Neuroanatomy and Physiology of Brain Dysfunction in Sepsis

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KEYWORDS

• Sepsis-associated encephalopathy • Sepsis • Neuroinflammation • Amygdala • Hippocampus • Neuroanatomy

KEY POINTS

- Sepsis-associated encephalopathy induces acute and long-term brain dysfunction.
- Its pathophysiology involves neuroinflammation, microcirculatory alterations, and excitotoxicity.
- Excitotoxicity might occur in specific areas and be involved in the increased mortality, psychological disorders, and cognitive impairment reported in septic patients.

INTRODUCTION

Sepsis-associated encephalopathy (SAE), a major complication of sepsis, is characterized by impaired consciousness, including delirium and coma. Additionally SAE associates with changes in electroencephalogram (EEG) patterns.[1–3] Neuroimaging is usually unremarkable; white matter hyperintensities or some evidence of ischemic stroke may be seen.[4,5] SAE is associated with increased mortality[6] as well as long-term cognitive impairments,[7–10] including impaired memory, attention and verbal fluency difficulties,[7,8] and psychological disorders including depression,[8] anxiety, and posttraumatic stress disorders.[11–13] The pathophysiology of SAE remains unclear; 3 major processes seem to be involved, including diffuse neuroinflammation, circulatory dysfunction, and excitotoxicity. Whereas neuroinflammation and microcirculatory alterations are diffuse, pathologic examination of the brain of fatal cases of sepsis consistently exhibits increased apoptosis in specific structures (ie, the amygdala, *nucleus tractus solitarii* and *locus ceruleus*). These structures activate in response to stress and are especially sensitive to hypoxia, leading to excitotoxic processes, structural changes, and neurologic dysfunction.[14,15] Theses structural dysfunctions may be responsible for the clinical signs of sepsis-associated brain dysfunction. We review the clinical characteristics of SAE and present an overview of the current knowledge of its pathophysiology.

CLINICAL PRESENTATION

Acute Brain Response During Sepsis

The response of the central nervous system to sepsis is triggered by multiple peripheral

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mediators involving complexly interconnected structures that control both the behavior and cognition, as well as the autonomic and neuroendocrine systems, which in turn drive the immune response.[16–20] This response may broadly be described as either adapted to the severity of sepsis or maladapted/pathologic.[21,22] Such a distinction supposes that the response of the central nervous system may either contribute to the recovery from or a worsening of sepsis. However, such a categorization is not based on well-established clinicobiological criteria. Before disruption of the blood–brain barrier (BBB), 2 distinct pathways are responsible of transmitting inflammatory signals to the brain, namely, the vagal nerve, which senses peripheral inflammatory mediators and transfers the information to the medullary autonomic nuclei,[23,24] and the circumventricular organs, which enables the passage of inflammatory mediators into the cerebral parenchyma.[25,26] The neural first centers to be activated through these neural pathways during sepsis are the *nucleus tractus solitarii* and *locus ceruleus*,[23,24] which are involved in the control of blood pressure, heart rate, and arousal. These neural centers then relay the signal to the other autonomic nuclei as well as the behavioral and neuroendocrine centers. Thus, behavioral changes, coined sickness behavior, are the earliest feature of sepsis.[15] Sickness behavior is characterized by decreased interaction with the environment (social withdrawal), impaired cognitive function (psychomotor retardation, impaired attention), and altered vigilance (anxiety, hypersomnia, fatigue, sleepiness), as well as eating disorders (anorexia, weight loss, thirst). Sickness behavior is partly a physiologic reaction to stress associated with reduced metabolic expenditure. Impaired attention or fluctuating vigilance found in SAE are similar to signs exhibited during hypoactive delirium.[27] Anxiety, which is regulated by the limbic system, may have deleterious effects when too intense. The exact significance and prognostic value of anxiety and behavioral changes in critically ill patients are currently being assessed in a prospective multicenter observational study (ClinicalTrials.gov, NCT02355626).

Sepsis may be associated with acute brain dysfunction, or encephalopathy, characterized by altered consciousness ranging from delirium to coma[6,28] and with focal deficits[5] or even seizures.[29] Delirium induced by sepsis is usually hypoactive, although the hyperactive subtype that is associated with agitation may also be observed.[27] In sedated critically ill patients, abolished brainstem reflexes may be a marker of brainstem dysfunction.[30] Acute brain dysfunction should routinely be identified using validated scales assessing the existence of delirium (ie, Intensive Care Delirium Screening Checklist or Confusion Assessment Method for the ICU),[31] coma (Glasgow Coma Scale), as well as brainstem reflexes in comatose patients (Full Outline of UnResponsiveness [FOUR] score).[32] A full medical history followed by clinical examination and routine blood chemistry are required to reject other causes of acute brain dysfunction including electrolyte disturbance, renal or liver dysfunction, drug side effects (notably antibiotic overdose), and alcohol or drug withdrawal. Cerebrospinal fluid should be obtained whenever meningitis is suspected (in the absence of contraindication) and vitamins B_1 and B_6 systematically given to alcoholic or malnourished patients.

Neurophysiologic Tests and Neuroimaging Procedures

SAE may be associated with anomalous EEG patterns. Observed EEG patterns include slow waves, rhythmic delta or theta activity, triphasic waves or burst suppression, periodic epileptiform discharges, electrographic seizures, and absent reactivity.[1,2,5,29] The prevalence of these neurophysiologic patterns depend on the severity of encephalopathy,[1] the severity and the time course (ie, acute vs postacute phase) of sepsis, the type of patients (medical vs surgical), and the prior use of sedation.[1,29] A recent prospective study assessed 110 subjects monitored by standard EEG within 3 days of admission to the intensive care unit (ICU) for sepsis. Predominant theta rhythm was observed in 48%, low voltage in 65%, triphasic waves in 6%, periodic epileptiform discharges in 19%, electrographic seizure in 15%, and absence of reactivity in 25% of cases.[1] Electrographic seizures were associated with delirium at the time of recording, whereas a delta-predominant rhythm was associated with the subsequent occurrence of delirium. Continuous EEG makes the detection of periodic epileptiform discharges and electrographic seizure easier[29]; however, its routine use is not recommended.[2] Of note, none of the previously mentioned pattern is specific for sepsis. Several classifications grading EEG patterns have been described, including the classification of Synek and the classification of Young, which was specifically developed for septic patients.[1] EEG monitoring does not demonstrably impact the management or the outcome of septic associated brain dysfunction and is therefore not recommended in routine care. However, EEG monitoring in septic patients developing an acute brain