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Sepsis and the brain: a review for acute and general physicians

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ABSTRACT

Sepsis-associated encephalopathy (SAE) describes acute cognitive dysfunction secondary to systemic or peripheral infection occurring outside of the central nervous system (CNS). Symptoms can range from mild confusion to coma and may precede the clinical signs of sepsis. Recognition that SAE is a potential differential diagnosis in patients presenting with delirium is important, as SAE is a diagnosis of exclusion. Physicians should also be aware that severe SAE is associated with a high mortality. Although mortality is often secondary to multiorgan failure rather than neurological sequelae, long-term cognitive and psychological morbidities have been reported in sepsis survivors. Early treatment (which can include prompt identification and source control of the infection) and good supportive care might improve cognitive outcomes. Future work should aim to improve understanding of both acute and chronic SAE with a focus on therapeutic interventions and improving patient outcomes.

Introduction: definitions, pathophysiology and epidemiology

Sepsis-associated encephalopathy (SAE) is a term that has been used to describe acute cognitive dysfunction in patients with systemic or peripheral infections in the absence of central nervous system (CNS) infection and other causes of encephalopathy. SAE is a frequent complication of sepsis, affecting up to 70% of patients, and is a leading cause of delirium; a commonly encountered, but poorly understood, acute disorder of consciousness that is estimated to affect 20%–30% of patients on medical wards.[1,2] SAE is prevalent within intensive care units, perhaps in part because patients with single- or multi-organ failure are more frequently affected than those without organ failure.[3] Patients with SAE have higher mortality rates when compared with those with pre-existing altered mental status or no change in mental status (49%, 41% and 26%, respectively) in association with infection.[4] However, exact incidence, prevalence and mortality data for SAE remains limited, as the spectrum of clinical presentations of SAE and lack of a consensus definition makes diagnosis challenging.

Evaluating cerebral physiology and cognitive function during episodes of sepsis in humans has also proven challenging for researchers, so much of our knowledge regarding SAE comes from animal models.[5] A post-mortem study of delirium in humans found activated microglia and astrocytes as well as elevated levels of interleukin-6 (IL-6) in the hippocampus of brain tissue samples, suggesting that inflammatory mechanisms play a significant role in cognitive dysfunction.[6] However, the exact pathophysiology of SAE remains incompletely understood, and several other mechanisms have been proposed (Fig 1).[7]

Key points

Sepsis-associated encephalopathy (SAE) describes an acute cognitive dysfunction that occurs secondary to systemic or peripheral infection outside of the central nervous system.

SAE is an important cause of delirium and acute cognitive dysfunction in the context of infection, it is associated with increased mortality, and it may be associated with a greater risk of subsequent cognitive decline / dementia in survivors.

The pathophysiology is poorly understood but likely involves systemic inflammation in response to infection driving microglial activation and blood–brain barrier dysfunction.

Numerous cognitive assessment tools are available for the detection of delirium with varying sensitivity, although none are specific for SAE. The 4AT is a useful bedside tool to test for significant SAE and delirium.

Prompt source control and antimicrobial therapy with good supportive care are the cornerstones of management. Specific agents, such as the alpha-2 agonist dexmedetomidine, have shown some promise in postoperative delirium and may be useful in SAE, but further trials are needed.

KEYWORDS: sepsis, encephalopathy, delirium, brain

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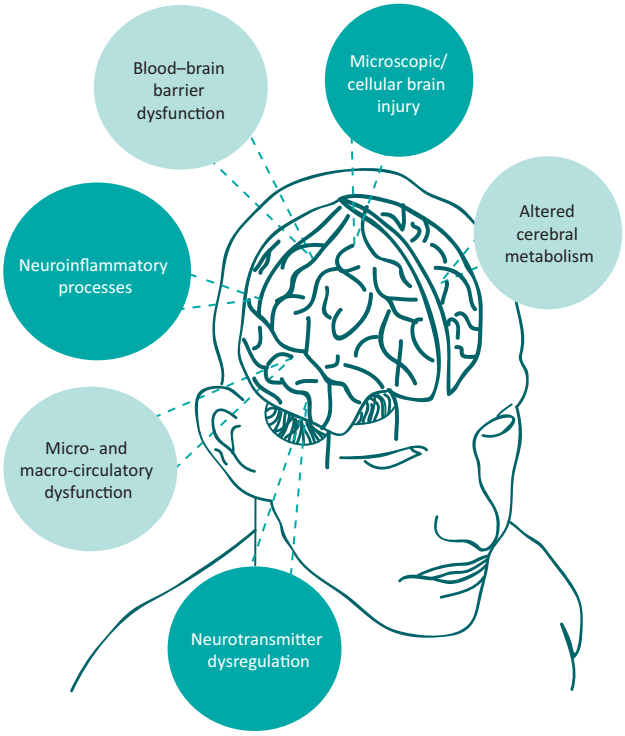

Fig 1. Proposed mechanisms of sepsis-associated encephalopathy.

In reality, the aetiology of SAE is likely to be multi-factorial, with the role and significance of different factors varying between individual patients and clinical contexts. Another key consideration is the degree of pre-existing brain injury and 'cognitive reserve' that patients have, as this influences the magnitude of insults needed to perturb brain homeostasis such that overt cognitive dysfunction is evident.[8]

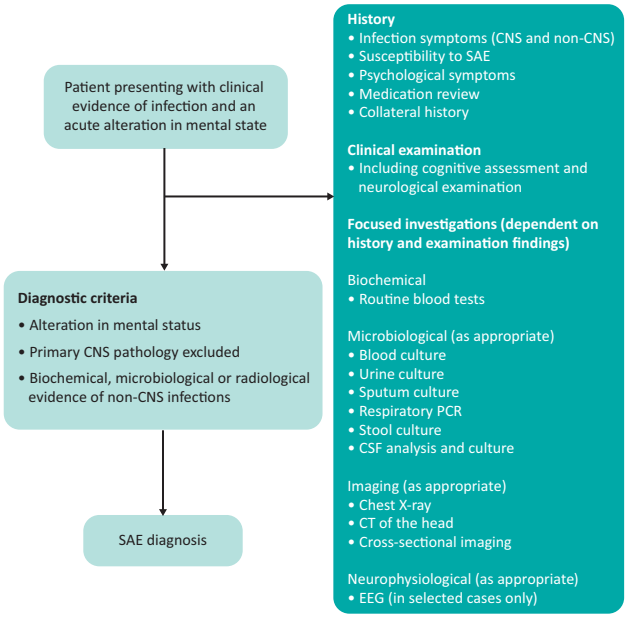

Fig 2. Diagnostic algorithm for sepsis-associated encephalopathy.
CNS = central nervous system; CSF = cerebrospinal fluid; CT = computed tomography; EEG = electroencephalography; SAE = sepsis-associated encephalopathy.

Clinical assessment and investigations

SAE should be suspected in patients presenting with evidence of infection and an acute alteration in mental state. The spectrum of cognitive dysfunction seen in SAE can range from reduced concentration to mild confusion, with or without agitation and auditory/visual hallucinations, to fluctuations in consciousness and even coma.[7]

Although abnormalities have been noted on computed tomography and/or magnetic resonance imaging, electroencephalography (EEG), somatosensory evoked potentials, and elevated biomarkers of brain injury (such as neuron-specific enolase and protein S100b testing in some cases of SAE), it is worth noting that there are currently no specific neuroradiological, physiological or biochemical investigations that can reliably diagnose SAE.[9]

SAE is essentially a diagnosis of exclusion, so the primary focus of clinicians should initially be on rapidly ruling out primary CNS pathologies. Concurrently, sources of non-CNS infection should be identified and investigated appropriately. Differential diagnoses for SAE can include bacterial or viral meningitis, encephalitis, cerebral abscess, malignancy, significant electrolyte disturbances, illicit or prescription drug use, traumatic brain injury, or cerebrovascular disease.

Overall, SAE remains a predominantly clinical diagnosis (Fig 2) and relies on physicians undertaking thorough clinical histories, physical examinations and cognitive assessments in all patients suspected of having SAE. Clinicians should be mindful that SAE is a much more common cause of acute confusion in a patient presenting with a fever than primary CNS infections (such as HSV encephalitis) and, given the breadth of differential diagnoses available, a pragmatic approach to diagnosing SAE should be encouraged. If, for example, a 75-year-old presenting with isolated acute confusion is found to have pneumonia, an exhaustive search to exclude co-existent CNS infection is unnecessary and SAE can be diagnosed.

Key points in history taking and physical examination

Clinical history taking in suspected SAE should include an exploration of current, or recent, infection symptoms (both CNS and non-CNS), symptoms of organ dysfunction, susceptibility to SAE (eg previous CNS pathology or episodes of delirium), symptoms suggestive of alteration in mental state, mood disturbance and substance misuse. A medication review should also be carried out.

Physical examination should be focused on determining a potential source of infection. Specific types of organ dysfunction can also have observable clinical signs (for example, jaundice in liver failure) and may indicate alternative causes of encephalopathy. Neurological examination in SAE is often unremarkable, with focal signs (such as hemiparesis or cranial nerve dysfunction) suggesting an alternative aetiology. However, patients with SAE may demonstrate signs of delirium including agitation, hallucinations, reduced concentration and inattention throughout the clinical exam. Patients with SAE may also be expected to have a fluctuating or reduced level of consciousness. This can progress to coma, so physicians should be vigilant for any change in a patient's mental status.

Table 1. Rapid delirium screening tools

Assessment tool	Questions	Outcome
Short Confusion Assessment Method[10]	1. **Acute onset and fluctuating course** 2. **Inattention** 3. **Disorganised thinking** 4. **Altered levels of consciousness**	Positive for delirium if both '1' and '2' are present, with at least one of '3' or '4'.
4 'A's Test[11]	> **Alertness:** Normal = 0 Mild sleepiness for <10 seconds after waking, then normal = 0 Clearly abnormal = 4 > **AMT-4 (age, date of birth, place, year):** No mistakes = 0 1 mistake = 1 ≥2 mistakes = 2 > **Attention (list months of the year in reverse):** Lists ≥7 months correctly = 0 Lists <7 months, or refuses to start = 1 Untestable = 2 > **Acute change or fluctuating course:** No = 0 Yes = 4	Score ≥4 is possible delirium and/or cognitive impairment

AMT-4 = Abbreviated Mental Test-4.

History and examination may be complicated by SAE, so rapid delirium screening should be undertaken early to determine the reliability of information obtained from the patient. Collateral history is often essential to determine baseline cognitive function and trajectory of changes.

Assessment of delirium

While the early detection of delirium is valuable for the eventual diagnosis of SAE, it is important that physicians remember that delirium and SAE are not synonymous, as SAE is only one of many causes of delirium. Gofton and Young suggest using the Confusion Assessment Method (CAM) to detect delirium in non-intensive care unit patients due to its sensitivity (94%–100%) and high positive predictive value (91%–94%).[7] However, a full CAM assessment is often impractical during the acute assessment of patients on the medical take. Alternatively, rapid screening tools such as the short CAM and the 4 A's Test for Delirium (4AT; Table 1) are more specific than tests that don't appropriately test attention, such as the Abbreviated Mental Test-4 (AMT-4).[10,11] This test has good sensitivity but poor specificity for delirium.[12] For the acute medical take, months of the year backwards (MOTYB) is likely the most reliable single item bedside test for delirium.[13]

Key aspects of management

Prompt treatment of sepsis limits the opportunity for development of adverse cognitive sequelae. As SAE does not correlate with direct CNS infection, treatment should be directed towards the most likely source of peripheral or systemic infection. In the absence of an overt infection source, or identified causative organism, broad-spectrum antibiotics should be administered after appropriate cultures have been taken. Once an infection syndrome (such as pneumonia) or causative organism has been identified, antibiotic therapy can be narrowed in accordance with antibiotic resistance patterns and local antibiotic guidelines. Care should also be taken to consider common viral causes of SAE (such as respiratory viruses) as potential therapeutic options are available for influenza (eg antivirals) and COVID-19 (eg antivirals, immunomodulators and other agents). Supportive management is also crucial to avoid further neurological insults, particularly addressing abnormal physiology, comorbidities, nutrition and electrolytes.

Despite numerous trials of pharmacological interventions, no effective treatment options have been identified for the management of SAE.[7] Additionally, some commonly used drugs (such as psychotropic medications, benzodiazepines and opioids) can be independent risk factors in the development/maintenance of delirium, and should be withheld where possible in cases of SAE.[14] Low-dose haloperidol remains the only medication currently licensed for use in delirium, although it is typically reserved for cases of severe agitation or psychosis and has not been shown to significantly reduce the incidence of delirium when used prophylactically.[2,15] More recently, trials of prophylactic dexmedetomidine have shown some promise in reducing postoperative delirium, and these findings may translate to patients with SAE due to a potential common mechanism involving attenuation of the pro-inflammatory cytokine (IL-6) response.[16]

Given the limited pharmacological therapies available, non-pharmacological strategies are important for managing acute delirium in SAE, such as maintaining a normal sleep–wake cycle; natural light; reduction of environmental stimulation, where possible; music therapy; ensuring patients have their glasses, hearing aids or communication aids, if needed; and access to devices that encourage orientation (such as clocks or windows).[17]

Prognosis

The relationship between SAE and long-term cognitive impairment is unclear. However, there are data to suggest that significant infections (ie those that cause hospitalisation) are associated with subsequent significant cognitive decline.[18] Similarly, systemic inflammatory events, the majority of which were secondary to infections, have been reported to hasten the onset of dementia and accelerate progression in those with an established diagnosis.[19,20] Therefore, understanding the pathophysiology of SAE and testing therapeutics in clinical trials is important with an ageing and increasingly comorbid society.

Conclusion

SAE is a heterogenous condition due to variability in culprit pathogens, pathophysiology and treatment. It remains a frequent, acute complication of sepsis with chronic sequelae in some,

highlighting that the brain is an organ that can be profoundly affected during episodes of infection. ■

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