

SEPSIS ASSOCIATED ENCEPHALOPATHY (SAE): A REVIEW

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1. ABSTRACT

Sepsis associated encephalopathy (SAE) is a poorly understood condition that is associated with severe sepsis and appears to have a negative influence on survival. The incidence of encephalopathy secondary to sepsis is unknown. Amino acid derangements, blood-brain barrier disruption, abnormal neurotransmitters, and direct CNS effect are possible causes of septic encephalopathy. Research has not defined the pathogenesis of SAE.

2. INTRODUCTION

Sepsis associated encephalopathy (SAE) is a poorly understood condition that is associated with severe sepsis and appears to have a negative influence on survivability. However, little is known about this clinical process or whether the process is the result of other organ dysfunctions or a primary response to sepsis. What is recognized is that it has prognostic significance. For example a large Veterans Administration study revealed a mortality of 49% in patients with sepsis and acute mental status changes compared to a mortality of 26% in patients with normal mental status (1). There did not appear to be a correlation between the organism isolated and the degree of mental status changes. It is also unclear how mental status changes correlate with other organ failures.

3. SEVERE SEPSIS

As demonstrated in figure 1, sepsis has steadily risen over the past twenty years. Approximately 750,000 cases of sepsis occur in the United States yearly, resulting in approximately 200,000 deaths (2). Sepsis is defined as a systemic inflammatory response generated by an infectious insult. A systemic inflammatory response syndrome is characterized by at least two of the following: temperature greater than 38°C or less than 36°C; heart rate greater than

90 beats per minute; respiratory rate more than 20/minute or PaCO₂ less than 32 mm Hg; and an alteration in white blood cell count (>12,000/mm³ or <4,000/mm³) (3). Septic shock is further defined as severe sepsis with hypotension not responsive to fluid resuscitation and evidence of inadequate organ perfusion (4).

Over the past several years our understanding of the pathogenesis and treatment of severe sepsis has increased significantly. New treatments such as activated protein C, aggressive control of serum glucose with intensive insulin regimens, goal oriented fluid resuscitation and treatment of relative adrenal insufficiency has led to a new era in the treatment of sepsis (5,6,7,8). Plasmapheresis is also being investigated as an adjunct therapy for patients with severe sepsis and septic shock (9). Antibiotics are not the only weapons available to fight this devastating process.

In spite of these recent advances in the understanding and treatment of severe sepsis, there are many aspects of severe sepsis and sepsis related organ failures that remain poorly understood. Leading this list is the neurologic complications related to sepsis.

4. INCIDENCE OF SAE

Severe sepsis can lead to several major organ dysfunctions with lung failure the most frequently involved system. As shown in figure 2, cardiovascular, renal and CNS dysfunction follow close behind with these systems occurring in over 20% of patients with MODS. The exact incidence of encephalopathy complicating sepsis is unknown. Several studies have reported the impact of SAE on mortality. Sprung *et al* reported that 23% of patients enrolled in the Veterans Administration Systemic Sepsis Cooperative Group developed mental status changes. There was significantly higher mortality in the SAE group (49%)

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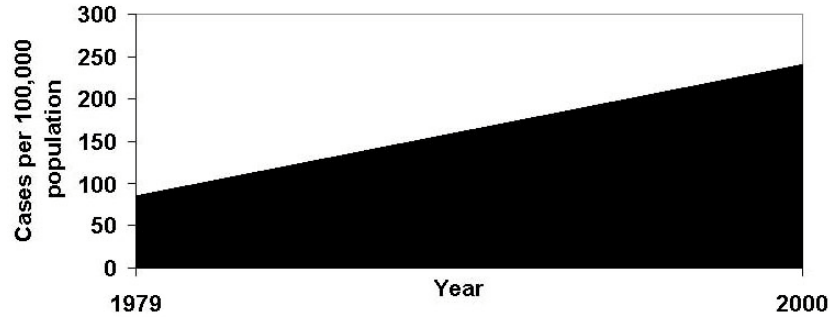


Figure 1. Incidence of sepsis from 1979 to 2000.

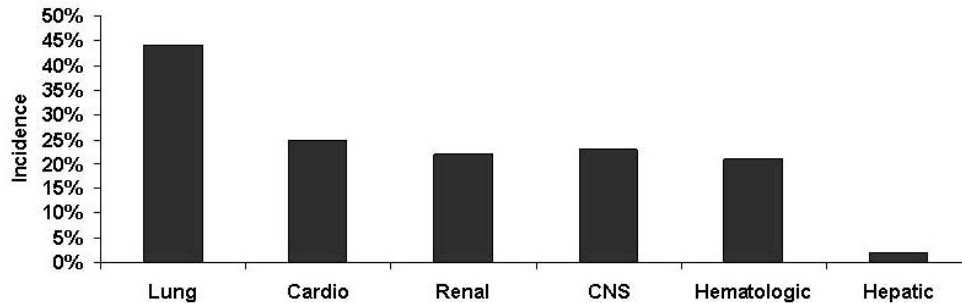


Figure 2. Organ failure frequency in patients with severe sepsis and MODS.

compared to similar patients without mental status changes (26%, $p < .000001$) (10). The mental status changes in this group were independent of blood culture positivity or type of organism isolated.

5. PATHOGENESIS

The etiology of encephalopathy associated with sepsis is unclear. A documented decrease in the ratio of branched chain amino acids to aromatic amino acids has been reported in patients with sepsis and encephalopathy without evidence of liver disease (11). This amino acid ratio and mental status demonstrate a similarity of the encephalopathic changes noted in sepsis and porta-systemic encephalopathy. However, other pathophysiologic processes appear to enter into the mix.

Numerous animal and human studies have helped to explain SAE. The major focus appears to be the clinical relationship of SAE to porta-systemic encephalopathy. Focusing on this area has shed some light onto the understanding of SAE, however, numerous other hypotheses have been postulated.

There are many proposed mechanisms for the SAE. These include direct bacterial invasion and/or endotoxin effects, altered amino acid profiles, deranged neurotransmitters, and blood brain barrier alterations.

5.1. Bacterial Invasion/ Endotoxin

It has been proposed that SAE is caused by direct effect of bacteria and/or endotoxin on the brain. Jackson *et al* retrospectively reviewed twelve fatal cases of encephalopathy associated with sepsis. Although CSF

analysis and CT head were unremarkable, at autopsy eight patients were found to have disseminated brain micro-abscesses. They concluded that bacterial invasion of the brain was an important cause of septic encephalopathy despite negative clinical evaluation for CNS infection (12).

Endotoxin has also been implicated to cause direct effects on the brain. Kadoi *et al* demonstrated impairment of the beta-adrenergic system of the brain in mice treated with LPS (lipopolysaccharide) and CLP (cecal ligation and puncture). Epinephrine, norepinephrine and beta-adrenergic receptors were found to be significantly decreased in the forebrain of the mice with sepsis (13).

5.2. Blood-Brain Barrier

Previous studies have revealed that during sepsis, plasma and brain amino acids and neurotransmitters are significantly altered (14). It has been proposed that because both plasma and brain levels are altered, the blood-brain barrier must be affected during sepsis. Jeppsson *et al* studied neutral amino acid transport across the blood-brain barrier in septic mice. They demonstrated that elevated brain neutral amino acids were caused by increased transport and uptake by the blood-brain barrier. They also showed that elevated levels of brain aromatic amino acids were due to decreased competition between the neutral amino acids for blood-brain transport and the branched chain amino acids (15).

5.3. Amino Acid Derangements

Sepsis causes a severe prolonged, catabolic state. Muscle tissue is broken down to amino acids, both branched chain and aromatic. The aromatic amino acids

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are taken to the liver and metabolized, while the branched chain amino acids are used by muscle for energy in severe catabolic states. Several studies have demonstrated alterations of amino acids levels in the brain and serum in sepsis. Basler *et al* studied plasma amino acid concentrations in patients with sepsis and their correlation with procalcitonin (PCT) and interleukin-6 (IL-6) in patients with encephalopathy. They revealed significant decreases in plasma branched-chain amino acids and increased plasma aromatic amino acids in patients with documented encephalopathy. The changes were seen in early sepsis before multiorgan failure was present. Interleukin-6 and procalcitonin were both elevated in patients with septic encephalopathy. High levels of IL-6 and PCT correlated with more severe the metabolic derangements of the amino acids. They postulated that these metabolic disturbances were a significant contributing factor in the pathogenesis of encephalopathy of sepsis (16).

Sprung *et al* also evaluated the amino acid profiles in patients with encephalopathy due to sepsis. They concluded that patients with encephalopathy had higher levels of aromatic amino acids as compared to patients with infections and normal mental status. They also found that patients who died had significantly higher levels of aromatic amino acids than those who survived (17). Freund *et al* studied plasma amino acids as predictors of mortality in sepsis. They demonstrated that patients who died exhibited higher levels of aromatic and sulfur containing amino acids than those who survived sepsis. It was also demonstrated that patients who survived sepsis had higher levels of the branched chain amino acids (18). Based on this information, many groups have postulated that infusion of branched chain amino acids during sepsis would decrease muscle catabolism and improve mortality. VonMeyenfildt *et al* gave septic patients infusions of TPN enriched with branched chain amino acids and found no significant decrease in mortality (19). Bower *et al* also did not show improved mortality in surgical intensive care unit patients who received branched chain amino acid infusions (20).

Many of the current research and data focuses on hepatic failure with associated encephalopathy. In the study by Mizock *et al*, phenylalanine metabolism in sepsis was compared to hepatic encephalopathy. They concluded that there was a significant increase in the ratio of CSF/serum phenylacetic acid, a metabolite of phenylalanine, in patients with hepatic encephalopathy that was not seen in septic patients. They also found increased CSF concentrations of all the aromatics were found in patients with hepatic encephalopathy, while only phenylalanine was increased in those patients with septic encephalopathy (21).

5.4. Neurotransmitters

Altered neurotransmitters are thought to play a significant role in the development of acute Sepsis associated encephalopathy. Freund *et al* studied brain adrenergic and serotonergic neurotransmitter profiles in septic mice. They found significantly decreased levels of dopamine, norepinephrine, and serotonin metabolites in septic mice as compared to mice with mild sepsis and no

encephalopathy. They also demonstrated that the septic mice had higher levels of most essential amino acids (22). In a later study, Freund *et al* compared regional brain catecholamine and indoleamine neurotransmitter profiles in the septic mice (23). They found increased levels of indoleamines and increased brain tryptophan levels felt to be secondary to increased metabolism of serotonin.

Freund *et al* then gave the septic mice branched chain amino acids to see the effects of the neurotransmitter profile. Levels were again measured and the brain neurotransmitter profile and amino acids were restored. They postulated that these derangements in neurotransmitter profiles in septic mice play an important role in the development of encephalopathy .

Another possible hypothesis involves the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Winder *et al* studied plasma and brain GABA concentrations in septic mice and compared to controls. All the septic animals with clinical signs of encephalopathy had increased serum levels of GABA. Brain levels were increased in sepsis, but not significantly. They concluded that GABA was unlikely to play an important role in the pathogenesis of encephalopathy of sepsis (24). Minuk measured GABA production of common bacterial pathogens proposing their role in neuronal suppression in hepatic encephalopathy. The study suggested that both aerobic and anaerobic bacteria are able to produce large amounts of GABA (25). It is not known whether the GABA crosses the blood-brain barrier and exerts direct suppressive effects on the brain .

Another proposed theory involves the presence of false neurotransmitters. The elevated levels of tyrosine and phenylalanine in the brain during sepsis lead to increase levels of their breakdown products, B-phenylethylamine and octopamine. These products are may directly inhibit the central noradrenergic pathways. Cangiano *et al* studied the levels of false neurotransmitters in patients with hepatic coma. They demonstrated that the degree of hepatic encephalopathy correlated with levels of plasma octopamine and b-phenylethylamine (26). Nespoli *et al* also found that increased levels of the false neurotransmitters correlated with the amount of hepatic encephalopathy (27). No studies have been done on the role of false neurotransmitters in septic encephalopathy.

5.5. Miscellaneous

Several other mechanisms thought to play a role in encephalopathy of sepsis have been proposed, but limited data available. Soejima *et al* studied local glucose utilization in septic mice with encephalopathy. The results suggested that there are metabolic changes in discrete brain regions, those related to the serotonergic or noradrenergic system, in septic mice with encephalopathy (28).

Zhan *et al* demonstrated regional calcium deregulation at the cellular level in different regions of the brain in the mouse model of sepsis. They propose that this deregulation of calcium could contribute to the pathogenesis of encephalopathy (29).

It has also been proposed that cerebral blood flow alterations during sepsis are the cause of septic

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encephalopathy. Moller *et al* found that after injection of endotoxin cerebral blood flow was significantly reduced, although cerebral oxidative metabolism was not reduced (30).

Regardless of the cause, SAE is a real clinical process that has significant influences on outcome. Electroencephalogram data has confirmed characteristic changes that appear to correlate to the severity of encephalopathy and may be useful in monitoring patients in the intensive care setting (31).

6. FUTURE DIRECTIONS

Research on CNS disorders has entered a new era with the expanded use of microarray technology. This technology permits the analysis of thousands of genes at one time point allowing the simultaneous assessment of numerous pathways (32). Understanding the genetic information of a particular disorder can lead to the identification of the pathways involved and can also help to discover previously unidentified pathways that may contribute to a disorder. Encephalopathy associated with sepsis seems particularly well suited for this technology due to the multifactorial pathways that appear to contribute to this disorder.

7. CONCLUSION

The etiology of the Sepsis associated encephalopathy remains unclear. The differing theories and biochemical alterations described suggest SAE involves many metabolic pathways and biochemical derangements. What is known is that the presence of SAE has a negative impact on survival and therefore deserves further investigation.

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