

Sepsis-associated Encephalopathy

a report by

L Keith Scott, MD

*Assistant Professor of Emergency Medicine, Medicine, Pediatrics and Bioinformatics and Computational Biology,
Louisiana State University Health Sciences Center*



L Keith Scott, MD, is Assistant Professor of Emergency Medicine, Medicine, Pediatrics and Bioinformatics and Computational Biology at Louisiana State University Health Sciences Center (LSUHSC), Shreveport, Louisiana. He is also Director of Renal and Plasma Services for the Extracorporeal Life Support Service at LSUHSC. Dr Scott's research interests include the central nervous system (CNS) response to critical illness, genomics and computational biologic evaluation of sepsis and inflammation, and the use of plasma therapy as an adjunct treatment in severe sepsis. Additional interest includes the use of spontaneous respiration in the critically ill as a lung protective strategy and nutritional support in the critically ill.

Sepsis-associated encephalopathy (SAE) is a poorly understood central nervous system condition that is associated with severe sepsis and has a wide range of manifestations, from lethargy to overt delirium. Little is known about this clinical process. What is becoming widely recognized, however, is that it has serious prognostic significance. A large Veterans Administration (VA) study revealed a mortality of 49% in patients with sepsis and acute mental status changes compared with a mortality of 26% in patients with normal mental status.¹ There does not appear to be a correlation between a specific organism isolated and the degree of mental status change observed. Currently, it remains unclear how mental status changes contribute to mortality or whether the mental status changes are a sign of disease severity or represent maladaptation to a disease process. Either way, it has profound influences on outcome and needs to be raised to a level of concern given other organ system failures such as renal, hepatic, or hematological.

Pathogenesis

The etiology of encephalopathy associated with sepsis is unclear. Numerous animal and human studies have been undertaken to help explain SAE. The major focus, however, appears to be on the clinical similarity of SAE to portal-systemic encephalopathy. Focusing on this area has shed some light onto understanding SAE; however, numerous other proposed mechanisms have also been postulated.

Bacterial Invasion

Jackson et al. retrospectively analyzed 12 fatal cases of encephalopathy associated with sepsis. Although cerebrospinal fluid (CSF) analysis and computed tomography (CT) imaging of the brain were

unremarkable pre-mortem, at autopsy eight of the 12 patients were found to have disseminated brain microabscesses. They concluded that bacterial invasion of the brain was an important cause of septic encephalopathy despite negative clinical evidence for a central nervous system (CNS) infection.²

Endotoxin

Endotoxin has also been implicated to cause direct effects on brain homeostasis. Kadoi et al. demonstrated impairment of the beta-adrenergic system of the brain in mice treated with lipopolysaccharide (LPS) and in mice that underwent cecal ligation and puncture. Epinephrine and norepinephrine concentrations, along with beta-adrenergic receptors, were found to be significantly decreased in the forebrain of the mice with sepsis (cecal ligation and puncture (CLP) group) and in mice that received endotoxin (LPS group). The investigators concluded that endotoxin caused down-regulation of the beta-adrenergic system.³

Blood-Brain Barrier Transport

Previous studies have revealed that during sepsis, plasma and brain amino acids and neurotransmitters are significantly altered. Because of the alteration of both plasma and brain levels, it has been proposed that 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.⁴

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2. Jackson A C, Gilbert J J, Young G B, Bolton C F, "The Encephalopathy of Sepsis", *Can. J. Neurol Sci.* (1985), Nov; 12 (4): pp. 303-307.
3. Kadoi Y, Saito S, Kunitomo F, Imai T, Fujita T, "Impairment of the brain beta-adrenergic system during endotoxemia", *J. Surg. Res.* (1996), Mar; 61 (2): pp. 496-502.

Amino Acid Derangements

Several studies have demonstrated alterations of amino acid levels in the brain and serum in sepsis. Basler et al. studied plasma amino acid concentrations in patients with sepsis. 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 and apparently before multi-organ failure was present. They postulated that these metabolic disturbances were a significant contributing factor in the pathogenesis of encephalopathy with sepsis.

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 compared with 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.⁵ 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.⁶ Based on this information, many groups have postulated that infusion of branched chain amino acids during sepsis would decrease muscle catabolism and improve mortality; however, clinical trials failed to demonstrate improvement.^{7,8}

Much of the current research and data focuses on relating SAE to hepatic failure with associated encephalopathy. Comparing the two, Mizock et al. looked at phenylalanine metabolism in sepsis and compared it with 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. 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.⁹

Neurotransmitters

Altered neurotransmitters are thought to play a significant role in the development of acute altered mental status of sepsis. 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 compared with mice with mild sepsis and no encephalopathy. They also demonstrated that the septic mice had higher levels of most essential amino acids.¹⁰ In a later study, Freund et al. looked at regional brain catecholamine and indoleamine neurotransmitter profiles in the septic mice. They demonstrated 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.¹¹

Another possible hypothesis involves the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Winder et al. studied plasma and brain GABA concentrations in septic mice. All the septic animals with clinical signs of encephalopathy had increased serum levels of GABA. However, brain levels were increased in sepsis, but not significant. They concluded that GABA

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was unlikely to play an important role in the pathogenesis of encephalopathy of sepsis.¹² 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.¹³ It is not known whether the GABA crosses the blood–brain barrier and exerts direct suppressive effects on the brain.

Miscellaneous

Several other mechanisms thought to play a role in encephalopathy of sepsis have been proposed, but limited data is available. Soejima et al. studied local glucose utilization in septic mice with encephalopathy. The results suggest that there are metabolic changes in discrete brain regions. These are related to the serotonergic or noradrenergic system, in septic mice with encephalopathy.¹⁴

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.¹⁵

ICU Delirium in the Critically Ill

An alteration in the mental status of the critically ill mechanically ventilated patient with or without sepsis has profound implications. Ely et al. have championed this cause for years with very extensive investigations and publications along with web-based educational services.^{16,17} In a recent study looking at outcome data, their group found delirium was an independent predictor of higher six-month mortality (34% versus 15%, $p=0.03$) and had a 10-day longer hospital stay.¹⁸

Of equal importance, the development of acute delirium in the intensive care unit (ICU) can translate into long-term cognitive impairment.¹⁹

SAE and Basic Science

An obvious void in understanding SAE and alterations in the mental status of the critically ill is the lack of basic science investigation. This paucity of basic investigation, and the absence of an agreed-upon animal model, hamper attempts to test interventions or drug targets. This inhibits attempts to mitigate SAE and further prevents testing non-CNS sepsis therapies to see whether they could cause or exacerbate SAE or delirium. The numerous theories attempting to explain the cause of SAE is testament to this void in basic understanding and further reflects the lack of appreciation of the importance of this clinical marker.

One area of investigation that has not generated much attention, as of yet, is the CNS microcirculation during sepsis or critical illness. The Louisiana State University Health Sciences Center recently found significant alterations in the endothelial leukocyte adhesion of the brain of obese and non-obese mice after CLP (*Microcirculation*, in press). Of note, the difference between the sham and CLP in all groups, either lean or obese, was significant. It has also demonstrated differences in the genomic expression of the brain, using microarray technology, between mice that receive LPS injection versus saline.²⁰ Our group is also currently looking at behavior differences between CLP and sham groups, correlating them with genome expression and CNS microcirculatory changes. What seems apparent is that SAE is not a linear process and therefore may not be amenable to non-linear methods of investigation.

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The Future

There are still many questions to be answered. Is an alteration in mental status related to microvascular changes, the other theories proposed above, or is it a combination of effects? Could it be a response to the insult or a maladaptation to the insult induced by the illness? Do other measures that patients receive, such as sedatives, resuscitation fluid, environmental stimuli, etc have minor or major influences on the development of SAE or critical illness-associated delirium?

So as to not look haphazardly, is it possible to apply the new science of systems biology to this problem and generate global models instead of traditional reductionist models? SAE and critical illness-associated delirium seems well suited for a systems biology approach using genomic and proteomic information on a large scale to develop global theories based on non-linear approaches. Clearly, SAE and critical illness-associated delirium is a non-linear, open complex system that can receive ‘energy’ from numerous sources, on numerous levels and may alter both forward stimulus and feedback loops. Therefore, working towards a complex system computational model may offer the best hope for studying this complex process in a way that will best advance future investigation and perhaps clinical discussion-making.²¹

Conclusion

The etiology of SAE remains unknown. The differing theories and biochemical alterations described above suggest SAE involves many metabolic pathways and

biochemical derangements that either occur at different times or all at once, or vary due to other factors such as genetics, underlying diseases, pre-existing diseases, etc. What is known is that the presence of SAE has a significant negative impact on survival and therefore deserves further investigation and a great deal more attention and appreciation than it has received to date. Pushing forward, a basic science understanding of SAE seems paramount in devising future interventions and therapeutic modalities. This also applies to testing non-CNS critical care modalities or drugs to better understand how they may influence the brain function.

Another major challenge will be to develop animal models that truly represent human CNS physiology during acute and severe illness. It is a tall order that has been difficult in other acute illnesses such as acute lung injury and sepsis. Although these models exist for sepsis and lung injury, having them truly correlate with human conditions and translating animal success into human clinical improvement has been illusive. However, the quest should not be abandoned due to previous failures.

Understanding components of an illness does not mean there is understanding of the disease dynamics or the component dynamics. Therefore, developing complex models may be required. The challenge will be the development of a systems approach to understanding this little known, but seemingly profound, process of SAE and critical care-associated delirium. Utilizing the tools of systems analysis and multiple pathway integration seems a logical first step. ■

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