

The Encephalopathy of Sepsis

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ABSTRACT: Twelve fatal cases of encephalopathy associated with sepsis were examined in a ten-year retrospective study. The sources of infection and organisms isolated were variable. Six of the patients had focal neurologic signs; five had seizures. The level of consciousness varied from drowsiness to deep coma, and electroencephalograms revealed diffuse or multifocal abnormalities. Computed tomographic head scans and cerebrospinal fluid examinations were usually unremarkable. Eight patients had disseminated microabscesses in the brain at autopsy. Four patients had proliferation of astrocytes and microglia in the cerebral cortex, a feature associated with metabolic encephalopathies. Additional findings included cerebral infarcts, brain purpura, multiple small white matter hemorrhages, and central pontine myelinolysis. Although sepsis may cause encephalopathy by producing disturbances in cerebral synaptic transmission and cerebral energy production through a toxic mechanism, bacterial invasion of the brain with the formation of disseminated microabscesses is also an important cause.

RÉSUMÉ: L'encéphalopathie de la septicémie Au cours d'une étude rétrospective de 10 ans, nous avons étudié 12 cas mortels d'encéphalopathie associée à une septicémie. Les sources d'infection et les organismes isolés sont variables. Six patients avaient des signes neurologiques focalisés; 5 avaient des crises épileptiques. L'état de conscience variait d'un assoupissement au coma profond alors que les électroencéphalogrammes révélaient des anomalies diffuses et multifocales. La tomodensitométrie et l'analyse du liquide céphalorachidien étaient normales. À l'autopsie on trouva chez 8 patients des micro-abcès diffus au cerveau. Chez 4 patients on trouva une prolifération des astrocytes et de la microglie dans le cortex cérébral, une caractéristique souvent associée aux encéphalopathies métaboliques. On nota aussi des infarctus cérébraux, du purpura, des petites hémorragies de la substance blanche et la myélinolyse centrale de la protubérance. Une septicémie peut causer une encéphalopathie en produisant des changements dans les mécanismes de la transmission synaptique ou la production d'énergie par toxines, mais l'invasion bactérienne elle-même du cerveau en produisant des micro-abcès diffus peut également être une cause.

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Sepsis causes malfunction of many organs, including the brain (Eiseman et al 1977; Finley 1976; Pine et al 1983; Polk and Shields 1977). The mortality rate is high (Pine et al 1983). In sepsis there is bloodstream invasion by microorganisms or absorption of their toxins with overt, usually severe, clinical symptoms or signs (Sanford 1985). The brain malfunction occurring in association with sepsis has not been studied systematically, and has received little attention in the literature (Drayna et al 1981; Pendlebury et al 1983; Pine et al 1983). In a ten year retrospective study of clinical and neuropathologic records, twelve patients were identified who developed a diffuse encephalopathy without any recognized cause other than sepsis itself. The clinical and pathologic features of this encephalopathy are described, and possible mechanisms of its production are discussed.

METHODS

Consecutive neuropathologic autopsy records at Victoria Hospital between July 1, 1973 and June 30, 1983 (2,172 cases) were reviewed. Patients with encephalopathy, defined as a diffuse or multifocal disturbance of cerebral function, were initially identified from an index of neuropathologic diagnoses. All records were then reviewed, and only patients with evidence of sepsis, including a source of bacterial or fungal infection and a febrile response, were included. Most patients had positive blood cultures. Patients with other recognized causes of encephalopathy including major biochemical abnormalities, drug intoxication, major structural central nervous system (CNS) meningitis were excluded. Patients with infective endocarditis were also excluded because the clinical features and neurologic

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complications of this disorder are well-known (Pruitt et al 1978). The hospital charts, electroencephalograms (EEGs), and computed tomographic (CT) head scans (performed on an EMI-Scanner CT1010) were reviewed. The neuropathologic records and slides, including special stains, were reviewed by a single neuropathologist (J.J.G.).

RESULTS

Twelve patients met the above criteria (Table 1). These criteria were rigid, and sepsis was likely to have contributed to encephalopathy in many additional cases. The mean age of the patients was 62 years (range: 34-83). The initial sites of infection were variable. The encephalopathy was present on admission to hospital in five patients. In seven it developed while in hospital, with a mean onset of 17 days (range: 2-52 days) following admission. The mean survival in hospital after the development of the encephalopathy was 26 days (range: 5-131 days). Four patients had surgical procedures, including abdominal surgery in three. The mean interval between surgery and development of encephalopathy was 18 days. The patients' level of consciousness ranged from drowsiness to deep coma. Ten patients were comatose at some point during hospitalization, and two had waxing and waning levels of consciousness. Focal neurologic signs were present in six patients. These included hemiparesis (two patients), partial abducens palsies, conjugate gaze paresis, internuclear ophthalmoplegia, and upper motor neuron facial paresis. Five patients had focal or multifocal seizures, and one had generalized convulsions. Disorders that predisposed to infection were present in 75% of the patients.

The infections were polymicrobial in six cases (Table 2), and included *Candida albicans* in three. Bacteremia was documented with positive blood cultures in ten of the twelve cases. All patients had received multiple antibiotics, including drugs that penetrate the blood-brain barrier. Eight patients had cerebrospinal fluid (CSF) examinations, which were performed a mean of 6.0 days either following admission to hospital or after the onset of encephalopathy. Only two patients showed a mild pleocytosis, one predominantly lymphocytic with 7 white cells per mm³ (case 1) and the other predominantly neutrophilic with 35 white cells per mm³ (case 7). All CSF cultures were sterile. The CSF protein ranged from 0.17-0.90 g/L, and glucose from 4.9-11.0 mmol/L. EEGs revealed diffuse or multifocal abnormalities. One patient had a questionable single small hypodense lesion in the parieto-occipital region on a CT head scan. No corresponding lesion was found subsequently on neuropathologic examination (18 days later). Seven patients had normal CT scans (six received contrast enhancement). Four patients did not have CT scans performed.

The most common neuropathologic finding present in 8 of the 12 patients, was multiple microabscesses disseminated throughout the brain. The microabscesses consisted of a collection of polymorphonuclear leukocytes, macrophages, microglia, and necrotic debris (Figure 1). Reactive astrocytosis was often present around the microabscesses. Occasionally the offending organisms were demonstrated with special stains. The microabscesses were not diagnosed during life, and microbial isolation studies were not performed on fresh brain tissue. Although the level of consciousness was more impaired in patients with microabscesses, there was no correlation with the presence of

Table 1: Clinical findings in 12 patients with encephalopathy associated with sepsis

Case	Age (yr.)	Sex	Initial Site of Infection	Focal Signs	Seizures	Predisposing Factors
1	60	F	Lungs	Absent	Multifocal	Diabetes Mellitus
2	68	M	Gall Bladder	Present	None	Ethanol Abuse
3	54	F	Kidney	Terminal	None	None
4	65	M	Vascular Graft	Absent	Multifocal	Ethanol Abuse
5	82	F	Joint	Absent	None	Rheumatoid Arthritis
6	69	M	Uncertain	Present	None	Ethanol Abuse
7	58	F	Lungs	Present	Multifocal, Generalized	None
8	83	F	Intra-abdominal Perforation	Present	Multifocal	Diabetes Mellitus
9	34	M	Kidney	Absent	None	Gastric Adenocarcinoma
10	61	F	Intra-abdominal Perforation	Absent	Focal	None
11	54	F	Intra-abdominal Perforation	Present	None	Diabetes Mellitus
12	59	M	Uncertain	Present	None	Ethanol Abuse

Table 2: Laboratory and pathologic features

Case	Organisms	Blood Cultures	EEG Findings	Pathology
1	Polymicrobial	Positive	Diffuse suppression	Multiple microabscesses, central pontine myelinolysis
2	<i>Klebsiella pneumoniae</i>	Positive	Not done	Multiple microabscesses
3	<i>Staphylococcus aureus</i>	Positive	Diffuse suppression	Multiple microabscesses, cerebral infarcts (terminal)
4	<i>Pseudomonas aeruginosa</i>	Positive	Multifocal epileptiform activity	Proliferation of astrocytes and microglia
5	<i>Staphylococcus aureus</i>	Positive	Multifocal epileptiform activity	Multiple microabscesses, cerebral infarcts
6	Polymicrobial	Positive	Diffuse suppression	Proliferation of astrocytes and microglia
7	<i>Pseudomonas aeruginosa</i>	Negative	Multifocal epileptiform activity	Brain purpura
8	Polymicrobial	Positive	Not done	Proliferation of astrocytes and microglia
9	<i>Escherichia coli</i>	Positive	Not done	Multiple microabscesses, metabolic encephalopathy, central pontine myelinolysis, hemorrhages
10	Polymicrobial	Negative	Burst suppression	Multiple microabscesses, central pontine myelinolysis
11	Polymicrobial	Positive	Technically unsatisfactory	Multiple microabscesses
12	Polymicrobial	Positive	Burst suppression	Multiple microabscesses, cerebral infarcts

microabscesses and focal signs, seizures, or EEG abnormalities. Of the four patients with an infection caused by a single Gram negative organism, only two had microabscesses. Microabscesses or abscesses were commonly found in other organs at autopsy. Four patients had mild proliferation of astrocytes and microglia in the cerebral cortex, changes commonly associated with metabolic encephalopathies (Adams and Sidman 1968). Three of these four patients had no other structural brain lesions. The patient with brain purpura (case 7) had thrombotic thrombocytopenic purpura which developed in association with a bacterial infection. The patient with multiple small white matter hemorrhages had laboratory features and pathologic lesions of disseminated intravascular coagulation (case 9). Only one of the three patients with microscopic evidence of central pontine myelinolysis had documented hyponatremia with rapid correction of the serum sodium.

DISCUSSION

Numerous metabolic derangements are associated with sepsis, including a hyperdynamic circulation, hypercatabolic state, and altered hormonal patterns with elevated catecholamines (Finley 1976). When sepsis is associated with failure of multiple organ systems, a state of critical illness exists in which there is a

mortality rate of about 45% (Eiseman et al 1977). An encephalopathy has been noted previously in critically ill, septic patients (Finley 1976; Jeppsson et al 1981; Pine et al 1983), but the

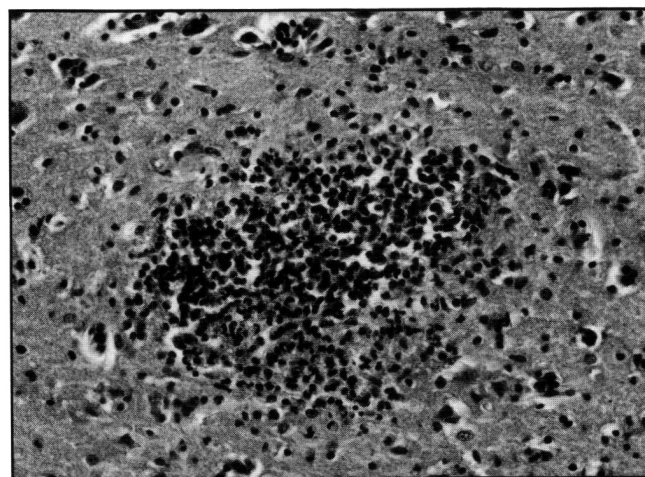


Figure 1 — Microabscess in cerebral cortex. Inflammatory infiltrate of polymorphonuclear leukocytes, macrophages, lymphocytes. The surrounding brain shows microglial proliferation. (Mag. X 627)

clinical and pathologic features have not been described. Recently, Pine et al (1983) reported a prospective study of 109 patients who had intra-abdominal sepsis, and found that ten (9%) developed central nervous system malfunction which was not further characterized. All the cases with such malfunction were fatal. We have observed that polyneuropathy, potentially reversible, occurs in a small, but significant, number of patients with sepsis (Bolton et al 1984).

Evidence for a Metabolic Encephalopathy Caused by Sepsis

There is little documentation in the literature to explain how systemic infections disturb cerebral function. Some experimental work has been directed towards possible toxic or metabolic factors. Lesions of telencephalic white matter, including hypertrophic astrocytes, are associated with human perinatal bacterial infection (Leviton and Gilles 1973; Leviton and Gilles 1984). In neonatal kittens, endotoxin has been shown experimentally to produce lesions of telencephalic white matter, focal necrosis, and changes in glia and endothelial cells (Gilles et al 1977). Endotoxin may have a direct effect on myelination. Thus, there is evidence that Gram negative sepsis, through endotoxin, can produce structural changes in the developing brain.

Disturbances in both cerebral synaptic transmission and cerebral energy production have been recognized in the metabolic encephalopathies (Plum and Posner 1980). Microbial toxins may act by similar mechanisms. In a rat model of sepsis, the brain uptake of several neutral amino acids was increased (Jeppsson et al 1981). A disturbance of the blood-brain barrier could lead to impaired synaptic transmission, as has been proposed in hepatic encephalopathy. An encephalopathy caused by hyperammonemia has been reported in a patient with infection of a neurogenic bladder (Drayna et al 1981). Endotoxins of Gram negative organisms have received the most attention in experimental studies. Bacterial exotoxins and fungal toxins may produce similar effects. Schumer et al (1970) demonstrated endotoxin-induced inhibition of hepatic mitochondrial respiration associated with ultrastructural abnormalities in the mitochondria of rats. Kato (1972) has shown that endotoxin blocks liver cell mitochondrial oxidative phosphorylation in mice. Schmahl (1973) did not find any experimental evidence for a direct effect of endotoxin on the energy metabolism of the cerebral cortex, as reflected by high energy phosphates, which was independent of changes in blood flow and oxygen supply. Electron microscopic studies did not reveal damage to the morphological substrates of the blood-brain barrier, including endothelial cells, basal membranes, and perivascular glia (Schmahl et al 1972). In animal studies of *in vivo* endotoxemia, Mela (1981) found early inhibition of brain mitochondrial function, which was followed by deterioration of mitochondrial function in the liver and kidney. However, the amount of *in vitro* endotoxin required for direct inhibition of mitochondrial function in the absence of other contributing factors was very high. Mela concluded that other factors including biological modification of the endotoxin, lowered tissue perfusion, formation of possible secondary toxins or mediators, activation of lysosomal enzymes, and altered sodium, potassium, magnesium and calcium concentrations should be taken into consideration. Moss et al (1984) and Middlebrook et al (1984) have recently reviewed the mechanisms of action of bacterial toxins at the cellular level.

Encephalopathy Caused by Direct Invasion of Micro-organisms

Micro-organisms can directly invade the brain during the course of a septic illness. Several decades ago, septic patients were described with multiple micro-abscesses in the brain, which were sometimes called embolic or metastatic encephalitis (Alpers et al 1944; Diamond 1928). Similar lesions have been observed in infective endocarditis (Pruitt et al 1978). In a preliminary report, Pendlebury et al (1983) found disseminated microabscesses of the brain in 34% of patients who suffered from central nervous system infections that were identified in a neuropathologic series. The microabscesses were associated with underlying chronic disease, and the patients presented with a progressive encephalopathy which caused waxing and waning in signs and symptoms. Although it is well known that micro-organisms can penetrate the brain during systemic infection and result in the formation of microabscesses, no specific clinical features have been described which allow this diagnosis to be made during life.

One study showed that part of the RNA of bacteria injected intraperitoneally in frogs was subsequently found in brain cells, as a result of the transcription of DNA transferred from bacteria to some brain cells (Anker and Stroun 1972). Thus, bacterial infection may have an effect on the brain through additional mechanisms which are poorly understood.

Etiology of the Encephalopathy of Sepsis

The features of the encephalopathy of sepsis resemble those in multifocal, diffuse, and metabolic brain diseases, which are grouped by Plum and Posner (1980) under the rubric "metabolic encephalopathy." Our patients frequently had focal neurologic signs (50%), but did not otherwise differ from this group. CT head scans and CSF examinations were usually unremarkable, and did not suggest the presence of microabscesses or other lesions. EEGs revealed diffuse or multifocal abnormalities, and reflected the severity of the encephalopathy. Clinical evaluation and investigations were poor predictors of the neuropathologic lesions. However, these patients were from an autopsy series and were identified on pathologic grounds, and they may not be representative of all patients with sepsis-associated encephalopathy. Often the cause of a metabolic encephalopathy is multifactorial, and we suspect sepsis is a common contributing factor. A prospective study would more clearly define the prevalence of various neuropathologic lesions in this syndrome, and allow assessment of the status of other organs and metabolic factors in a standardized manner.

The septic encephalopathy in our patients often developed insidiously in a critical care unit. Such patients are subject to a variety of biochemical derangements, hypoxic and ischemic episodes, and sedative drugs. We excluded patients where these provided an explanation for the encephalopathy. However, a combination of minor degrees of these factors may have an additive effect, a possibility which could not be eliminated.

Multiple microabscesses were common, occurring in eight of the twelve patients. Their precise contribution to the encephalopathy is unknown, and their presence did not correlate with focal signs, seizures or EEG abnormalities, but did correlate with a diminished level of consciousness. Moreover, these microabscesses did not occur simply as a terminal event, since there often was a reaction from the surrounding brain in the form of proliferation of astrocytes and microglia and an inflammatory infiltrate. The microabscesses probably played a significant role in producing the encephalopathy. Nonetheless, three

patients had no structural abnormalities other than mild proliferation of astrocytes and microglia, suggesting that the presence of microabscesses are not essential in producing the encephalopathy, and that toxic or metabolic processes are likely important factors.

Central pontine myelinolysis was an unexpected autopsy finding in three patients. Sepsis is a well known predisposing cause, but in one of our cases central pontine myelinolysis was probably related to rapid correction of hyponatremia. The small infarctions and hemorrhages, each present in two patients, likely represent hematologic complications of sepsis.

The present study suggests that patients with an encephalopathy of sepsis are not a homogeneous group. The encephalopathy is often of insidious onset, and is characterized by a diminished level of consciousness, seizures, and focal neurologic signs. Laboratory investigations are normal or reveal nonspecific abnormalities. In particular, CT head scans and CSF examinations are usually unremarkable, yet the brain may harbor microabscesses. Thus, we feel it is important that the clinician select antimicrobial agents, in appropriate dosages, which penetrate the blood-brain barrier. Although we believe toxic or metabolic factors may play an important role in producing the encephalopathy, there is a paucity of information on the mechanisms by which this occurs. Hence, while management of this aspect of the encephalopathy is still speculative, it seems sensible to treat seizures aggressively, and to attempt to bring the myriad of complications which arise in septic and critically ill patients under control.

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