IJMPR 2024, 8(8), 40-46

International Journal of Modern Pharmaceutical Research
www.ijmpronline.com

ISSN: 2319-5878
IJMPR
Review Article

SJIF Impact Factor: 6.669

INFLAMMATORY RESPONSE AND ALTERED MENTAL STATUS IN SEPSIS ASSOCIATED ENCEPHALOPATHY – A COMPREHENSIVE REVIEW

Silpa Siva Prasad[1], Arya Arun[2], Shaiju S. Dharan[3] and Sam Jeeva Kumar*[4]

[1]Pharm.D Intern (Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Trivandrum, Kerala, India).
[2]Pharm.D Intern (Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Trivandrm, Kerala, India).
[3]Principal/HOD (Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Trivandrum, Kerala, India).
[4]Assistant Professor (Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Trivandrum, Kerala, India).

Article Received on: 28/05/2024
Article Revised on: 19/a06/2024
Article Accepted on: 10/07/2024

***Corresponding Author**
Sam Jeeva Kumar
Assistant Professor (Department of Pharmacy Practice, Ezhuthachan College of Pharmaceutical Sciences, Marayamuttom, Trivandrum, Kerala, India).

ABSTRACT

Sepsis is defined as a life-threatening multi-organ dysfunction triggered by an uncontrolled host response to infectious disease. Systemic inflammation elicited by sepsis can cause acute cerebral dysfunction, characterized by delirium, coma, and cognitive dysfunction, known as septic encephalopathy. Recent evidence has reported the underlying mechanisms of sepsis. However, the reasons for the development of inflammation and degeneration in some brain regions and the persistence of neuro inflammation remain unclear. This mini-review describes the pathophysiology of region-specific inflammation after sepsis-associated encephalopathy (SAE), clinical features, and future prospects for SAE treatment. The hippocampus is highly susceptible to inflammation, and studies that perform treatments with antibodies to cytokine receptors, such as interleukin-1β, are in progress. Future development of clinically applicable therapies is expected. Sepsis is a major cause of death in intensive care units worldwide. The acute phase of sepsis is often accompanied by sepsis-associated encephalopathy, which is highly associated with increased mortality. Moreover, in the chronic phase, more than 50% of surviving patients suffer from severe and long-term cognitive deficits compromising their daily quality of life and placing an immense burden on primary caregivers. Due to a growing number of sepsis survivors, these long-lasting deficits are increasingly relevant. Despite the high incidence and clinical relevance, the pathomechanisms of acute and chronic stages in sepsis-associated encephalopathy are only incompletely understood, and no specific therapeutic options are yet available. Here, we review the emergence of sepsis-associated encephalopathy from initial clinical presentation to long-term cognitive impairment in sepsis survivors and summarize patho mechanisms potentially contributing to the development of sepsis-associated encephalopathy.[1.2]

KEYWORDS: Sepsis associated encephalopathy, neuro inflammation, inflammatory response in the body and brain dysfunction, delirium, dementia, cognitive deficits, pathophysiology, long-term sequelae.

INTRODUCTION

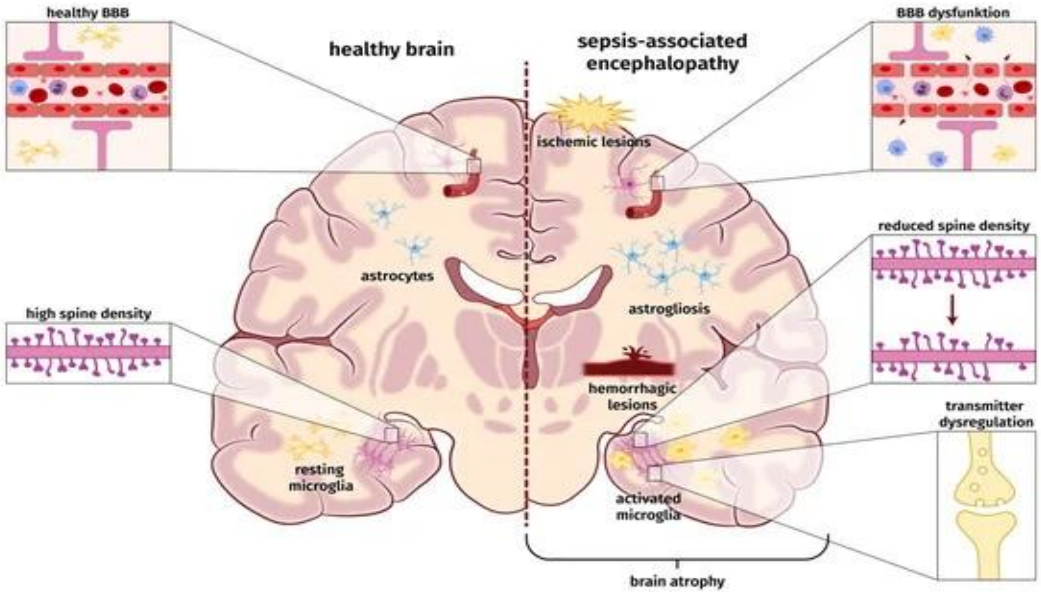
Sepsis is defined as a life-threatening multi-organ dysfunction triggered by an uncontrolled host response to infectious disease. Systemic inflammation elicited by sepsis can cause acute cerebral dysfunction, characterized by delirium, coma, and cognitive dysfunction, known as septic encephalopathy. Septic encephalopathy develops in 53% of patients with sepsis. Septic encephalopathy is considered a diffuse brain dysfunction resulting from a systemic inflammatory response to infection, and not a symptom of direct central nervous system infection. Moreover, septic encephalopathy is an extremely critical condition that affects the functional prognosis and life expectancy of septic patients, and there is a strong need to elucidate and control its mechanisms. Regarding the underlying mechanisms of sepsis, recent evidence suggests that endothelial cell degeneration, enhanced blood-brain barrier (BBB) permeability, and tight junction protein loss promote and trigger the influx of inflammatory mediators, such as interleukin (IL)-1β and tumor necrosis factor (TNF)-α, into the brain. However, the reasons why some brain regions develop inflammation and degeneration and the factors that determine the persistence of neuro inflammation remain unclear.[3.4]

EPIDEMIOLOGY

SAE is the most common cause for encephalopathies in ICUs worldwide[3], affecting up to 50% of patients during the course of sepsis. A proven bacteremia even increases the incidence of SAE up to 70%. Patients with renal, liver, or multi-organ failure are more frequently affected than sepsis patients without organ complications. The mortality rate of sepsis patients increases from 26% to 49% with SAE and is associated with higher values of the GCS, sequential organ failure assessment score (SOFA), and the APACHE II score. At hospital discharge, almost 45% of sepsis survivors show symptoms of long-term cognitive dysfunction. However, an exact evaluation of incidence, prevalence, and mortality is restricted due to lack of definite SAE diagnosis criteria in these studies and due to the variable clinical presentation of SAE. A prospective cohort study with a clear definition of SAE is needed to address current uncertainties in incidence, severity, and outcome of SAE in acutely ill sepsis patients.[5]

PATHOPHYSIOLOGY

According to SAE definition, an acute infection of the CNS must be ruled out to diagnose SAE. Thus, SAE is regarded as a consequence of the dysregulated host response induced by severe systemic infection. So far, the pathophysiology and underlying molecular mechanisms leading to SAE are only incompletely understood. The etiology of SAE is likely multi-factorial, and a number of pathomechanisms are involved in parallel, influence each other, and contribute to a varying degree to the development of SAE. These factors may involve ischemic/hemorrhagic lesions, a compromised blood–brain barrier (BBB), neuroinflammatory processes, e.g., microglia activation and astrogliosis, changes in neuronal synaptic spine density, and dysregulation of neurotransmitter. None of these factors seems to be obligatory to cause SAE.



Ischemic and Hemorrhagic Cerebral Lesions

Sepsis impairs both the macro-circulation and the micro-circulation of the brain. MRI studies, post-mortem analysis of sepsis patients, and also animal experiments confirm macro- and microscopic areas with ischemic and hemorrhagic lesions. Hypotensive episodes during sepsis and septic shock result in decreased cerebral perfusion, which has been shown in several clinical studies. In addition, disturbed systemic vasoreactivity and dysregulated autoregulation of cerebral arteries contribute to reduced cerebral perfusion. Physiologically, cerebral autoregulation controls constant brain perfusion by regulating vasoconstriction of cerebral arteries. Endothelial dysfunction during sepsis leads to inconsistent cerebral blood flow, especially during blood pressure fluctuations. A disturbed autoregulation was present in almost 50% of sepsis patients with SAE. However, this study was limited to evaluation of blood perfusion in large intra-cranial arteries, whereas dysfunction in the microcirculation was not analyzed. Recent animal experiments in sheep revealed impaired cerebral microcirculation during septic shock resulting in decreased cerebral oxygenation. In addition, coagulation disturbances might contribute to thrombotic occlusion of capillaries, resulting in neuronal anoxia and apoptosis.[6]

Impairment of Blood–Brain Barrier and Neuroinflammation

Under physiological conditions, the BBB is essential for the maintenance of a constant extracellular milieu enabling normal neuronal function. The BBB comprises endothelial cells, astrocytes, and pericytes composing a highly efficient border between the brain parenchyma and cerebral circulation. During sepsis-induced dysregulated host response, proinflammatory cytokines, such as TNF-α and IL-1β, activate endothelial cells.

Endothelial activation results in production of reactive oxygen species (ROS) and consequently in increased endothelial permeability. In addition, activated endothelial cells induce the expression of adherence proteins. These proteins support the transmigration of activated immune cells through the impaired BBB into the CNS. The increased release of ROS also harms macromolecules of the BBB, leads to mitochondrial dysfunction and activates matrix–metalloproteases. Subsequently, the BBB is impaired, and resident cells in the brain, e.g., astrocytes and microglia (neuroglia), can be activated. Neuroglia are responsible for the maintenance of cerebral homeostasis. Under physiological conditions, astrocytes mediate a wide range of important regulatory functions in the CNS, including ionostasis, neurotransmitter metabolism, fluid balance, neurogenesis, and maintenance of synaptic plasticity. The latter might be controlled by astrocyte-secreted synapse-modifying factors, such as hevin, SPARC, and TNF-α. Experimental studies consistently describe a reactive astrogliosis as a result of the dysregulated immune response during the course of SAE. The release of pro-inflammatory mediators and ROS by these cells may further aggravate the impairment of the BBB. At distinct areas, which are called the circumventricular organs, the BBB is physiologically leakier, and crossing of cytokines to into the CNS is facilitated.

Microglia, as the brain's resident mononuclear cells of the innate immune system, play a key role in protecting the brain from neuronal damage. In their resting state, microglia are essential for physiological, non-inflammatory surveillance functions and regulation of synaptic spines during development and are also critically involved in the regulation of synaptic plasticity. Microglia are activated in the course of sepsis and might contribute to aberrant neuronal function and loss of dendritic spines in CA1 hippocampal pyramidal neurons. There is growing evidence that activation of microglia may result from infiltrating peripheral monocytes bypassing the dysregulated BBB and induce long-term activation of resident microglia after sepsis.[7,8]

Dysregulated Neurotransmitter

Several neurotransmitters are discussed to be involved in the development and maintenance of SAE. Most studies so far have highlighted dysregulations of cholinergic pathways, but experimental studies also suggest that gamma-aminobutyric acid, norepinephrine, serotonin, and dopamine pathways are compromised. Massive cytokine release in sepsis might cause a dysregulation of neurotransmission in experimental sepsis. Due to these experimental findings and previous clinical observations that anti-cholinergic medication worsens delirium, it has been postulated that an affected cholinergic pathway might induce delirium in critically ill patients. However, a double-blind and placebo-controlled study revealed that treating ICU patients with rivastigmine—a cholinesterase inhibitor—results in even longer delirium and increased mortality, leading to an early study termination. Even though this study was not designed to investigate the effect of rivastigmine on SAE patients, these results suggest that cholinesterase inhibitors do not have a beneficial effect in sepsis patients. A previous study found a decreased concentration of tyrosine, tryptophan, and phenylalanine (amino acids essential for the neurotransmitter synthesis) in the serum of sepsis patients. However, it is unclear how these observational and partly controversial data are causative related to the development of SAE.[9,10]

Clinical Features in the Acute Stage of Sepsis

Acute and reversible deterioration of mental status is often associated with sepsis, and this disorder may lead to SAE. Diffuse cerebral dysfunction due to a systemic inflammatory response to infection is considered SAE, which does not include direct central nervous system infection. SAE is associated with abnormal biomarkers, such as elevated IL-1β levels, and by neuroradiologic imaging findings, such as hippocampus atrophy on brain magnetic resonance imaging (MRI). Moreover, it is assessed by various methods to identify which of the brain areas are affected. In patients with septic shock who develop acute brain dysfunction, leukoencephalopathy (confluent or diffuse white matter lesions), and ischemic stroke can be detected on magnetic resonance imaging (MRI). Ischemic stroke is associated with disseminated intravascular coagulation and increased mortality. The volumes of the cerebral cortex, hippocampus, amygdala, and cerebral white matter were smaller in patients with SAE than in healthy controls. Among the non-survivors of SAE, the volume of the hippocampus was smaller than that of healthy controls and SAE survivors.

Tissue samples from patients with delirium showed activated microglia and astrocytes and elevated levels of IL-6 in the hippocampus. This condition is associated with delirium in older patients, suggesting a relationship between delirium and inflammatory mechanisms.

Basic Studies on the Acute Phase of Sepsis

Various studies using mouse models of sepsis have been conducted on multiple brain regions. In an in vivo study, microglia in the hippocampus showed morphological changes at 6 h after the systemic administration of lipopolysaccharide (LPS), which is a characteristic of activation. Staining for ionized calcium-binding adaptor molecule, a protein expressed in microglia and macrophages and a cytoskeletal component involved in migration, increased. In previous works, the microglia and astrocytes were found to be activated in the cortex and hippocampus. Apoptosis of neurons in the cortex and hippocampus resulted in a decrease in the number of neurons. In one such study, activation of microglia in the hippocampus in a mouse model of CLP was reported to be stronger than that in the cortex. This suggests that microglial activation by sepsis is different in a region-

specific manner and that the hippocampus is more affected by sepsis.

In addition to these morphological changes, there were region-specific features related to cytokine expression. Under physiological conditions, brain IL-1 receptor 1 (IL-1R1) was expressed primarily in the choroid plexus and endothelial cells and rarely in astrocytes but was not expressed in the microglia.

In the microglia, where IL-1R1 expression was not originally found, IL-1ß mRNA was expressed when endothelial cells were stimulated with IL-1ß. In addition, IL-1R1 expression in the neurons was most strongly confirmed in the hippocampus, where multiple cell types expressing IL-1R1 mRNA have been identified in endothelial cells, astrocytes, ependymal cells, and choroid plexus cells. Peripheral administration of IL-1β and TNF-α significantly increased hippocampal IL-1β mRNA expression, while a 6.5-fold increase in IL-1β and a 15-fold increase in IL-6 mRNA expression were noted in the hippocampus at 6 h after LPS administration. IL-1β is secreted from microglia activated by LPS and can inhibit synaptogenesis.

In another study, positron emission tomography revealed that in the LPS model mice, regional cerebral blood flow (rCBF) was reduced in the cerebral cortex and alpha activity on electroencephalography decreased. In addition, cerebral glucose uptake was maintained in the hippocampus and thalamus but decreased in all neocortical regions. These findings suggested that there were differences in the regional vulnerability among brain areas.

In a report on functional impairment, locomotor activity clearly decreased at 2 h after administration of systemic IL-6, IL-1β, and LPS. The central nuclei of the amygdala are activated, and the frontal cortex is affected, which is thought to be associated with symptoms, such as increased anxiety, depression, and delirium. Dysfunction of working memory is induced by LPS via circulating IL-1β. In addition, direct action of IL-1β on the hippocampus may result in neuronal dysfunction and promote neuronal cell death. Indeed, the IL-1β level was found to be elevated. Especially, IL-1β inhibited synaptogenesis, with excitatory synapses in the hippocampus being reduced. In behavioral experiments, the cognitive index also decreased, consistent with the symptom course.

The Clinical Features in the Chronic Stage of Sepsis

There are also reports on the associations among delirium duration, imaging findings, and clinical symptoms. Longer duration of delirium was related to smaller hippocampal volumes on computed tomography (indicative of hippocampal atrophy) at discharge. In addition, volume reduction in the superior frontal lobes was observed on follow-up scan at discharge and at 3 months later. Moreover, patients with reduced superior frontal lobe volume displayed reduced executive function and visual attention at 3 months after discharge. MRI examinations also showed that the duration of delirium in the intensive care unit (ICU) caused white matter disruption on CT at discharge and at 3 months later; similarly, worse cognitive scores assessed by the Repeatable Battery for the Assessment of Neuropsychological Status at 12 months was associated with white matter disruption.[11,12,13]

Cerebral Imaging

Conventional computed tomography (CT) and magnetic resonance imaging (MRI) are most frequently used for brain imaging. In critically ill patients, a cerebral CT scan is primarily used to exclude intra-cranial brain edema and ischemic or hemorrhagic lesions. Nonetheless, except for hemorrhagic lesions, MRI has a higher sensitivity for the detection of structural lesions and is therefore preferred for cerebral imaging.

Despite severe symptoms, in 52% of SAE patients, cerebral imaging is unremarkable, especially in acute stages. Pathological imaging findings are usually unspecific and also occur in other diseases unrelated to sepsis. In a prospective observational study, MRI scans in acute stages of SAE identified ischemic lesions (29%) as the most common pathological findings. These lesions are displayed in diffusion-weighted imaging and represent cytotoxic edema usually caused by ischemia, hypoxia, or vasogenic edema and may indicate circulatory impairment (e.g., impaired macro- and micro-circulation). In addition, ischemic stroke was independently associated with increased mortality and poor neurologic outcome. In approximately 21% of sepsis patients, leukoencephalopathy can be found in MRI, which might be a possible marker of BBB leakage.[14,15] In this study, however, only a highly selective patient population fulfilling the criteria of septic shock and demonstrating severe neurological symptoms (coma, delirium, focal neurologic deficit or seizure) was included. There is no information about the prevalence of MRI lesions in less severely affected or neurologically asymptomatic sepsis patients. In some cases, signs of a posterior reversible encephalopathy syndrome can be detected. In a recent prospective MRI neuroimaging study, sepsis survivors revealed a global and/or partial atrophy with mesial temporal emphasis up to 12 months following hospital discharge. Due to the limited sample size, a general statement regarding the frequency and the degree of SAE induced atrophy is limited.[16]

Electroencephalography

Several case series and small studies describe a variable prevalence of electroencephalography EEG) abnormalities (ranging from 12% to 100%), e.g., appearance of theta and delta waves. This high range of abnormal EEG findings might be due to the small sample size and heterogeneity of the study population. Severe EEG abnormalities with periodic and rhythmic discharges (e.g., triphasic waves, frontal intermittent

rhythmic delta activity, general periodic discharges) may indicate severe SAE. Sometimes, epileptiform discharges (e.g., periodic lateralized, bilateral independent lateralized) can be recorded. In sepsis patients with bacteremia but no detectable cognitive deficits, abnormalities in EEG could be demonstrated in even 50% of cases. Thus, EEG as a non-invasive investigation tool is helpful to assess the severity of SAE, as it reflects the degree of encephalopathy in general. Absence of EEG modulation, a delta-predominant background, and periodic discharges might be independent predictors of mortality and were also associated with the occurrence of delirium in sepsis patients. In addition, seizures occur in almost 10%–20% of sepsis patients, most commonly non-convulsive seizures. At this point, seizures should be treated with anti-convulsants, as they worsen the outcome in critically-ill patients. However, it is important to note that none of these EEG abnormalities are specific for SAE and can also widely occur in encephalopathy of other etiology.[17]

Laboratory Testing—Cerebrospinal Fluid

To evaluate specific cerebrospinal fluid (CSF) biomarkers related to the diagnosis and prediction of long-term outcome of SAE. Clinical routine laboratory testing of CSF is restricted to the exclusion of other etiologies of encephalopathy, such as meningitis and encephalitis. Findings in SAE are limited to a slight protein increase as a sign of local inflammation or impairment of BBB without specific intrathecal immunoglobulin synthesis.[18]

Laboratory Testing—Blood

Due to numerous complications in patients with SAE, routine laboratory tests are essential, including complete blood cell count, electrolytes, and organ function parameters to identify possible modifiable risk factor. There exists no validated biomarker for prediction or confirmation of SAE so far. In several studies, a serum increase of neuron-specific enolase (NSE) in 53% and S100b in 42% in sepsis patients could be detected. S100b is a marker of glial cell damage, whereas NSE is a marker for neuron damage. Serum concentration of these markers was also associated with brain injury and neurological impairment. However, screening for S100b and NSE for the diagnosis of SAE or use as a prognostic marker is not recommended due to inconsistent study results. Very recent studies indicate a higher specificity and sensitivity for increased detection of neurofilaments, especially the light chain of neurofilaments (NFL light chain), in the course of SAE. Neurofilaments are essential structural proteins in neurons mainly located in the axonal cytoplasm. In response to neuronal damage, the concentration of NFL light chain increases in serum as well as CSF and can be measured using single-molecule array technology. Serum levels of NFL light chain are currently evaluated for diagnostic, prognostic, and monitoring purposes in a variety of neurological diseases. These promising results of NFL light chain serum concentrations in sepsis and their predictive value for SAE need to be evaluated prospectively. It will be interesting to see if these changes correlate to the development of cognitive dysfunction in the late phase of SAE.[19]

Screening Tests for Delirium in Acute SAE

Early detection of delirium is of great importance, since delirium can be the first symptom of sepsis and can even precede the fulfillment of sepsis criteria. In the management of SAE, a fast and sufficient treatment of the underlying infection, the control of organ dysfunction, and metabolic alterations is essential.

There are several screening tests available to test for delirium depending on the patient's condition. In the intensive care unit, the CAM-ICU or the intensive care delirium checklist (ICDSC) are most commonly used. The specificity of the CAM-ICU is 0.97. As the ICDSC has a higher sensitivity (0.99), it may be used as a screening tool and, if delirium is suspected, the CAM-ICU may be additionally performed to confirm delirium.[20]

THERAPEUTIC MANAGEMENT

Pharmacological Treatment

Although numerous pharmacological treatment strategies have been studied in recent decades, no evidence-based pharmacological treatment option is available which is able to convincingly demonstrate effects on delirium in SAE. Therefore, in clinical routine, no specific recommendation for a standardized pharmacological treatment can be given. It is unclear so far whether delirium as a manifestation of acute SAE should be treated with additive use of pharmacological substances, e.g., neuroleptic drugs. In a randomized, double-blind, placebo-controlled trial, commonly used neuroleptic drugs, such as haloperidol and ziprasidone, were not able to shorten delirium-free days as compared to placebo in ICU patients. This was confirmed by a recent systematic review showing that the use of highly potent neuroleptic agents, e.g., haloperidol or second-generation anti-psychotics, was not favorable regarding mortality, delirium severity, hospital length of stay, or cognitive function in delirium.

Pharmacological vigilance and non-pharmacological strategies should support delirium treatment, which has already been evaluated in small cohort studies. If possible, benzodiazepines and opioids should be avoided, as they are independent risk factors for the development of acute SAE at the ICU. Furthermore, in a sub-group analysis, the alpha-2 agonist dexmedetomidine revealed significant advantages regarding delirium-free days, shortening of mechanical ventilation, and decreased mortality rates in sepsis patients as compared to lorazepam. However, these results could not be replicated in a multi-center randomized clinical. A current randomized controlled trial evaluates the benefit of an early use of alpha-2 agonists (dexmedetomidine and clonidine, respectively)

in mechanically-ventilated patients. Additionally, there is evidence that starting a statin therapy in sepsis patients might lower daily risk of delirium, whereas stopping a pre-existing statin therapy might increase delirium risk.[21]

Non-Pharmacological Treatment

As there are so far no sufficient pharmacological treatment options, non-pharmacological treatment strategies are important and should be implemented in ICU patients and in less severely affected sepsis patients. These comprise a strict sleep protocol, occupational therapy with cognitive stimulation, use of glasses and hearing aid, early mobilization, as well as devices for orientation, such as clock, television, radio, pictures, and music therapy.[22]

DISCUSSION

Future experimental and clinical studies should focus on both the acute and chronic stages of SAE. We have to proceed with experimental and clinical research to elucidate the complex pathophysiological and molecular mechanisms in acute and chronic SAE to be capable of developing novel and specific concepts for preventing and treating SAE. Evaluating the role of neuroglia activation and BBB disruption in SAE may be especially promising, since this offers the possibility of a targeted intervention in the development of SAE in the acute stage. In clinical terms, it would be worthwhile to establish valid biomarkers, e.g., use of serum levels of NFL light chain in the acute stage or innovative imaging procedures for prognostic estimation of later neurocognitive dysfunction. In the post-acute stages, effects of individualized cognitive training need to be tested. Therefore, there is an urgent need for prospective and controlled clinical trials in SAE patients to expand empirical knowledge towards evidence-based medical interventions.[23,24]

CONCLUSION

The development of SAE is an acute and frequent complication of the dysregulated host response during the acute phase of sepsis, which often results in long-term cognitive deficits in sepsis survivors. This underlines the importance for an early screening for delirium or other SAE symptoms by trained medical staff. This is particularly important as SAE may precede clinical signs of sepsis, and early treatment may improve the neurocognitive outcome. In addition to source control of the infectious focus and antibiotic treatment, modifiable risk factors for delirium should be identified. So far, specific pharmacological delirium treatment is not available, and there is an urgent need to develop, to evaluate, and to finally implement effective therapeutic options to treat SAE.[25]

REFERENCE

1. Fleischmann, C.; Scherag, A.; Adhikari, N.K.; Hartog, C.S.; Tsaganos, T.; Schlattmann, P.; Angus, D.C.; Reinhart, K.; International Forum of Acute Care Trialists. Assessment of Global Incidence and Mortality of Hospital-treated Sepsis. Current Estimates and Limitations. Am. J. Respir. Crit. Care Med., 2016; 193: 259–272.
2. Kempker, J.A.; Martin, G.S. The Changing Epidemiology and Definitions of Sepsis. Clin. Chest Med., 2016; 37: 165–179.
3. Gofton, T.E.; Young, G.B. Sepsis-associated encephalopathy. Nat. Rev. Neurol., 2012; 8: 557–566.
4. Heming, N.; Mazeraud, A.; Verdonk, F.; Bozza, F.A.; Chretien, F.; Sharshar, T. Neuroanatomy of sepsis-associated encephalopathy. Crit. Care, 2017; 21: 65.
5. Iacobone, E.; Bailly-Salin, J.; Polito, A.; Friedman, D.; Stevens, R.D.; Sharshar, T. Sepsis-associated encephalopathy and its differential diagnosis. Crit. Care Med., 2009; 37: S331–S336.
6. Vilstrup, H.; Amodio, P.; Bajaj, J.; Cordoba, J.; Ferenci, P.; Mullen, K.D.; Weissenborn, K.; Wong, P. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology, 2014; 60: 715–735.
7. Baumgaertel, M.W.; Kraemer, M.; Berlit, P. Neurologic complications of acute and chronic renal disease. Handb. Clin. Neurol, 2014; 119: 383–39.
8. Sonneville, R.; de Montmollin, E.; Poujade, J.; Garrouste-Orgeas, M.; Souweine, B.; Darmon, M.; Mariotte, E.; Argaud, L.; Barbier, F.; Goldgran-Toledano, D.; et al. Potentially modifiable factors contributing to sepsis-associated encephalopathy. Intensive Care Med., 2017; 43: 1075–1084.
9. Eidelman, L.A.; Putterman, D.; Putterman, C.; Sprung, C.L. The spectrum of septic encephalopathy. Definitions, etiologies, and mortalities. JAMA, 1996; 275: 470–473.
10. Pandharipande, P.P.; Girard, T.D.; Jackson, J.C.; Morandi, A.; Thompson, J.L.; Pun, B.T.; Brummel, N.E.; Hughes, C.G.; Vasilevskis, E.E.; Shintani, A.K.; et al. Long-term cognitive impairment after critical illness. N. Engl. J. Med., 2013; 369: 1306–1316.
11. Girard, T.D.; Jackson, J.C.; Pandharipande, P.P.; Pun, B.T.; Thompson, J.L.; Shintani, A.K.; Gordon, S.M.; Canonico, A.E.; Dittus, R.S.; Bernard, G.R.; et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit. Care Med., 2010; 38: 1513–1520.
12. Gunther, M.L.; Morandi, A.; Krauskopf, E.; Pandharipande, P.; Girard, T.D.; Jackson, J.C.; Thompson, J.; Shintani, A.K.; Geevarghese, S.; Miller, R.R., III; et al. The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: The VISIONS cohort magnetic resonance imaging study. Crit. Care Med., 2012; 40: 2022–2032.
13. Hope, A.A.; Morrison, R.S.; Du, Q.; Wallenstein, S.; Nelson, J.E. Risk factors for long-term brain

dysfunction after chronic critical illness. Ann. Am. Thorac. Soc., 2013; 10: 315–323.
14. Iwashyna, T.J.; Ely, E.W.; Smith, D.M.; Langa, K.M. Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA, 2010; 304: 1787–1794.
15. Annane, D.; Sharshar, T. Cognitive decline after sepsis. Lancet Respir. Med., 2015; 3: 61–69.
16. de Azevedo, J.R.; Montenegro, W.S.; Rodrigues, D.P.; Souza, S.C.; Araujo, V.F.; de Paula, M.P.; Prazeres, P.H.; da Luz Leitao, A.; Mendonca, A.V. Long-term cognitive outcomes among unselected ventilated and non-ventilated ICU patients. J. Intensive Care, 2017; 5: 18.
17. Jackson, J.C.; Girard, T.D.; Gordon, S.M.; Thompson, J.L.; Shintani, A.K.; Thomason, J.W.; Pun, B.T.; Canonico, A.E.; Dunn, J.G.; Bernard, G.R.; et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. Am. J. Respir. Crit. Care Med., 2010; 182: 183–191.
18. Needham, D.M.; Dinglas, V.D.; Morris, P.E.; Jackson, J.C.; Hough, C.L.; Mendez-Tellez, P.A.; Wozniak, A.W.; Colantuoni, E.; Ely, E.W.; Rice, T.W.; et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. Am. J. Respir. Crit. Care Med., 2013; 188: 567–576.
19. Rothenhausler, H.B.; Ehrentraut, S.; Stoll, C.; Schelling, G.; Kapfhammer, H.P. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: Results of an exploratory study. Gen. Hosp. Psychiatry, 2001; 23: 90–96.
20. Sakusic, A.; O'Horo, J.C.; Dziadzko, M.; Volha, D.; Ali, R.; Singh, T.D.; Kashyap, R.; Farrell, A.M.; Fryer, J.D.; Petersen, R.; et al. Potentially Modifiable Risk Factors for Long-Term Cognitive Impairment After Critical Illness: A Systematic Review. Mayo Clin. Proc., 2018; 93: 68–82.
21. Semmler, A.; Widmann, C.N.; Okulla, T.; Urbach, H.; Kaiser, M.; Widman, G.; Mormann, F.; Weide, J.; Fliessbach, K.; Hoeft, A.; et al. Persistent cognitive impairment, hippocampal atrophy and EEG changes in sepsis survivors. J. Neurol. Neurosurg. Psychiatry, 2013; 84: 62–82.
22. Prescott, H.C. Variation in Postsepsis Readmission Patterns: A Cohort Study of Veterans Affairs Beneficiaries. Ann. Am. Thorac. Soc., 2017; 14: 230–237.
23. Iwashyna, T.J.; Speelmon, E.C. Advancing a Third Revolution in Critical Care. Am. J. Respir. Crit. Care Med., 2016; 194: 782–783.
24. Kaukonen, K.M.; Bailey, M.; Suzuki, S.; Pilcher, D.; Bellomo, R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA, 2014; 311: 1308–1316.
25. Wintermann, G.B.; Brunkhorst, F.M.; Petrowski, K.; Strauss, B.; Oehmichen, F.; Pohl, M.; Rosendahl, J. Stress disorders following prolonged critical illness in survivors of severe sepsis. Crit. Care Med., 2015; 43: 1213–1222.
26.