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UNDERSTANDING THE DISEASE

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Understanding coma in bacterial meningitis

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Introduction

Many patients with bacterial meningitis require intensive care unit (ICU) admission because of an abnormal conscious state, and 15 % of these patients are comatose upon presentation [1]. Such comatose state at presentation is a strong indicator of poor outcome [1–3]. At disease onset, bacterial invasion and the release of bacterial compounds promote inflammation, leukocyte invasion and stimulation of microglia. Inflammatory cells release free radicals, cytokines and excitatory amino acids, causing energy failure and cell death in various brain areas involved in awareness, including brainstem nuclei in the ascending reticular formation, basal forebrain, posterior hypothalamus, and thalamus. Compromised cerebral energy metabolism has been documented by intracerebral microdialysis, with a biochemical pattern of non-ischemic mitochondrial dysfunction [4]. Understanding the mechanisms of coma in patients with bacterial meningitis represents a major challenge for ICU physicians, notably to detect early major intracranial complications requiring additional treatment. Recent data suggest that approximately 20 % of comatose patients with bacterial meningitis will make a full recovery, suggesting the need for continued aggressive supportive care [2, 3, 5].

Causes of coma and their consequences

Cerebral oedema

Cerebral oedema is a common cause of altered mental status and secondary injury in bacterial meningitis. It is caused by a combination of vasogenic, cytotoxic and interstitial oedema (Fig. 1) and may be worsened by systemic hypotension.

In comatose patients with a suspicion of bacterial meningitis, cranial imaging should be performed before lumbar puncture. Therefore, the initial management is to

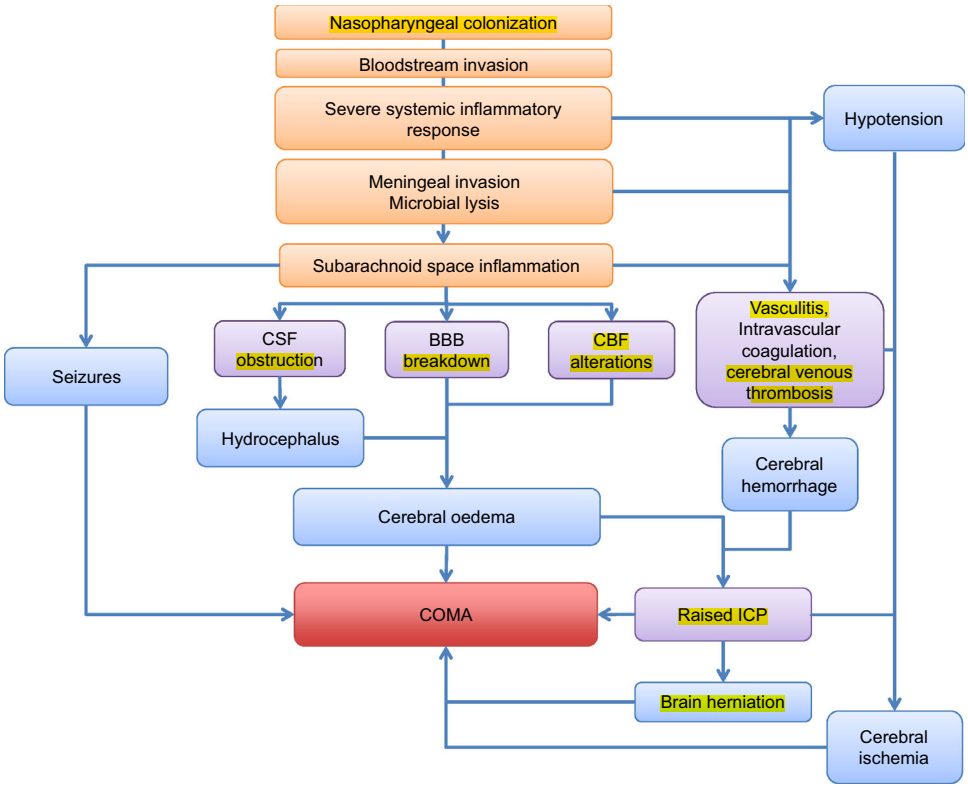

Fig. 1 Hypothetical model of the pathophysiology of coma in patients with acute bacterial meningitis. Coma may result from several complications in bacterial meningitis. Bacterial lysis and the release of pro-inflammatory mediators in the subarachnoid space contribute to cerebral oedema via different mechanisms, including meningeal and cortical inflammation, increased blood–brain barrier permeability and cerebral blood flow alterations leading to predominant vasogenic oedema. Development of cerebral oedema increases cerebral blood volume and intracranial pressure, leading to brain herniation. Various endothelial alterations, including vasculitis, diffuse cerebral intravascular coagulation, and cerebral blood flow dysregulation, lead to development of predominant cytotoxic oedema and cerebral ischemia. In patients with septic shock, acidosis and systemic hypotension may aggravate brain injury by increasing intracranial hypertension and decreasing cerebral perfusion pressure, respectively. Cortical inflammation may induce additional CSF obstruction and hydrocephalus (interstitial oedema). Subarachnoid space inflammation induces (non-convulsive) seizures that may worsen neurological status. *Orange boxes* initial events, *purple boxes* main mechanisms, *blue boxes* clinical manifestations. *CBF* cerebral blood flow, *BBB* blood–brain barrier, *CSF* cerebrospinal fluid, *CBV* cerebral blood volume, *CPP* cerebral perfusion pressure, *ICP* intracranial pressure

obtain blood cultures, initiate dexamethasone if indicated, and antimicrobial therapy as soon as possible. Beneficial effects of corticosteroids have been demonstrated only in high-income countries, with reduced hearing loss and neurological sequelae in all patients, and reduced mortality only in patients with *Streptococcus pneumonia* meningitis. On neuroimaging, early signs of brain oedema include the disappearance of Sylvian fissures and a compression of the ventricles. Neuroimaging abnormalities consistent with diffuse cerebral oedema include a loss of differentiation between grey and white matter, loss of sulcal markings, and absence of visualisation of perimesencephalic, suprasellar and/or quadrigeminal cisterns. Even if brain MRI is the radiologic modality of choice, in the emergency setting a contrast CT scan is a good alternative to promptly rule out any intracranial complications requiring additional invasive therapy, i.e. acute hydrocephalus or cerebral empyema.

Recent observational data suggest that intracranial pressure (ICP)-targeted therapy (mainly cerebrospinal fluid drainage using external ventricular catheters and osmotherapy) may improve the overall outcome in patients with severely impaired mental status [6]. However, no randomised controlled trials have been performed in this setting.

Cerebrovascular lesions

Acute ischemic lesions are observed in 15 % of patients with pneumococcal meningitis [7]. They may result from different intracranial mechanisms (Fig. 1) and may be worsened by hypotension and other systemic insults, including fever and hyperglycemia. Neuropathological data suggest that cerebral infarction in patients with bacterial meningitis is associated with brain

inflammation, microvascular proliferation, small vessel vasculitis, and blood clotting/vessel clogging [8].

Although ischemia resulting from small vessel vasculitis may only be diagnosed with brain MRI, transcranial Doppler (TCD) may help in detecting cerebral blood flow alterations due to cerebral oedema. In one study, an increase in peak systolic values above 150 cm/s on TCD was detected in more than 40 % of patients with bacterial meningitis and was associated with an increased risk of stroke and unfavourable outcome [9]. To date, no specific therapy has proven beneficial in this setting. Cerebral venous thrombosis may be detected in up to 10 % of patients with pneumococcal meningitis.

Seizures and status epilepticus

Seizures occur in 17–20 % of adult patients with bacterial meningitis [7, 10]. They are associated with CNS and systemic inflammation, acute structural CNS lesions, and pneumococcal meningitis [10]. Experts recommend EEG in patients with meningitis/encephalitis that are comatose or have unexplained neurological deficits to rule out non-convulsive seizures and assist with prognosis [11]. With use of continuous EEG monitoring, electric seizures (seizure activity seen on EEG) and/or periodic discharges (repetition of a waveform with no more than three phases with relatively uniform morphology and duration) are observed in 33 % and 40 % of patients with CNS infections, respectively [12]. Although the high associated morbidity and mortality rates may warrant a low threshold for starting anticonvulsant therapy, the potential benefits of systematic seizure prophylaxis have yet to be investigated.

Acute obstructive hydrocephalus

The prevalence of acute obstructive hydrocephalus is dependent on the etiology, occurring in approximately two-thirds of patients with tuberculous meningitis and in less than 5 % of adult patients with community-acquired bacterial meningitis [1, 13]. Although it may resolve completely with emergency external CSF drainage, acute hydrocephalus has an unfavourable impact on the prognosis [13].

Other factors

Hyponatraemia (below 135 mmol/l) and severe hyponatraemia (below 130 mmol/l) are detected at presentation in 35 % and 6 % of patients with bacterial meningitis, respectively [14]. Hospital-acquired hyponatraemia, occurring in approximately 10 % of patients, should be avoided as it may worsen cerebral oedema and neurological status.

High-dose beta-lactam regimens are frequently given to patients with a suspicion of bacterial meningitis. Neurotoxicity may seldom be observed in the form of persistent coma and an increased risk of seizures, especially in older patients with impaired renal function [15]. Therefore, monitoring of serum antibiotic concentrations and repeated EEG are mandatory in patients with unexplained altered mental status. Whether increased blood–brain barrier permeability contributes to a higher antibiotic toxicity is unknown.

Conclusions

The observed alteration of consciousness in bacterial meningitis is likely caused by a complex interplay between cerebral and meningeal inflammation, raised intracranial pressure and resulting intracranial complications in the form of infarction, seizures and obstructive hydrocephalus (Fig. 1). Persistent coma may result from diffuse cortical lesions or from brain injury involving one or more of the areas involved in awareness. Systemic insults, sedative drugs or neurotoxicity by antimicrobial drugs can act as additional confounders in the assessment of the neurological status. Future strategies to improve the outcome of patients should focus on attenuation of the inflammatory response in the subarachnoid space, use of neuroprotective agents that have proven beneficial in the experimental setting, ICP-targeted therapy and multimodal neuromonitoring.

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Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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