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Sepsis-associated encephalopathy: A review of literature

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Abstract

Sepsis is a leading cause of death in medical and surgical intensive care units (ICUs). Disturbance of consciousness of varying severity is an early warning sign of developing sepsis in the majority of cases. Sepsis-associated encephalopathy (SAE) is the most frequent type of encephalopathy in the ICU and is defined as a state of diffuse cerebral dysfunction caused by the inflammatory response of the body to various infections, where the inflammatory process does not affect the central nervous system (CNS) directly and the primary symptom is a disturbed level of consciousness. The aim of this comprehensive review was to collect the latest scientific knowledge regarding the epidemiology, clinical aspects, pathogenesis, diagnosis, and possible prevention strategies related to SAE.

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Full Text

Systemic sepsis and its subsequent complications are one of the most common causes of mortality in intensive care units (ICU). The related death rate can range from 10 to 50%,[1],[2],[3] which is significantly elevated if the condition is associated with a disturbance of consciousness.[4],[5] Sepsis-associated encephalopathy (SAE) is the most frequent type of encephalopathy in the ICU, and presumably often remains undiagnosed because of its diverse range of symptoms.[6] Since Wilson and Young's publication on the subject, the expression 'sepsis-associated encephalopathy' has become widely accepted in the international literature.[7] The brain has a crucial role in sepsis because it mediates the immune response and acts as a susceptible target of the process. It can be defined as a state of diffuse cerebral dysfunction caused by the inflammatory response of the body to various infections, where the inflammatory process does not affect the central nervous system (CNS) directly and the primary symptom is a disturbed level of consciousness. Fungicemia, and gram-positive and negative bacterial infections can trigger SAE; however, sometimes SAE occurs without specific microbes, which suggests that, apart from infecting organisms, other mediators may also play an important role. The significance of SAE has to be emphasized because disturbance of consciousness is one of the first symptoms of septic infection; therefore, it should be identified as an early warning sign and treated in an early phase before further complications develop.[8] The aim of this comprehensive review was to collect the latest scientific knowledge regarding the

epidemiology, clinical aspects, pathogenesis, diagnosis, and possible prevention strategies related to SAE. Therefore, a directed, systematic search of the literature was carried out using PubMed, OVID, and Google Scholar databases.

Epidemiology and Incidence of Sepsis-Associated Encephalopathy

SAE is a complex disease that has two separate forms of clinical appearance – an early predictable form, and a late form with often irreversible brain damage, accompanied by complex metabolic encephalopathy. The prevalence of delirium in the ICU was 32.3%, according to a recent international survey.[9] The prevalence of SAE is hard to define due to the nonuniform nomenclature; however, it is predicted to be in the range of 9–71% in patients with severe sepsis.[1],[2],[4] Patients with bacteriemia and diagnosed renal, hepatic, or multiorgan disturbances have a higher incidence of encephalopathy. 70% of the patients showed neurological symptoms ranging from lethargy to coma, and more than 80% had electroencephalography (EEG) abnormalities.[10] SAE is responsible for 9.17% of all acute febrile encephalopathies, which are leading causes of a poor outcome from a non-traumatic etiology.[11] A retrospective study registered an incidence of 17.7% related to the developing of SAE among ICU patients during a 3-year period.[12] The mortality of SAE correlates with the seriousness of neurological disturbances, as determined by the Glasgow Coma Scale (GCS),[12],[13] suggesting that the mortality is crucially influenced by the degree of CNS involvement. A study carried out by Eidelman et al., showed that the degree of consciousness disturbance correlated with the APACHE II (Acute Physiology and Chronic Health Evaluation II) scores;[13] therefore, regular monitoring of consciousness during the course of the disease, even in the early stages, is essential. An accurate diagnosis is often complicated by the underlying metabolic disturbances because septic patients often have accompanying liver and kidney failure, hypoglycemia, or hypoxemia.[14]

Clinical Features of Sepsis-Associated Encephalopathy

A wide range of neurological manifestations can be detected, such as disturbed cognitive functions and consciousness, lack of concentration, personality changes, and depression; occasionally, flapping tremors, paratonic rigidity, or even focal and generalized seizures can be associated with the disease.[13] The diagnosis is often difficult to establish because impaired consciousness can occur after a surgical intervention, or spontaneously, or due to hyponatremia in elderly patients, and can be considered as a manifestation of postoperative delirium; hence, caregivers occasionally misinterpret the signs and do not treat them as a part of the septic phenomenon. A moderate disorder of consciousness is characterized by the fluctuation of vigilance, whereas, a severe encephalopathy is more commonly associated with delirium or coma and appears in up to 82% of mechanically-ventilated septic patients.[15] In addition, administration of a sedative agent is common during treatment, which limits the objective, that is, the detection and diagnosis of neurological disorders. Cranial nerves are hardly involved in the process, and unilateral symptoms such as hemiparesis almost never occur as well. On the other hand, critical illness polyneuropathy (CIP), a condition that affects peripheral nerves, is observed in 70% of the cases, which makes weaning from the mechanical ventilator prolonged and complicated.[7],[16]

Although SAE is known as a reversible syndrome, depressive and long-lasting cognitive disturbances have been registered in patients after the disease has subsided.[17],[18] Cognitive dysfunction was seen in approximately 45% of the patients who had successfully recovered from sepsis, 1 year after their hospitalization.[19],[20] As part of the prolonged cognitive signs, depression, post-traumatic stress disorder, and anxiety were diagnosed in 36%, 39%, and 62% of the survivors, respectively.[21] The hypothesized key mechanisms responsible for the long-term cognitive decline are neurodegenerative microglial activation and diffuse ischemic damage.[22] Depending on the seriousness of the mental impairment, a huge burden is placed on families, caregivers, and the social system.

Pathology and histopathology of sepsis-associated encephalopathy

Typically, the cerebral cortex is involved in the process whereas the deeper structures and the spinal cord are rarely affected. Although clinical studies have ruled out direct involvement of CNS in the infection, disseminated

microabscesses have been detected in the brain tissue in numerous cases.[23]

The most frequent morphological changes are ischemic lesions, particularly in the autonomic system nuclei such as locus ceruleus. Further pathological findings include purpura, central pontine myelinolysis, multifocal necrotizing leukoencephalopathy, perivascular edema, swelling of astrocytic endfeet, and signs of neuronal apoptosis.[7] Microscopic examination of the neurons show shrunken nuclei and broken cell membrane.[24] Nevertheless, in most cases, neither macroscopic nor microscopic abnormalities were detected. Presumably, the reversible forms of SAE are free of macroscopic structural changes, whereas detectable morphological brain damage has a multifactorial origin (metabolic and circulatory background), primarily in severe cases.

Pathophysiology of sepsis-associated encephalopathy

The complete pathophysiology of SAE is unknown; however, numerous mechanisms have been identified as potential causative factors. Bacterial endotoxins, changes in blood–brain barrier permeability,[25] oxidative stress,[26] direct neuronal damage, increased level of cytokines and proinflammatory factors,[27] disturbed cerebral circulation,[28] mitochondrial and vascular endothelial dysfunction,[29],[30] neurotransmitter disturbances, and changes in amino-acid levels [31] are involved in the process. The combination and synergism of all these factors, where the onset of one element leads to the activation of others, could be the underlying cause of SAE.

Although sepsis is most frequently caused by bacterial infection, numerous studies have been unable to detect the presence of infective agents in the CNS.[12],[32] Bacterial endotoxins, such as lipopolysaccharide (LPS), are the key factors in inducing inflammation by bonding to circulating LPS-binding proteins (LBP), which activate the immune system after forming a complex with the membrane-bound cluster of differentiation (CD) 14 receptors of monocytes, macrophages, and neutrophils.[33] LPS–LBP–CD 14 complexes are responsible for the synthesis of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin- 1β (IL- 1β), and interleukin-6 (IL-6)[34] through Toll-like receptors 2 and 4.[35],[36] They activate the synthesis and secretion of nitric oxide (NO)[37] and reactive oxygen radicals (ROS).[26] Moreover, by activating the sympathetic nerve system and the hypothalamic-pituitary-adrenal axis, SAE can cause progressive immunosuppression leading to a possibly uncontrollable infection and initiation of a further vicious circle.[14]

Disorders of the Blood–brain Barrier

The blood–brain barrier (BBB) regulates cerebral capillary blood flow and maintains the internal microenvironment by regulating the transmission of nutrients, metabolites, and toxins through specific transport mechanisms to secure an efficient neuronal functioning. The earliest structural phenomenon to be observed among septic animal models was perimicrovascular edema,[24] where the perivascular endfeet of astrocytes, surrounding the endothelium of cerebral capillaries, became swollen and ruptured, and abandoned the microvascular wall; thus, the oxygen-, metabolite-, and nutrient transport were disturbed.[38] Loss of BBB impermeability leads to a disturbed water transport to the brain, which is tightly regulated by aquaporin 4,[39] resulting in perivascular edema, destruction of the astrocytic endfeet,[29] and secondary damage to the nerve tissue.[40] The investigation of animal models have made it clear that the BBB becomes permeable within the first few hours after the development of septicemia.[41] Under these circumstances, aromatic amino acids (AAA) pass through the BBB in a much easier way than branched chain amino acids (BCAA); altered mental status is known to be associated with higher AAA levels.[42]

BBB permeability is also augmented by complement activation, inflammatory cytokines,[43],[44],[45] and the overexpression of the intercellular adhesion molecule (ICAM) in cerebral capillaries, which contributes to the entry of activated leukocytes into the brain, thereby further enhancing the inflammatory process.[46] Intensified pinocytosis [25] and the induction of nitric-oxide-synthase (NOS) within the vessel endothelium [47] lead to the influx of active substances across the barrier despite intact tight junctions between endothelial cells. Cerebral imaging of SAE showed tissue ischemia primarily in the white matter, suggesting an exaggerated BBB permeability, which is known to be associated with a poor outcome.[40]

The Role of Oxidative Stress, Excitotoxicity, and Mitochondrial Dysfunction

Bacterial endotoxins are released into the circulation during the septic process, thereby increasing the cerebral concentration of proinflammatory cytokines such as interferon-γ (INF-γ) and tumor necrosis factor (TNF). After leukocytes accumulate at the site of inflammation under the influence of numerous chemotactic agents such as TNF, angiopoetin-2, IL-1b, and proteins of the complement system,[48] their activation generates oxygen free radicals. Due to the oxidative stress, the membranes of erythrocyte cells disrupt and became swollen, thus worsening the cerebral hypoperfusion and resulting in impaired mitochondrial function and limited oxygen delivery to the brain. IFN-γ stimulates the inducible isoform of nitric-oxide-synthase (iNOS) in astrocytes, whereas TNF-α activates the expression of the same enzyme in other glial cells.[49] iNOS enzyme generates superoxides as a byproduct of NO production, thus enhancing the degree of oxidative stress and playing a key role in neuronal dysfunction and damage. The unique characteristics of brain tissue, such as low antioxidant levels and high rate of oxygen requirement, make it prone to oxidative damage.[50] The concentration of endogenous antioxidants (such as ascorbic acid), that act against the active inflammatory processes, quickly decrease as they wear out fast and no de novo synthesis takes place in the brain.[51] The elevated level of NO alters cerebral autoregulation, hence disturbing the coupling between blood flow and metabolism. It can also modulate the synaptic neurotransmission by an increased cyclic guanosine monophosphate (GMP) production, which is manifested in disturbed memory function, behavioral activity, and neuroendocrine functions. NO also exerts its deleterious effects through the production of highly reactive peroxynitrite, a key component of the cellular damage.[52] In addition, NO efficiently inhibits mitochondrial respiration by competing with oxygen and repressing cytochrome oxidase, which causes depletion of cellular adenosine triphosphate (ATP), disruption of neuronal Ca 2+ homeostasis, and leads to neuronal apoptosis.[52],[53],[54] Elevated NO levels can induce cell death through mediated necrosis caused by energy depletion and mediated apoptosis due to oxidative/nitrosative stress.[55] In human studies, the endothelial expression of iNOS is correlated with neuronal cell death in autonomic areas [47] as well as in the hippocampus.[56]

The role of mitochondria is not limited to energy production but also involves diverse metabolic pathways and calcium homeostasis.[57] Reduced mitochondrial ATP generation is a characteristic finding in the early stages of sepsis, mediated by NO, reactive oxygen species (ROS), and cytokines,[58] which leads to energy deficit and metabolic failure. Twenty-four hours after the onset of sepsis, the efficiency of oxidative phosphorylation decreases due to increased permeability of inner mitochondrial membrane, reduced cytochrome concentration, and lower complex IV activity.[59] Furthermore, being a target of oxidative stress, mitochondria also serves as a crucial source of ROS. Sepsis is associated both with functional and structural mitochondrial dysfunctions with remarkable consequences and include disturbed cellular Ca 2+ homeostasis, swollen structure,[60] and deactivation of mitochondrial enzymes such as eletron transport chain (ETC) complex IV, cytochrome-c oxidase, [61] adenine nucleotide transporters, and mitochondrial dehydrogenases.[59],[62] It might also trigger cellular apoptosis in the advanced stages of the disease by cytochrome-c release.[57] The direct effect of ROS in the mitochondrial membrane can result in the activation of apoptotic cascades as well.[55] Recently, treatments that target mitochondrial dysfunctions have been proposed as possibilities to treat multiple organ dysfunctions.[63]

The glutamate concentration of the cerebral interstitial fluid rises during sepsis, which worsens excitotoxic activity. Extracellular glutamate activates N-methyl-D-aspartate (NMDA)-type glutamate receptors, and thereby stimulates or damages the affected nerve cells, as well as contributes to the downregulation of these receptors. This mechanism may play a pivotal role in the pathogenesis of seizures as well. The harmful effect of lipopolysaccharides (LPS) on cholinergic cells could be ameliorated by the administration of NMDA-receptor antagonists in animal studies.[64] Due to the increased extracellular concentration of glutamate in the synaptic gap, the Na +-dependent clearance of glutamate is inhibited; thus, cellular ATP concentration decreases, whereby Na/K-ATPase is inhibited and neural cells become swollen.[7]

Microvascular Dysfunction and Cerebral Perfusion Disturbances in Sepsis-Associated Encephalopathy

The altered cerebral perfusion may also play an important role in the pathology of SAE. The cerebral perfusion pressure (CPP) is determined by the mean arterial pressure (MAP) and intracranial pressure (ICP) as CPP = MAP − ICP. The value of intracranial pressure is affected by the cerebral blood flow (CBF) and cerebral blood volume

(CBV). The regulation of the latter indicators occurs at the level of cerebral arterioles, ranging from 40–200 μm in diameter. Vasodilatation occurs through the enzyme induction of endothelial NOS, whereas vasoconstriction occurs through the release of endothelin.[65] According to previous studies, the cerebral blood flow reduces, and parallel increase of the cerebrovascular resistance can be registered in SAE.[66]

The acetazolamide-induced vasomotor reactivity of septic patients was found to be disturbed, suggesting an early involvement of resistance arterioles during the course of SAE. The rate of dilation in cerebral arterioles was slower and significantly smaller in degree when compared to healthy controls, which was represented in the decrease of cerebral blood flow velocities. Pulsatility index (PI), an indicator of cerebrovascular resistance, was significantly higher prior to the administration of vasoactive medication, as well as during the entire investigation, if compared to normal controls [66] or nonseptic critically ill patients,[67] which indicates the presence of endogenous catecholamine in the CNS. This phenomenon explains the increased cerebrovascular resistance and the reduced ability of cerebral arterioles to dilate. Another study has also confirmed that cerebral microcirculation disturbances occur prior to neuronal dysfunction.[68] Pierrakos et al., found that the early clinical symptoms of SAE correlate with cerebral vascular constriction only when the value of PI was above 1.3. These patients with increased PI have also exhibited a lower Glasgow Coma Scale (GCS) during the first 24 hours of sepsis; therefore, in clinical practice, PI above 1.3 should be considered as a risk factor for delirium among septic patients.

The study states that functional cerebral alterations are related to impaired oxygen transport possibly only in the early phases of sepsis.[67]

Endogenous catecholamine penetrates into the brain through the damaged BBB and causes eNOS enzyme inhibition that leads to permanent vasoconstriction. Systemic hypotension observed during the course of sepsis manifests in reduced cerebral perfusion and consequential cerebral hypoxia and hypercapnia. The increased partial carbon dioxide ($PaCO_2$) concentration in cerebral arterioles is capable of inducing eNOS enzyme only to a limited extent because of the presence of endogenous catecholamine.[30] Thus, the cerebral auto- and metabolic-regulation of septic patients is impaired because the reduced vasodilatory properties of arterioles ranges between 40 and 200 μm. Consequently, the body's ability to counteract the reduced systemic blood pressure is heavily limited. However, cerebrovascular autoregulation disturbances were reported by another study only in septic patients who showed signs of delirium.[69]

Sepsis-related cerebral microcirculation alterations are characterized by a lower density of perfused capillaries, which can be related to elevated cerebrovascular resistance.[70] An increased distance between capillaries and cerebral cells can result in an unsatisfactory oxygen supply. High cerebrovascular resistance and disturbed cerebral autoregulation may expose septic patients to a decreased CBF if a compensatory elevation in CPP is absent. An experimental study showed that 18 hours following the onset of sepsis, cerebral hypoxia was registered only in animals with 65 mmHg of MAP or less, although they had similar density of functional cerebral capillaries and proportions of small perfused cerebral vessels compared to patients with higher MAP values.[71] A major reason for the microcirculatory disturbances of the brain and other organs is the inhibition of eNOS enzyme produced NO molecules by circulating cytokines (TNF-α, IFN-γ, IL-1, and IL-8), which causes vasoconstriction and deteriorates blood flow. Another cause is that the self-inducing inflammatory process and cytokine-storm disturbs the balance of pro- and anti-thrombotic system, and reduces the concentration of protein-C, as well as the amount of activated protein-C (APC) level. In addition, the dysfunction of vascular endothelial cells also contributes to the disease and propagates the formation of edema-associated cerebral inflammation.[24] In this manner, the system shifts towards procoagulatory processes, and parallel with platelet accumulation,[72] leads to microthrombi formation, culminating in tissue hypoperfusion and multiple organ failure.[73] The administration of activated recombinant human protein-C improves organ perfusion, however, its effect on SAE is still unknown.[74]

The peripheral microcirculation of septic animals has shown a crucial impairment by the first hour, whereas change in the modified shock index has been registered first after 3 hours. In this porcine model, the impaired skin microcirculation during bacteremia was detectable hours before the deterioration in hemodynamic parameters.[75]

Impairment of the Amino-Acid and Neurotransmitter Homeostasis

Both human studies and animal models have proven that amino acid and neurotransmitter levels of the plasma and brain differ significantly in septic patients compared to healthy controls. Sprung et al., have shown that aromatic amino acid (AAA) levels were elevated and branched chain amino acid (BCAA) levels decreased in the plasma of septic patients.[76] AAAs are the precursor molecules of neurotransmitters and easily penetrate into the CNS. Several studies have demonstrated a positive correlation between elevated AAA concentration, APACHE II, scores and mortality rates.[31],[76] High plasma level of AAA was proclaimed to be an independent predictor of mortality in septic patients.[77] Septic catabolic processes such as insulin resistance, impaired glucose tolerance, and proteolysis of the muscles can serve as a basis of amino acid imbalance. Muscle proteolysis elevates the level of unbranched amino acids in the circulation because most branched molecules are degraded within the cells.[31] The concentration of dopamine, norepinephrine, and serotonin metabolites in the brain of septic rats decreases; however, the infusion of BCAAs can restore the imbalance.[78] A research found that the ratio of BCAA/AAA in plasma, following the infusion of Escherichia coli LPS, declined mainly due to the elevated concentration of phenylalanine and decreased concentration of valine and isoleucine in the serum.[42] Phenylalanine is a potentially neurotoxic agent and can play a role in generating false neurotransmitters. Although volunteers showed no signs or symptoms of SAE, these results confirm the significant relation between BCAAs and AAAs.[42]

The alteration of neurotransmitter levels in the brain has long been postulated to be a key factor in SAE. The inflammatory process promotes changes in numerous neurotransmitter systems, including the glutamatergic, monoaminergic, and neurotrophic pathways, which could lead to behavioral changes. The pharmacological inhibition of glutamate release into the synaptic space by riluzole reduces the seriousness of neurological symptoms of experimentally-induced sepsis in rats, and also improves the survival rate.[79] This finding indirectly implicates the pivotal role of glutamate, glutamatergic neurotransmission, and disturbed receptor expression in SAE.

Failure in the cholinergic neurotransmission, especially acetylcholine (Ach), is a well-known mechanism that explains delirium and symptoms of SAE. The cholinergic system, through the nicotinic and muscarinic receptors, modulates the memory, learning abilities, arousal level, and other major cognitive functions that are seriously affected in delirium. Ach mediates neurophysiological functions including memory forming, learning, and panic response. Increasing evidence supports the theory that an interaction between Ach and cytokines is partially responsible for the development of delirium.[80] Behavioral changes and long-term memory deficits have been registered in rats after the infusion of bacterial LPS, which could be related to disturbed cholinergic function of the cortex, prefrontal cortex, and hippocampus.[81] These studies suggest that long-term neurological effects of SAE are induced by the altered cholinergic signaling and neuronal apoptosis, where LPS and inflammatory cytokines serve as mediator molecules. The hypothesis is supported by the fact that delirium can be easily triggered by anticholinergic drug treatment in the clinical setting. Further investigations showed that animals challenged with LPS have no cognitive deficits, whereas cholinergic deficient animals after LPS injection have displayed acute and temporary working memory difficulties.[82] The administration of the acetylcholinesterase inhibitor managed to partially treat these disturbances, thereby confirming the idea that sepsis-induced impairments are related to disturbed cholinergic signaling.[83] Therefore, anticholinergic pharmacological agents should be considered as risk factors in delirium because the brain possesses no cholinergic anti-inflammatory features.[84] Cholinesterase inhibitors have not presented any benefits in the prevention or treatment of delirium among human patients;[85] nevertheless the elevation of Ach could theoretically ameliorate systemic inflammation through a central muscarinic receptor and vagal dependent pathways.[86] In advanced stages of SAE, the diminished vagal function, due to the progressive Ach loss, might enhance proinflammatory activity through the lack of intrinsic cholinergic anti-inflammatory processes.

Amines could also be involved in numerous different symptoms associated with brain dysfunction. Excessive level of norepinephrine and dopamine has been associated with the hyperactive type of delirium.[87] This theory is supported by the fact that dopamine agonists cause frontostriatal abnormalities, that are closely correlated to the severity of delirium, and the treatment of hyperactive delirium is mainly carried out with dopamine antagonists.[88],[89] Despite this, dopamine antagonists do not necessarily shorten the duration of delirium and decrease the disease severity in critically ill patients,[90],[91] and vasoactive drug administration is associated with a higher incidence of delirium.[92] Moreover, a high serotonin concentration in the CNS has been registered in hepatic encephalopathy, and the manifestations produced by the withdrawal of serotonin reuptake inhibitors resemble the

clinical appearance of SAE.[93],[94]

The Role of Complement System

Clinical studies have confirmed that complement system could contribute to inflammation by enhancing cytokine and chemokine production, leukocyte recruitment, edema, neuronal cell apoptosis, and BBB degradation.[95], [96] Complement proteins could also compromise the chemotactic ability and ROS productive capacity of neutrophil immune cells.[97],[98] The activation of complement cascade leads to the cleavage of C3 and C5 proteins, resulting in the formation of anaphylatoxins such as C3a and C5a molecules. The increase in C3 concentration leads to BBB disruption and enhanced gliosis, elevated water volume, as well as altered iNOS, TNF, and aquaporin 4 activity.[99],[100],[101] Byproducts such as C3b form immune complexes while C5b contributes to the production of C5b-9 complexes, known as 'membrane attack complex', that can cause cell activation or apoptosis. The concentration of complement anaphylatoxin C5a increases following the administration of bacterial endotoxin in a time-dependent manner – first in the cerebral endothelial, followed by the microglial cells and eventually in the deeper brain parenchyma tissues. According to a previous study, the systemic infusion of neutralizing anti-C5a antibodies in peritoneal sepsis has prevented BBB fragmentation and blunted neuronal response in the paraventricular nuclei and amygdala areas.[95]

The Effects of Cytokines in Sepsis-Associated Encephalopathy

Cytokine-mediated inflammatory process and the so-called cytokine-storm are known to be the hallmark of sepsis as SAE and the resulting disturbances in consciousness and psychological abnormalities could be a consequence of active inflammatory mediators acting on neural cells. Cytokines affect a wide range of cells in many different pathways, and thereby modulate numerous physiological processes. Due to their hydrophilic feature and size, they are unable to passively diffuse through the intact BBB, whereas in SAE, the damaged membrane allows cytokines to enter the CNS. By activating the MAP-kinase pathways and stimulating Ca 2+ channels, cytokines exert neurotransmitter-like functions; furthermore, they also influence the concentration and effect of the naturally occurring neurotransmitters. Immediately after reaching the cerebral parenchyma, the mediators modulate cellular metabolism by inducing mitochondrial dysfunction, oxidative stress, and microglia activation.[102] Consequently, neuropathological abnormalities are triggered and are finally culminated as delirium. Cytokine mediators affect GABAergic, β-adrenergic, and cholinergic neurotransmission and mediate the secretion of adrenocorticotropic hormone, corticotropin-releasing factor, and vasopressin,[64] which further aggravates SAE.

The development of SAE is associated with excessive microglial activation and the subsequently increasing expression of immune cytokines.[102] Proinflammatory cytokines (IL-1α, IL-1β, IL-6, and TNF-α) are released by activated neutrophils and monocytes in high quantities. A clinical study showed that elevated levels of serum IL-8 were detected among patients with delirium who suffered from an underlying inflammatory process, whereas amyloid-β and IL-10 were increased in patients with delirium and noninflammatory disease.[103] IL-1 provokes "pathological behavior" such as loss of appetite, mood changes, and cognitive disorders by affecting the brain stem, limbic system, and hypothalamus through the stimulation of the vagus nerve. Furthermore, IL-1 stimulates the endothelial prostaglandin E-2 (PGE-2) synthesis, which leads to fever and increased cortisol production through the hypothalamic–pituitary–adrenal axis.[73] One subgroup, the IL-1β, directly stimulates the area postrema and choroid plexus, which causes depression and anorexia by affecting the limbic-system. TNF-α also contributes to the development of depression by influencing the tryptophan metabolism, and thereby increasing kinurinin production and decreasing serotonin level. In addition, TNF-α could play a role in the development of cerebral edema by influencing the water-transport in the brain.[39] An animal study identified the prompt elevation of TNF-α in the CNS of mice following the peripheral administration of LPS, which remained pathologically high for 10 consecutive months.[104]

Additional evidences suggest that advanced stages of sepsis are often associated with a loss of immune function, reflected by lymphopenia, the downregulation of monocytic human leukocyte antigen (HLA)-DR expression, and increased plasma IL-10 level.[14],[105] It can be hypothesized that these cytokines mediate immunosuppression

in SAE in a similar manner as it occurs in brain injury. The compromised immunity manifesting at the later stages of sepsis could also be the result of enhanced activity of the sympathetic nervous system and the hypothalamus–pituitary–adrenal axis.[14]

Diagnostic Possibilities

The diagnosis of SAE is a challenging process and is usually based on exclusion, where conditions such as drug use, electrolyte disturbances, and CNS disorders have to be ruled out before the final diagnosis is made. Numerous diseases with various backgrounds, such as rheumatic diseases and inflammations, can mimic its appearance.[106] Patients in the ICU with brain dysfunction usually have multiple risk factors.[107],[108] In SAE, the clinical symptoms serve as the basis of diagnosis. The major difficulty with recognizing the symptoms of SAE is the fact that most septic patients are usually sedated, which tends to hide neurological disturbances. Therefore, CNS involvement is often diagnosed only during the autopsy, which emphasizes the importance of postmortem examinations. Patients who were dealing with febrile neutropenia, due to treatments with broad-spectrum antibiotics, corticosteroids, or cytotoxic drugs, should be at the center of interest.[109] Diagnostic tools that are commonly used for the objective evaluation of mental state, the course of disease, and predicting mortality are the GCS, the Confusion Assessment Method for the ICU, the Ramsay-Scale, and the Richmond Agitation Sedation-Scale.[110]

EEG is one of the most sensitive instrumental techniques for identifying SAE and a valuable tool in the ICU when clinical assessment is difficult. Normal alpha (7.5–12.5 Hz) rhythm slows down and theta (4–8 Hz) waves appear in patients with no clinical evidence of CNS involvement or with mild-to-moderate encephalopathy (confusion, delirium), which indicates limited cortical dysfunction; these changes are usually reversible in nature. Advanced and more serious stages of consciousness disturbances (stupor and coma) are associated with the appearance of delta (4 Hz) activity, the generalization of triphasic waves, and the occurrence of more burst-suppression patterns. These malignant wave forms indicate disturbances in the deeper brain structures such as basal ganglia and diencephalon, which makes differential diagnoses for distinct CNS disturbances such as myoclonic encephalopathy possible.[111] The estimated mortality of septic patients without pathological EEG signs is 0%, 19% when theta waves are present, 36% with delta waves, 50% with triphasic waves, and even worse, could be as high as 67% if the clinical picture is associated with more malignant EEG results.[10] The administration of sedative agents often heavily affects EEG findings. The typical changes due to sedation is a progressive increase in slow (<1 Hz) and alpha wave activity,[20],[112],[113],[114] a pattern that is hardly observed in septic-associated and metabolic encephalopathy. Periodic or rhythmic patterns or the occurrence of theta and delta activity without superimposed alpha waves is mainly associated with SAE in sedated patients. The presence of malignant triphasic waves, suppression-burst, or electrical cerebral inactivity patterns are unlikely to be the consequence of moderate sedative drug usage.

CT and MRI images are usually physiological, especially in the early stages of encephalopathy. During the course of the disease, vasogenic edema appears in varying degrees on the MRI.[115] Nevertheless, in serious cases of SAE, non-specific structural changes could be detected on MRI of the brain,[115],[116],[117] such as leukoencephalopathy, cerebral infarction, and vascular edema.[40] Furthermore, corpus callosum abnormalities with minimal subcortical and deep cerebellar white-matter involvement have also been registered with MRI.[118] Brain imaging also displays cerebral atrophy and edema in combination with periventricular lesions and pathologically low density of the whole white matter.[119]

In some cases, the analysis of cerebrospinal fluid (CSF) shows a slight increase in protein concentration; however, the cell count and glucose concentration is usually normal; therefore, changes in the CSF are not specific.

Transcranial Doppler serves as a source of reliable information regarding real-time cerebral blood flow changes, enabling easy and noninvasive examinations.[120],[121] Changes in PI are associated with clinical symptoms and seriousness of SAE in the first 24 hours. PI values higher than 1.3 could be used in clinical practice as a warning sign of delirium. However, if PI is measured 72 hours after the first signs of sepsis, it cannot predict the occurrence of delirium confidently.[67]

Elevated levels of plasma C-reactive protein (CRP) and procalcitonin of both septic and nonseptic patients are correlated with the duration of brain dysfunction after the admission to ICU.[122] A correlation was registered by Pfister et al., between the increased level of CRP, cerebrovascular autoregulation alternations, and SAE.[123]

Elevated serum levels of S100β (marker for glial lesions) and neuron-specific enolase (NSE; marker for neuronal lesions) were found in severe sepsis and septic shock, however, they were proven to be nonspecific and could also be detected in many CNS lesions.[124],[125] A decrease in CPP was in correlation with increased serum S100β levels among patients with severe sepsis and septic shock.[126] Although, a low CPP is a key-factor in the pathogenesis of SAE, the measurement of its alteration has not proven to be a diagnostic tool. However, it still counts as an indirect sign of CNS disturbance.[127]

Treatment Options

During the last years, progress has been made in our understanding of the pathophysiology of sepsis; however, still no target-directed treatment for SAE is available. Thus, its therapy corresponds to the treatment of systemic sepsis. Seizures can be rare symptoms and should be treated with standard antiepileptic drugs. Numerous previous studies support the hypothesis that decreased CBF plays an important role in the genesis of delirium; therefore, an increase in perfusion pressure could positively influence CBF and serve as a potential therapeutic measure in such patients.

Strategies that aim to reduce the administration of sedative drugs to ICU patients have promising results in the prevention of delirium,[83] because enhanced sensitivity towards benzodiazepines is present in systemic inflammatory processes. Synaptic activity is significantly reduced during the course of SAE, and because GABA-A receptors are responsible for the majority of neuronal inhibitory synapses, GABA-A could be a new target for therapeutic strategies to prevent and treat delirium. Clinical findings that show increased GABA-ergic neurotransmission in patients with hepatic encephalopathy confirm this theory.[128] In human studies, an alpha-agonist agent, dexmedetomidine, has proven to have neuroprotective effects in septic patients who had more delirium-free days and lower mortality rate in a 28-day time frame, when compared to patients treated with lorazepam.[129] In addition, dexmedetomidine exerts its positive effects through the inhibition of neuronal apoptosis and the reduction in the sepsis-associated inflammatory response as well.[129] Whether specific treatments such as recombinant activated protein C or cholinesterase inhibitors in addition to the standard intensive care is useful has not yet been evaluated in prospective human studies.[46],[130]

Summary

Sepsis affects the brain in many unique pathways, therefore, further in-vitro and in-vivo studies should be conducted to acquire a deeper and more complex understanding of the multiplex presentation and pathophysiology of SAE. Up-to-date special therapies are required that interact with the unique pathways of the disease rather than merely trying to control the clinical symptoms of SAE.

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Conflicts of interest

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