	—	—	35
17th 15 mg%	18	17	20 39	40	23	28	—	40
1st 4.2 mg%	10	8	14		20	30	—	61
38th 15 mg%	28	?	21	—	38	45	approx. 90	approx. 120
21st 12 mg%	25		—	—				50
4th week reduced	6	½	4	—	14	28	50	—

apallic syndrome with coma vigile, flexion tendency of the arms, flexion-extension posture of the legs, and stabilization of vegetative functions. On the 35th day the symptoms of an acute midbrain syndrome reappeared without lateralization, and changed 8 h later to an acute bulbar-brain syndrome. The patient died of circulatory failure.

Morphological Report. Acute pulmonary congestion, bilateral focal pneumonia.

Neuropathological Report. Opaqueness of the meninges over the basal cisterns, slight internal hydrocephalus. The histological examination revealed florid exudative caseating basal tuberculous meningitis with endangiitis and panangiitis of meningeal vessels, but not progressing into the brain vessels; no vascular focal lesion.

Case 3. L.K., a young man of 19 felt completely healthy, when suddenly pains occurred in the left side of his chest. Four weeks later he complained of diffuse headaches accompanied by intermittent attacks of fever. After 2 more weeks a meningeal syndrome had developed and the patient was hospitalized. CSF examination showed a cell count of 334/3 and slightly increased protein values; 2 weeks later he was somnolent and exhibited minor frontal symptoms. Signs of the initial stage of a midbrain syndrome with right side lateralisation were observed 3 days later. CSF examination: cell count 503/3 (80% granulocytes), protein 128 mg%, sugar 15 mg% (blood sugar was normal), CSF chlorides 600 mg%. Miliary tuberculosis of the lung was diagnosed and tuberculostatic therapy was initiated. After 2 more days the patient was in the third stage of an unlateralized midbrain syndrome which developed 24 h later into the fully intensified picture of an acute midbrain syndrome changing 3 days later to an apallic syndrome; the extension spasms ceased, vegetative functions stabilized. The fully intensified apallic syndrome had developed 28 days after the onset of meningitis; the increase of muscle tonus was strikingly weak, reflexes were reduced. Primitive motor patterns occurred. On the 39th day the patient had septic temperatures and presented again the complete acute midbrain syndrome, which changed within 12 h to an acute bulbarbrain syndrome. Respiratory and cardiac arrest lead to the patient's death on the 40th day after the onset of meningeal symptoms.

Table 2. Neuropathological findings

Case No.	Initials	Stage of basal meningitis	Increase of brain volume	Basal signs of pressure	Internal hydrocephalus	Specific vasculitis	Vascular lesions
1	E.R.	Exudative + +miliary tubercles	+++	+++	–	?	0
2	S.S.	Exudative-florid	++	+	+	++	0
3	L.K.	Productive-caseating +miliary tubercles	++	++	–	+++	Basal striatum, thalamus, hypothalamus, midbrain and pontine tegmentum
4	D.U.	Productive-caseating	–	–	+++	+++	Pallidum, thalamus, hypothalamus, basal insula right more than left
5	E.K.	Defective state with basal tuberculoma	–	–	+++	+++	Striatum – insula (supply area of middle cerebral artery) right; pallidum – thalamus (supply area of anterior chorioidal and thalamoperforate arteries) left; midbrain and pontine tegmentum
6	J.S.	Productive-caseating	++	–	+	++	Microinfarctions in midbrain and pontine tegmentum; acute hemorrhagic infarctions in med.-bas. temporal lobe right

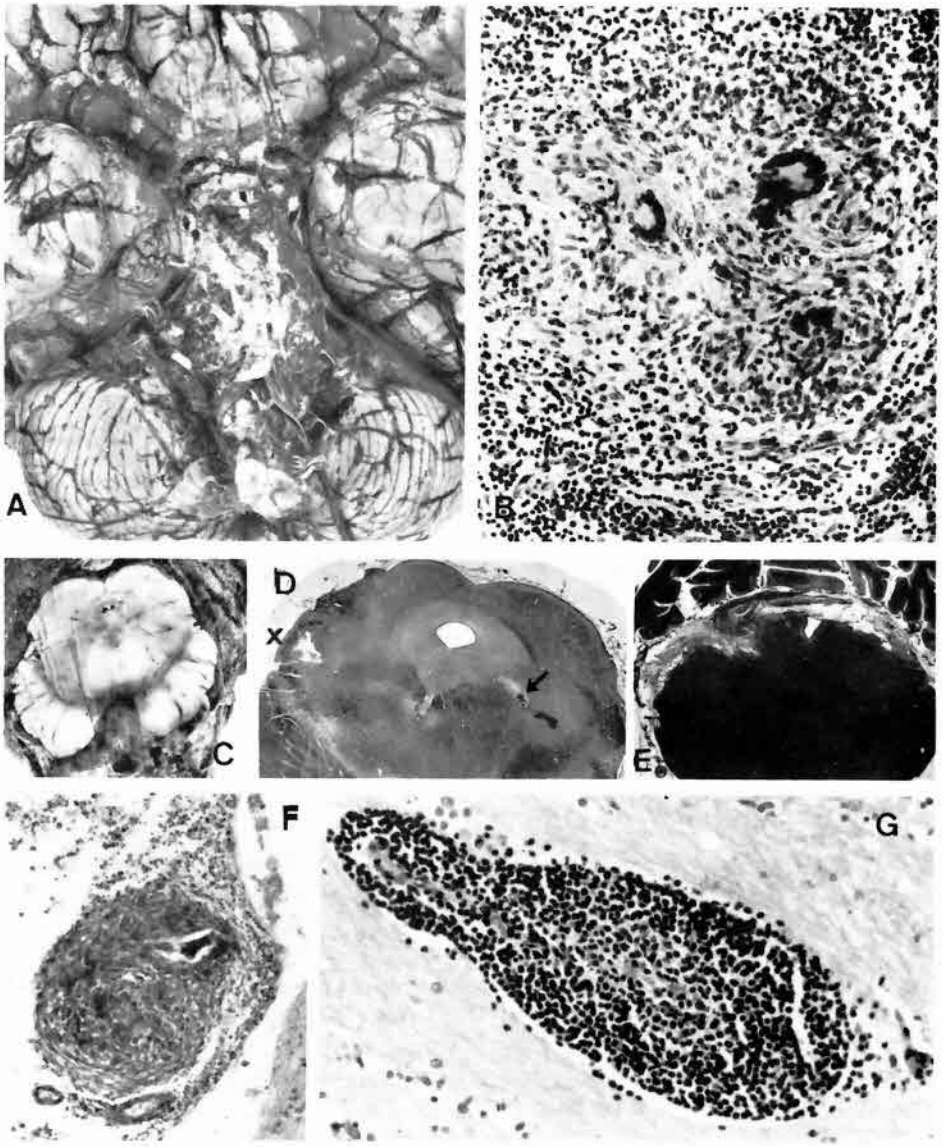

Fig. 1A–G. Case 3. **A** Basal meningitis: basal cistern filled with fibrous exsudate. **B** Granulomatous meningitis with Langhans type giant cells. H & E × 112. **C** Basal meningitis: cisterna ambiens filled with exsudate. **D** Multiple small vascular lesions in pontine tegmentum *(x)*. Klüver-Barrera. **E** Extensive destruction of pontine tegmentum with superficial necroses due to obliterative angiitis of circumflex vessels. Klüver-Barrera. **F** Obliterating panangiitis of small pial artery. H & E × 67. **G** Granulomatous angiitis of small vessel in pontine tegmentum. H & E × 150

Morphological Report. Tuberculous caseous focus in the upper left pulmonary lobe, miliary tuberculosis, lymphadenitis, pleuritis and tuberculous peritonitis.

Neuropathological Report. Productive caseating basal meningitis with opacity and fibrous scarring of the basal cisterns and disseminated miliary tubercles in the subarachnoid space of

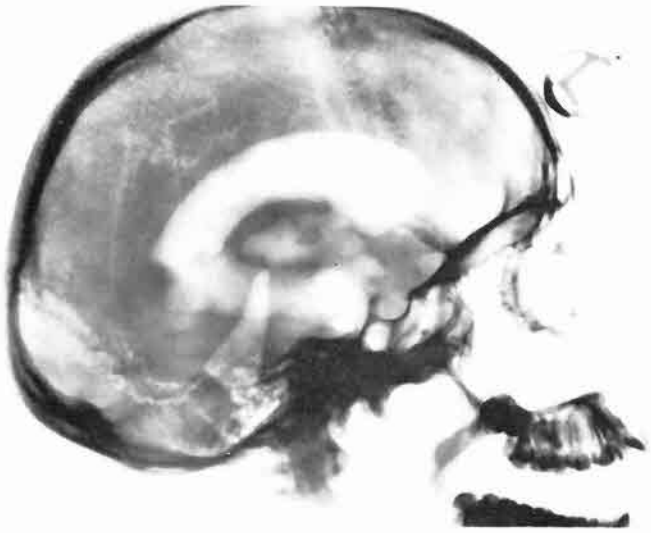

Fig. 2. Case 4. Transitional stage to apallic syndrome; pneumoencephalogram shows marked hydrocephalus and enlargement of whole ventricular system and basal cisterns

the basal gyri. The histological examination showed severe productive caseating basal tuberculous meningitis (abundant acid-fast rod cells) with stenosing and obliterating endangiitis and panangiitis of basal cerebral arteries, and granuloma in the ventricular wall. Multiple vascular infarctions of different age were found bilaterally in the basal striatum, the basal nucleus, the fornix and the posterior corpus callosum, in the ventral and dorsal thalamus, in the anterior and median hypothalamus, in the right Ammon's horn, as well as in the midbrain and pontine tegmentum together with destruction of superficial parts of the pontine tegmentum and fibrous scarring of superjacent meninges. The infarctions corresponded with supply areas of perforating basal and circumflex arterial branches supplying basal ganglia and brainstem (Fig. 1).

Case 4. D.U., a girl, 15 years old, had an attack of fever. In the third week of her illness she was hospitalized because of headaches, stiff neck and somnolence; CSF findings were: cell count 1100/3 (predominantly granulocytes), raised protein values, sugar 4.2 mg%. As somnolence increased in the following week with marked rigidity of the neck muscles, symptoms of a beginning midbrain syndrome with rightside lateralisation were observed. Results of the CSF test were: cell count 448/3 (predominantly granulocytes), protein 115 mg%, sugar 3.5 mg%. The bacteriological test was negative. The EEG revealed signs of marked cerebral functional lesion accentuated on the left side. In the 5th week of the disease, 10 days after the onset of meningitis, tuberculous meningitis was diagnosed and tuberculostatic therapy was started, whereupon the pleocytosis of the spinal fluid receded to 100/3 cells (mainly lymphocytes), protein values became normal, but sugar values remained very low. One week later the full midbrain syndrome had developed while signs of lateralization persisted. Transition to an apallic syndrome took place 20 days after the onset of meningitis. The pneumoencephalogram showed symmetrically enlarged ventricles and enlarged basal cisterns (Fig. 2). After 10 days the complete picture of an apallic syndrome developed without remission tendency. Gastrointestinal hemorrhage occurred in the 9th week followed 2 days later by lung infarction and pleuritis. The patient died 2 days later of circulatory arrest. A postmortem spinal fluid culture for mycobacterium tuberculosis was positive.

Morphological Report. Tuberculous primary complex in the right lower lobe and caseous degeneration of the regional lymphytic nodes, peripheral lung infarction, deep saphenous phlebothrombosis, ulceration and erosion of the gastrointestinal tract, terminal pulmonary edema.

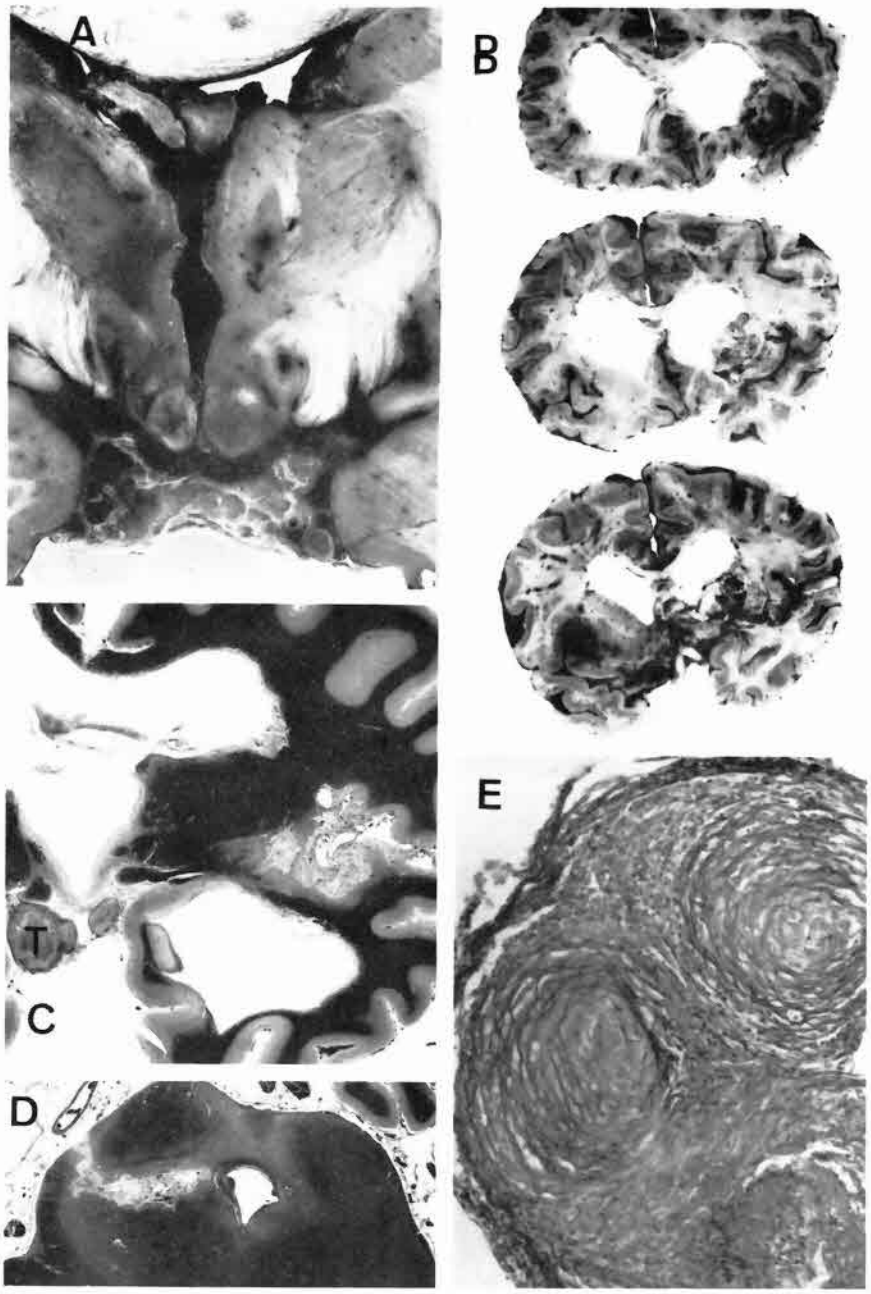

Fig. 3. **A** Case 4. Basal cisterns filled with exsudate and multiple small vascular necroses and hemorrhages in wall and bottom of third ventricle, thalamus and hypothalamus. **B—E** Case 5. **B** Frontal section of brain showing internal hydrocephalus and multiple cystic necroses in pallidum, hypothalamus and insula. **C** Frontal section showing internal hydrocephalus, small tuberculoma (T) in corpus mamillare, and old infarctions in insula and hypothalamus. Klüver-Barrera. **D** Small perivascular infarct in mesencephalic tegmentum along perforating branch of long circumflex brainstem artery. Klüver-Barrera. **E** Obliterating vasculitis in basal cistern. van Gieson elastic stain × 90

Fig. 4. Case 5. Transitional stage to apallic syndrome; extension posture of all extremities and opisthotonus

Neuropathological Findings. Productive basal meningitis with opacity and fibrous scarring of the basal cisterns, advanced internal hydrocephalus and older infarctions in the globus pallidus and the ventral thalamus (Fig. 3A, B). Histological inspection revealed severe productive caseating basal tuberculous meningitis with advanced lateral and 3rd ventricular hydrocephalus without inflammatory reaction of the ventricular walls. Obliterating endangiitis of basal cerebral arteries with older infarctions in the pallidum, the hypothalamus, in the periventricular thalamus and in the basal areas of the insula, right more than left, mainly in the supply area of the anterior choroidal artery and other perforating basal branches. The brainstem showed some vascular focal lesions (Fig. 3C—E).

Case 5. E.K. was a boy of 2 years and 8 months, whose birth had been normal. Walking and talking had been delayed and at the age of $1\frac{1}{2}$ years absences occurred more and more frequently. From the second year onward the boy had been suffering from repeated tonsillitis and pulmonary complaints. About that time tuberculosis was diagnosed in the father. At the age of 2 years and 7 months the boy was hospitalized for increased pulmonary complaints and the suspicion of a specific hilar process. Within 3 weeks he became increasingly somnolent and developed the symptoms of the complete picture of an acute midbrain syndrome with meningeal signs. CSF test results were: cell count 496/3 (mainly lymphocytes), protein 72.5 mg%, sugar and chlorides were normal. The EEG was diffusely abnormal and slightly accentuated on the left side. The ventriculogram showed a massive enlargement of the lateral ventricles without filling of the basal cisterns and the fourth ventricle. In spite of normal CSF sugar values tuberculous meningitis was suspected and tuberculostatic therapy was started 1 month after hospitalization. The symptoms of an apallic syndrome with distinct opisthotonus posture were observed 10 days later (Fig. 4). CSF test revealed: 100/3 lymphocytes, slight increase in protein, sugar 15 mg%; a culture for mycobacterium tuberculosis was positive. Within the next week the apallic symptoms intensified fully and primitive patterns, in particular of the oral type, appeared (suction reflexes could be elicited by acoustic and tactile stimulation), together with Babkin reflex, marked vegetative instability and emergency reaction. After 2 months treatment signs of remission appeared. (The patient could fix his eyes upon an object, pain stimulation elicited primitive reactions of fear, the sleep-waking-cycle changed to a day-and-night-rhythm, generalized extension posture diminished, the primitive motor patterns were reduced, in particular the Babkin reflex, vegetative functions stabilized.) Pneumonia set in 4 months after the beginning of the disease and the patient died of circulatory arrest 3 days later.

Morphological Report. Final stage of pulmonary tuberculosis with specific dissemination; calcified tuberculous lymphatic nodes.

Neuropathological Report. Fibrous scarring of the basal cisterns with small tuberculomas over the basal diencephalon; severe internal hydrocephalus. Multiple older infarctions in the right striatum and insula corresponding to the central supply area of the right median cerebral artery as well as in the thalamus and left globus pallidus. Histological examination: Defective state after basal tuberculous meningitis with fibrous scarring of the basal cisterns; tuberculomas as large as a cherry stone over the diencephalon and severe postinflammatory internal hydrocephalus. Obliterating specific endangiitis of basal cerebral arteries with multiple older infarctions in the right striatum and insula as well as in the left thalamus and globus pallidus (supply area of the anterior choroidal artery). Multiple vascular necroses in the midbrain tegmentum, often following perforating branches of long circumflex brainstem arteries.

Case 6. J.S., aged 48, male, showed meningeal symptoms with headaches after a fever period of 3 weeks. Cell count and protein in the spinal fluid were elevated; CSF sugar was 34 mg% while blood sugar was normal. After 3 more weeks the patient became somnolent, the right pupil dilated and hyperreflexia was observed. Bilateral carotid angiography was normal. Somnolence increased and symptoms of basal meningitis appeared: optomotor disturbances, hyperreflexia, pyramidal signs accentuated on the left and signs of diffuse hemispheric involvement. The CSF contained WBC (430/3, predominantly lymphocytes), protein 287 mg%, sugar 12 mg%. Although tests for tuberculosis were negative tuberculostatic therapy was started $6\frac{1}{2}$ weeks after the beginning of the disease and 25 days after the onset of meningeal symptoms. After 6 days of treatment the patient exhibited Korsakoff's syndrome, at the same time vigilance cleared and local midbrain symptoms accentuated on the left side were observed. Spinal fluid values improved. During the following 4 weeks only minor changes in the patient's overall condition occurred, occasionally he was somnolent. The EEG indicated a diffuse functional brain lesion. The pneumoencephalogram (performed 7 weeks after the onset of meningitis) showed enlargement of the lateral ventricles and pontine cistern. CSF sugar was normal, protein was moderately increased and there was slight pleocytosis. In the 8th week the fever rose again and symptoms of a Klüver-Bucy syndrome were observed (oral and prehensile patterns, masturbation tendency). Distinct signs of a local midbrain lesion persisted. CSF: normal cell count, markedly increased protein values, sugar 34 mg%, chlorides 522 mg%. The patient died of cardiovascular failure 71 days after the beginning of the disease and 50 days after the onset of meningitis.

Morphological Report. Tuberculous primary focus in the right upper lobe; miliary tuberculosis of the pleura and the lungs; generalized miliary dissemination; tuberculoma of the spleen. Florid portal liver cirrhosis.

Neuropathological Report. Productive caseating basal meningitis with opacity and fibrous scarring of basal cisterns; slight internal hydrocephalus. Miliary tubercles in the ventricular plexus. Fresh hemorrhagic infarctions in the right mediobasal temporal lobe. Histological examination: subacute productive caseating basal tuberculous meningitis with stenosing-obliterating endangiitis and panangiitis of basal cerebral arteries; granulomatous ventricular infection with moderate internal hydrocephalus and multiple small new and old micro-infarctions in midbrain and pontine tegmentum, following perforating branches of long circumflex arteries brainstem.

Case 7. H.J., a boy of $3\frac{1}{2}$ years had his appendix removed because of abdominal pain and fever. The fever increased and a stiff neck was observed on the 4th postoperative day. After 4 more days Jackson attacks occurred on the left side; these could be elicited by tactile stimulation. In the course of 12 h right midbrain symptoms developed. CSF test: cell count 730/3 (80% lymphocytes), slightly increased protein values, sugar 40 mg%. Ziehl-Nielsen staining revealed rods in the sputum. Tuberculostatic treatment was begun 10 days after appendectomy. Three days later the patient was in coma and exhibited symptoms of the third stage of an acute midbrain syndrome. The transition to an apallic syndrome developed in the next 10 days with beginning coma vigile and cat-like cries. During the following weeks the apallic symptoms intensified to the complete picture of the disease with flexion-extension posture of the extremities. CSF

examination: cell count 100/3, increased protein and reduced sugar values. Within the next 3 weeks the apallic symptoms began to reced, primitive emotional reactions reappeared, particularly fear reactions. The patient began to fix his eyes upon objects and to follow them with his eyes; later he paid attention to optic stimulation. Mass movements of arms and legs were observed; primitive motor patterns and vegetative dysfunction subsided. A superimposed right spastic hemiparesis appeared. During the further course of recovery Klüver-Bucy symptoms occurred. The patient was dismissed 10 weeks after the beginning of treatment at his parents request. Later, recovery continued until a defective stage was reached in which all higher brain functions were severely impaired and control of emotional reactions was lost. The patient could carry out simple commands, such as opening the mouth, humming nursery songs maintaining the rhythm; verbal expressions were missing, primitive motor patterns, particularly of the oral type, continued. The residuals of Klüver-Bucy symptoms persisted and motor stereotypes, such as rocking the trunk and shaking the head or rhythmical extension movements of the arms, were seen. The right spastic hemiparesis continued; hyperreflexia and positive pyramidal signs appeared on the left side also. Walking with assistance was possible. The EEG showed a general functional brain lesion with left frontoparietal and right central accentuation. The psychological test revealed high grade dementia (developmental age of 12 months).

In six of the above seven cases (Cases 1—5 and 7) an initial stage preceded the development of an acute midbrain syndrome, which took an atypical course in Cases 4 and 7. Patient 4 experienced no extension synergisms, and the course of Case 7 was protracted. Both patients had previously received tuberculostatic therapy. While in Case 1 the acute midbrain syndrome changed directly into an acute bulbarbrain syndrome ending with the patient's death, Cases 2—5 and 7 developed a transitional stage to the apallic syndrome, followed in Cases 3, 4, 5, and 7 by the complete picture of the syndrome and in Cases 5 and 7 by remissions. Patients 2 and 3 died in the apallic syndrome after reappearance of acute midbrain and bulbarbrain syndromes; intercurrent diseases were the cause of death in Cases 4 and 5. Only in Case 7 did recovery progress until a severely defective state was reached. In Case 6 the disease took an atypical course as no acute midbrain symptoms developed and the clinical picture was characterized by symptoms of a diffuse hemispheric lesion and only a slight local lesion in the midbrain area. Without developing an acute midbrain syndrome or an apallic syndrome, the patient showed symptoms similar to those of the remission stage of an apallic syndrome. Klüver-Bucy symptoms being conspicuous.

The morphological reports revealed acute cerebral edema with signs of tentorial and foraminal herniation in Cases 1 and 2. Case 3 presented signs of new tentorial and basal herniations apart from extended vascular lesions in the midbrain. The vascular lesions were predominant in Cases 4 and 5, occurring not only in the midbrain but also in subcortical regions. Marked internal hydrocephalus was also present in both cases. Case 6 exhibited local lesions in the midbrain as well as cerebral edema, but no signs of herniation.

Tuberculous meningitis was bacteriologically demonstrated in three of the seven cases (Cases 4, 5, and 7). Typical spinal fluid changes and characteristic morphological findings led to the final diagnosis in the remaining four cases.

Discussion

Robert Whytt was the first author to distinguish a prodromal, a meningeal and a paralytic stage of tuberculous meningitis. If no specific therapy is applied death

occurs usually after 3 to 6 weeks. If tuberculostatic therapy is started too late, chronic tuberculous meningoencephalitis may develop [9]. The morphological basis of such cases is a change of exudative to proliferative inflammatory processes [15]. The clinical course is determined by the extent of the hydrocephalus developed during the disease as well as by vascular occlusion and inflammatory tissue alterations [12]. As the disease progresses decerebrate rigidity may develop as the most severe form of tuberculous meningitis [14]. Müller [12] was the first to suggest the designation "midbrain syndrome in tuberculous meningitis", motivated by typical patho-anatomical alterations. He assumed that local pressure on the upper brainstem due to communicating hydrocephalus caused by limited CSF passage with increased supratentorial volume, was responsible for the development of acute midbrain syndromes, apart from the encasing ("walling in") of the brainstem by the exudate, local inflammation with edema, and a circulatory lesion due to the pressure of the exudate on the basilar artery. The anatomical substrate as well as the clinical picture of the most severe form of tuberculous meningitis thus correspond to the most severe form of subarachnoid hemorrhage [2, 13] in which also supratentorial herniation by brain edema and local pressure by encasement are also present.

Six of the seven patients described developed an acute midbrain syndrome during the initial stage; one patient showed signs of a local lesion in the midbrain side by side with symptoms of a diffuse hemispheric lesion. In case of supratentorial herniation the symptoms of the acute midbrain syndrome develop in stages [6, 13]. Bilateral herniation (pressure from both sides) leads to four different stages with increasing loss of consciousness, optomotor disturbances, mass and rolling movements, extensor posture of all extremities and impairment of vegetative functions. Unilateral herniation produces lateralization symptoms characterized by unilateral flexion-extension posture or extension posture of the extremities and homolateral deviation of head and eyes, gradually changing to the complete picture of acute midbrain syndrome, while lateralization symptoms disappear [6, 11]. Cases 1, 3, 4, and 7 exhibited lateralization symptoms during the developmental stage of the midbrain syndrome, a demarkation of phases 1 and 2 of lateralization being impossible.

Cases 1, 2, 3, and 5 presented the typical complete picture of an acute midbrain syndrome, the clinical course in Cases 1, 2, and 3 resembling the acute secondary midbrain syndrome caused by herniation such as cerebral edema, hematoma etc., and in Case 5 representing a primary midbrain syndrome caused by a local lesion. In Cases 4 and 7 the course of the midbrain syndrome was protracted and the characteristic complete picture never developed fully (no signs of acute impairment of vegetative functions, no extension synergisms, continuing lateralization symptoms). While Case 1 directly developed an acute bulbar brain syndrome, Cases 2 and 3 exhibited a transitional stage and the complete picture of an apallic syndrome, and death occurred after reappearance of the acute midbrain and bulbar syndromes. The morphological examination in Cases 1, 2, and 3 revealed cerebral edema and signs of tentorial and foraminal herniation. Cases 2 and 3 presented, moreover, distinct vascular changes in the brainstem so that a mechanical and a vascular lesion of the brainstem caused by the exudate together with cerebral edema and mass displacement must be held responsible for

the midbrain symptoms. The increase of cerebral edema caused massive preterminal herniation during the apallic stage. In Cases 4, 5, and 7 local lesions in the brainstem must be considered predominantly responsible for the development of midbrain symptoms. Group 1 (Cases 1—3) and group 2 (Cases 4—7) do not differ as regards the time it took for midbrain symptoms to develop; it was between 3 and 6 days (Table 1).

Case 6 differs insofar as midbrain symptoms were rather insignificant and, parallel to the midbrain lesion, the symptoms of a diffuse hemispheric lesion appeared comparable to the "coma course" in chronic mercury poisoning [7]. The morphological examination, therefore, demonstrated lesions in both areas. In five cases (2, 3, 4, 5, and 7) a transitional stage to the apallic syndrome developed 3 to 10 days after the appearance of the midbrain syndrome, which, after 6 to 10 days more, intensified to the complete picture (with the exception of Case 2). The transitional stage to the apallic syndrome is characterized by fading signs of acute vegetative impairment, which is present during the midbrain syndrome, by the occurrence of coma vigile and of primitive motor patterns [1]. According to Kretschmer [10] the fully intensified picture of the apallic syndrome is characterized by the loss of all cerebral function and simultaneous release of autonomous brainstem systems and manifests itself by coma vigile with lack of emotional reactions, fatigue-controlled sleep-waking-cycle, high grade optomotor disturbances, flexion-extension posture of all extremities, instability of vegetative functions and primitive motor patterns (chewing-sucking automatisms, oral and prehensile patterns, posture and position reflexes etc.). The complete picture of the apallic syndrome of the patients described here was peculiar insofar as Cases 4 and 5 retained an extreme extension posture and Cases 4 and 7 the lateralizing symptoms. These features may also be observed in traumatic apallic syndromes [4], the first being caused by a pronounced secondary lesion of midbrain and pontine tegmentum and the second by unilateral accentuation of the lesion in the oral brainstem [4]. The morphological findings of Cases 4 and 5 (Table 2) show that corresponding changes are also demonstrable in the apallic syndrome of tuberculous meningitis.

The seven cases described here lead us to the conclusion that there are two different groups of the most severe form of tuberculous meningitis, to which a third must be added. In group 1 the formation of the basal exudate is accompanied by the development of acute cerebral edema with increased supratentorial volume and tentorial and foraminal incarceration (Cases 1, 2, and 3). The cases in group 2 exhibit a local lesion of the brainstem caused by exudative "walling in" and secondary vascular compression or by specific inflammatory affection of the brainstem vessels (Cases 2—5 and 7). In group 3 (Case 6) diffuse hemispheric dysfunction caused by parenchymal lesions may be assumed apart from the local brainstem lesion. Thus the course and prognosis of the most severe form of tuberculous meningitis seem to depend on the rate and extent of exudate formation, the development of accompanying cerebral edema with increased intracranial pressure and vascular secondary lesions in brainstem and diencephalon. Rapid formation of cerebral edema with increased volume leads to rapid development of midbrain and bulbarbrain syndromes.

In all cases reported here the diagnosis was delayed or even established only postmortem. Therefore specific treatment was initiated too late or not at all. Apart from the deceptive course, the atypical CSF findings were also misleading in some cases. Moreover, diagnosis might have been delayed due to the fact that tuberculous meningitis is considered today to be a rare disease.

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