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Neurochemical effects of sepsis on the brain

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Abstract

Sepsis is a life-threatening organ dysfunction triggered by a dysregulated host immune response to eliminate an infection. After the host immune response is activated, a complex, dynamic, and time-dependent process is triggered. This process promotes the production of inflammatory mediators, including acute-phase proteins, complement system proteins, cytokines, chemokines, and antimicrobial peptides, which are required to initiate an inflammatory environment for eliminating the invading pathogen. The physiological response of this sepsis-induced systemic inflammation can affect blood–brain barrier (BBB) function; subsequently, endothelial cells produce inflammatory mediators, including cytokines, chemokines, and matrix metalloproteinases (MMPs) that degrade tight junction (TJ) proteins and decrease BBB function. The resulting BBB permeability allows peripheral immune cells from the bloodstream to enter the brain, which then release a range of inflammatory mediators and activate glial cells. The activated microglia and astrocytes release reactive oxygen species (ROS), cytokines, chemokines, and neurochemicals, initiate mitochondrial dysfunction and neuronal damage, and exacerbate the inflammatory milieu in the brain. These changes trigger sepsis-associated encephalopathy (SAE), which has the potential to increase cognitive deterioration and susceptibility to cognitive decline later in life.

Introduction

Sepsis is a life-threatening organ dysfunction triggered by a dysregulated host response to infection [1]. Every year, more than 19 million people develop sepsis. Among them,

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Tatiana Barichello: Conceptualization, Writing—original draft. **Vijayasree V Giridharan:** Conceptualization, Writing—original draft. **Carlos Henrique R Catalão:** Conceptualization, Writing—original draft. **Cristiane Ritter:** Conceptualization, Writing—review & editing. **Felipe Dal-Pizzol:** Conceptualization, Writing—review & editing.

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half of the sepsis survivors fully recover after hospital discharge, one-third die the following year, and one-sixth have long-term cognitive impairment, including memory dysfunction, anxiety, and depression. Patients with sepsis can develop neurological problems through several processes, including cerebral ischaemia, metabolic abnormalities, and neuroinflammation, and they frequently present with delirium and reduced consciousness [2]. Neuroinflammation elicited by sepsis can trigger an acute dysfunction known as sepsis-associated encephalopathy (SAE), which does not imply a central nervous system (CNS) infection. Additionally, SAE can lead to long-term cognitive impairment in patients who survive sepsis.

In sepsis survivors, moderate-to-severe cognitive impairment was reported to increase by 10.6% and was associated with a threefold increase in the risk of cognitive impairment [3]. Delirium has also been associated with increased rates of long-term cognitive impairment [3,4]. Another cohort analysis of Medicare data showed that 75% of people who were aged 65 and older and survived sepsis for 3 or more years had a residual functional disability, with 16.7% of them experiencing moderate-to-severe cognitive impairment [5]. Moreover, in a population-based study, cognitive impairment was associated with previously diagnosed sepsis, with an odds ratio of 2.60 [6]. Additionally, after hospital discharge, sepsis survivors with high circulating levels of proinflammatory or immunosuppressive biomarkers had a higher risk of hospital readmission or death than those with standard circulating biomarkers [7]. All these studies suggest that sepsis can originate from neuroinflammation, potentially increasing cognitive deterioration, susceptibility to neurodegenerative diseases, and risk of developing cognitive dysfunction later in life [8,9].

In the present narrative review, we discuss the effect of sepsis-induced peripheral host immune response on the blood–brain barrier (BBB) and brain, role of gliosis in neuroinflammation, biomarkers associated with neuroinflammation in sepsis, SAE, and cognitive decline in sepsis survivors.

Systemic immune response and sepsis

The systemic immune response during sepsis is a complex, dynamic, and time-dependent process. Pathogen invasion and replication usually release cellular components, including peptidoglycans, lipopolysaccharides (LPS), exotoxins, and DNA [10]. These compounds originate from microorganisms and are denoted as pathogen-associated molecular patterns (PAMPs). Pattern recognition receptors (PRRs) and non-PRRs recognise these PAMPs, triggering cell signalling and activating multiple transcription factors. These alterations promote the production of inflammatory mediators, including acute-phase proteins, complement cytokines, chemokines, and antimicrobial peptides, which are required to activate the inflammatory environment for eliminating the invading pathogen [11]. In contrast, damage-associated molecular pattern molecules (DAMPs) are components derived from damaged cells that initiate or perpetuate immune responses, either in the presence or absence of pathogens [12].

An essential function of innate immunity is the rapid recruitment of myeloid cells (including neutrophils) to the site of infection and activation of PRRs. These responses initiate cell

signalling through the activation of transcription factors, such as nuclear factor-kappa B (NF-κB), for the production and release of cytokines, including tumour necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6 [13]. Many cytokines, including IL-6 (the major inducer of C-reactive protein [CRP] in the liver), trigger serum amyloid A (SAA) levels, haptoglobin, fibrinogen, and acute-phase proteins [14]. The liver can also produce complement proteins that bind to complement receptors (CR1, CR3, and CR4), which activate the phagocytic cells to internalise microorganisms and dead or dying cells into phagolysosomes. In addition to hydrolases, oxidative bursts in phagocytes produce reactive oxygen species (ROS) and nitric oxide (NO) intermediates with antimicrobial properties [15]. ROS can also stimulate neutrophils to produce myeloperoxidase (MPO), neutrophil elastase (NE), and calprotectin, triggering cell depolarisation, chromatin decondensation, and plasma membrane rupture. Together, these cellular compounds are released as neutrophil extracellular traps (NETs) or nonlytic NETosis via the degranulation and expulsion of nuclear chromatin [16]. Figure 1 shows the sepsis and innate immune response, focusing on cytokines, acute-phase protein release, phagocytosis, and NET formation.

Inflammatory changes in the CNS in sepsis

Toxicity of cytokines

Proinflammatory cytokines, particularly IL-1β and TNF-α, play an essential role in learning and memory processes [17]. However, exogenous administration or excessive endogenous levels of these cytokines produce detrimental cognitive-behavioural effects [18]. Moreover, synergistic interactions between IL-1β and other cytokines, such as TNF-α and IL-6, may potentiate cognitive dysfunction [19].

Recent evidence suggests that the influx of IL-1β and TNF-α into the brain that occurs due to endothelial cell degeneration, enhanced BBB permeability, and tight junction (TJ) protein loss [20,21] contributes to SAE. Cytokine-induced neurotoxicity can disturb brain homeostasis by altering the activity of glial and neuronal cells responsible for autonomic [22], neuroendocrine [23], and, mainly, cognitive functions [21]. Preclinical studies have demonstrated the toxicity of IL-1β in animal models of systemic inflammation and sepsis. For example, the blocking of the IL-1 signalling pathway attenuated LPS-induced inflammation, reduced microglial activation, and prevented behavioural deficits [24]. Additionally, the impairment of memory retention caused by LPS administration was reversed by IL-1β antagonist treatment [25]. In a peritonitis sepsis model, the administration of an IL-1β receptor antagonist reversed the increase in IL-1β, IL-6, and TNF-α levels in the prefrontal cortex and striatum, which in turn improved cognitive impairment [26]. *In vivo* and *in vitro* studies have shown that IL-1β secreted by LPS-activated microglia can inhibit synaptogenesis and cause cognitive impairment [27].

In sepsis-surviving animals, elevated IL-1β and IL-6 levels and sustained glial activation were associated with increased apoptosis and memory loss in the hippocampal and prefrontal cortex [28,29]. In addition to neuroinflammatory conditions, cytokine neurotoxicity also plays an essential role in normal aging. Clinical studies have shown that older subjects and those with age-related cognitive decline have increased IL-6 plasma levels associated with reduced hippocampal volume [30,31]. However, healthy young humans

who received endotoxin showed temporal deterioration of episodic and working memory, which was associated with increased IL-6 and TNF-α levels [32]. These and similar findings demonstrate that cytokine toxicity is not necessarily restricted to normal aging and reinforce the role of systemic inflammation and neuroinflammation in sepsis [33]. However, hospitalised patients with sepsis and delirium had increased IL-6 and IL-8 levels [34]. Additionally, the profile of inflammatory biomarkers differs between patients with SAE and sepsis and those with delirium, suggesting that pathways related to SAE are different from those of delirium itself [35]. In SAE, the activation of the microglial neurotoxic phenotype (M1) contributes to the maintenance of chronic inflammation, which plays a critical role in neuronal apoptosis and cognitive dysfunction [36]. After activation, these M1 microglia exhibit discernible morphological changes and secrete more cytokines along with other inflammatory mediators such as inducible NO synthase (iNOS), one of the main markers of M1 microglia polarisation that is observed in several CNS diseases [37]. Studies have reported that elevated NO production triggers neuronal apoptosis and permanent brain damage, manifesting as cognitive dysfunction [38,39]. Neurotoxicity mediated by NO and its metabolites have been shown to alter the balance between pro- and antiapoptotic proteins through the upregulation of Bax and down-regulation of Bcl-2 expression [40] in cells located in the prefrontal cortex and hippocampus of septic rats [38,41]. Decreased Bcl-2 expression and increased caspase 3-positive apoptotic cells were associated with cognitive impairment in the prefrontal cortex, dentate gyrus, and CA1 region of the hippocampus in cecal ligation and puncture (CLP) rats [28,29]. Elevated iNOS levels and increased MPO enzyme activity were accompanied by cellular loss and neurological deficits in a rat model of LPS-induced acute neuroinflammation and neurodegeneration [42]. Several mediators regulate neuronal apoptosis via complex molecular mechanisms. NF-κB is one of the determinant mediators in this regulation that can be activated by proinflammatory cytokines, such as TNF-α and IL-1β, through the canonical pathway [43]. Furthermore, the NF-κB pathway has been previously reported to be involved in the mechanism underlying SAE-related CNS damage [44]. NF-κB activation promotes NLRP3 inflammasome up-regulation through the nuclear translocation of p65, a subunit of the NF-κB heterodimer [45]. BAY11-7082, an NF-κB-specific inhibitor, suppresses the activation of the NLRP3 inflammasome induced by ZnO-NPs in A549 cells, demonstrating the relationship between these inflammatory mediators [46]. Recent studies have demonstrated a decrease in neuronal apoptosis and improvement in cognitive decline associated with the inhibition of the NF-κB/NLRP3 inflammasome signalling pathway in animals with SAE [44]. Moreover, the administration of NLRP3 inhibitors reversed the increase in gasdermin-D (GSDMD) found in the hippocampus of sepsis-surviving mice, suggesting that the NLRP3/caspase-1 pathway is involved in neurotoxicity and cognitive impairment in SAE [47].

Neuroinflammation and mitochondrial dysfunction

Neuroinflammatory conditions are also related to deleterious changes in mitochondrial function [48,49]. Under these conditions, mitochondrial dysfunction may occur in the form of cytochrome C (CytC) release [49], excessive mitochondrial fission [50], and dysregulation of mitochondrial fusion [51]. CytC is a mitochondrial protein in the mitochondrial intermembrane space, where it acts as an electron carrier in the electron transport chain and as a ROS scavenger [52]. Mitochondrial dysfunction in sepsis is

characterised by ineffective oxygen utilisation in tissues [53]. In the brain, neurons and glial cells have a high metabolic rate and are more susceptible to hypoxaemic effects. Under these conditions, apoptosis may occur because of the triggering of a cascade mechanism initiated by the cytosolic release of CytC, which is facilitated by an increased permeability of the mitochondrial membrane [54,55]. Apoptosis may also arise due to abnormalities in electron transport by the cytochrome chain and inefficiency in aerobic energy generation in the form of ATP [56]. Administration of the SS-31 peptide inhibited mitochondrial dysfunction associated with apoptosis induced by CytC release and reversed cognitive deficits in SAE mice [57]. Mitochondrial fission is triggered by dynamin-related protein 1 (Drp1), which binds to the mitochondrial membrane protein Fis1, leading to mitochondrial fragmentation and ROS production. The use of P110, a peptide inhibitor that blocks Drp1 from binding to the Fis1 protein, prevents the mitochondrial fission signalling cascade, thereby preserving mitochondrial integrity and improving membrane potential [58]. In septic encephalopathy, blocking the Drp1–Fis1 interaction seems to be crucial for reducing oxidative stress and mitochondrial failure resulting from increased BBB permeability [50]. Mitofusin-2 (Mfn2) plays a key role in regulating mitochondrial function. In experimental models of neurodegenerative diseases, Mfn2 has been investigated for its role in controlling mitochondrial fusion [51], a process essential for mitochondrial function that includes complex respiratory assembly [59], ATP production [60], Ca^{2+} homeostasis [61], and ROS production [62]. Transgenic mice overexpressing neuronal Mfn2 showed decreased LPS-induced mitochondrial fragmentation in neurons. Additionally, Mfn2 up-regulates the expression of CX3CL1, a chemokine constitutively produced by neurons for suppressing microglial activation [63]. During sepsis, mitochondrial function is compromised in the CNS. In experimental sepsis animal models, sepsis survivors with cognitive deficits had significantly reduced ATP and *ex vivo* oxygen consumption levels in the prefrontal cortex and hippocampus [64].

Neuroinflammation and synaptic dysfunction

Glial cells secrete cytokines and trophic factors to maintain brain plasticity. However, an imbalance in their levels during neuroinflammation can harm neurons and cause alterations in neurotransmitter expression and activity [65]. In SAE, reduced synaptic functioning is associated with cerebral damage and dysfunction [20] and occurs through excitotoxic processes [66], which is characterised by an imbalance caused by the increased release and insufficient reuptake of neurotransmitters in the synaptic cleft [67]. Several synapses as well as changes in neurotransmitter release or concentrations seem to be involved in SAE pathophysiology [68–70]. Furthermore, patients with sepsis-experiencing cognitive dysfunction have significantly increased acetylcholinesterase activity, suggesting that acetylcholine is involved in sepsis-related cognitive impairment [71]. Preclinical studies have shown that a substantial loss of cholinergic boutons in the parietal association and somatosensory cortical areas is accompanied by cognitive decline in sepsis-surviving rats [41]. Acetylcholinesterase inhibitors can prolong the availability of acetylcholine, thus attenuating the release of proinflammatory cytokines by microglia and improving survival in sepsis models [72]. Microglial activation releases more glutamate, while in sepsis, damaged astrocytes reuptake less glutamate, causing brain excitotoxicity and cognitive impairment [73]. Additionally, septic animals showed elevated GABAergic transmission in hippocampal

neuronal circuits, while selective blocking of $GABA_A$ receptors reversed LPS-induced cognitive impairment [74]. In summary, all these alterations in neurotransmitter metabolism are crucial for understanding the development of SAE. However, these changes should not be interpreted as being singly responsible for SAE, since its pathophysiology involves multifactorial mechanisms and multiple neurotransmitter interactions.

BBB changes in sepsis

The BBB is a highly selective and regulated interface between the blood and brain that is formed by a complex molecular system, including the glycocalyx and basement membrane, in addition to a cellular system comprising endothelial cells, pericytes, and the end-feet of astrocytes [13]. A crucial function of the BBB is to protect the neural brain cells from circulating toxic compounds, systemic inflammation, and infections [13]. During sepsis, systemic inflammation can affect BBB function [75]. Circulating inflammatory mediators target the BBB endothelial cells through PRRs, including receptors for IL-1β, TNF-α, and IL-6 and Toll-like receptors (TLRs) [76]. Activation of the PRRs is stimulating NF-κB to produce and release cytokines [75]. Cytokines, ROS, and other mediators can activate and increase the expression of matrix metalloproteinases (MMPs), which are present in increased concentrations in damaged, inflamed, or repairing tissue [77,78]. MMPs degrade TJ proteins, claudin, occludin, and junctional adhesion molecules, leading to BBB permeability, peripheral leukocyte infiltration, and brain oedema in sepsis [13,79]. In animal models, MMP inhibition prevents BBB breakdown and brain inflammation [80]. One study showed that MMP3, MMP7, MMP8, and MMP9 plasma levels of patients with sepsis admitted to the intensive care unit (ICU) were more than triple that of controls [81]. In a study evaluating the plasma levels of occludin, claudin-5, and zonula occludens-1 (ZO-1) in 51 patients with sepsis, occludin and ZO-1 levels were higher in nonsurvivors than in survivors. Furthermore, the occludin and ZO-1 levels were correlated with disease severity and Sequential Organ Failure Assessment (SOFA) scores, while the ZO-1 level was positively correlated with APACHE II [82]. Morever, in a postmortem study of brain samples of patients with sepsis, occludin expression was absent in the endothelium of cerebral microvessels in 38% of the samples, with SOFA scores being positively correlated with BBB injury [83].

The permeability of the BBB enables peripheral immune cells to reach the brain for the release of inflammatory mediators and activation of glial cells [10,79]. The vascular end-feet of astrocytes play a central role in BBB integrity. They work as an adhesive along all parts of the cerebral vasculature for establishing the perivascular space, which allows for fast and low-resistance transport of cerebrospinal fluid (CSF) into the brain [84]. The end-feet of astrocytes contain the water channel aquaporin-4 (AQP4), which facilitates CSF movement into and out of the nervous system [85]. The glymphatic system comprises the end-feet of vascular astrocytes with their AQP4 channels facing the perivascular spaces filled with CSF [86,87]. During inflammation or infection, AQP4 expression decreases in astrocytes, enhancing the accumulation of waste compounds and thereby causing neuronal damage and neuroinflammation [88].

Neuroinflammation: microglial and astrocytic activation

The neuroinflammatory response that triggers SAE is not due to the invasion of a pathogen into the brain but due to the systemic inflammation that activates the brain immune response [21]. Cytokines released in the bloodstream during sepsis (such as IL-1α, IL-1β, IL-6, and TNF-α) can cross the BBB through the respective saturable transporters [89] or due to BBB dysfunction [13]. Microglia, the brain's housekeepers, then express a range of receptors, including chemokine (CCR5, CX3R1, and C3aR1) and cytokine receptors (IL-R, TNFR, INF-R, TGFR, PPR, TLR, NOD-like, and NLRP3) [90]. Activation of TNFRs mediates a wide range of biological reactions, such as cell differentiation, proliferation, survival, inflammation, and apoptosis [91,92]. TNF-α can induce miR-342 production in microglial cells, leading to NF-κB activation and triggering of a neurotoxic phenotype that releases proinflammatory cytokines, nitrites, and TNF-α as a positive feedback loop [91]. In addition, the IL-1 receptor induces cyclooxygenase-2 production, leading to the synthesis of endothelial cell prostaglandins (PGE2). Consequently, PGE2 activates the prostaglandin receptor in microglial cells, triggering the production of iNOS, IL-1β, IL-6, and TNF-α and exacerbating inflammation in the brain [21]. Proinflammatory microglia also secrete IL-1α, IL-1β, TNF-α, and C1q, which modify the astrocytic phenotype into neurotoxic A1 astrocytes that release neurotoxins, leading to the death of neurons and oligodendrocytes [93]. Similar pathological pathways are activated in Alzheimer's disease (AD), wherein the deletion of C1q, C3, or CR3 has been shown to prevent synaptic loss and cognitive impairment [94]. Moreover, C3 up-regulation was associated with BBB disruption, gliosis, up-regulation of TLR4, and changes in AQP-4 in a model of endotoxin-induced septic encephalopathy [95].

Microglia, neurons, and astrocytes exhibit strong NLRP3 inflammasome-related responses. The cytosolic protein complex, including NLRP3, adaptor ASC protein, and CARD, forms the NLRP3 inflammasome, which on activation releases caspase-1 that cleaves pro-IL-1β and pro-IL-18 into their mature forms [96]. In pyroptosis, proinflammatory caspase-1 and caspases-11/4/5 cleave GSDMD, the pore-forming executioner protein, generating an N-terminal cleavage product. This cleavage product then forms a pore that releases mature IL-1β and disrupts the osmotic potential of the cell, leading to swelling or cell death [97]. A preclinical study showed that NLRP3 was associated with sepsis pathology, contributing to brain damage and memory impairment [98]. Furthermore, lipid peroxidation triggers GSDMD-mediated pyroptosis in severe polymicrobial sepsis [99], whereas the inhibition of caspase-1 suppresses the expression of GSDMD in the brains of SAE mice [100]. Additionally, NLRP3 has been associated with the pathophysiology of sepsis [101], lending support to the hypothesis of sepsis-triggered AD [21,102]. Therefore, neuroinflammation and neurodegeneration trigger inflammasome activation and pyroptosis via DAMPs, PAMPs, mitochondrial dysfunction, ion flux, and aberrant protein aggregates. AD, stroke, SAE, and other CNS diseases are associated with pyroptosis [21]. For more details on brain neuroinflammation in sepsis pathophysiology, see Figure 2.

Biomarkers associated with neuroinflammation in sepsis

Brain-specific biomarkers: C-type natriuretic peptide, S-100β protein, and neuron-specific enolase

Markers such as the amino-terminal propeptide of the C-type natriuretic peptide (NT-proCNP), S-100β protein, and neuron-specific enolase (NSE) can be measured in the plasma or CSF and be used to target different CNS structures involved in pathophysiological processes. For example, the presence of S-100β in the serum of patients indicates glial cell injury and abnormal BBB function, whereas the presence of NSE, an intraneuronal enzyme, suggests neuronal injury [103]. One study showed that elevated levels of NSE were found in the serum of approximately half of ICU patients with sepsis [104]. A retrospective analysis of 124 patients from a larger sepsis cohort identified high plasma concentrations of NSE associated with mortality and delirium in critically ill patients with sepsis [104]. A prospective observational study found that serum S100β levels were significantly higher in patients with SAE than in patients without SAE. In that study, compared with NSE, serum S100β was better for diagnosing SAE and predicting sepsis outcome. Although the efficacy and sensitivity of S100β in diagnosing SAE are high, it has low specificity [105]. A comparison of the biomarkers, NSE, S100 β, and NT-proCNP, showed that the plasma levels of NT-proCNP were superior. A high concentration of this biomarker in the early sepsis phase may predict SAE emergence [106]. Furthermore, the fact that NT-proCNP release is triggered by acute-phase inflammatory mediators such as IL-1β and TNF-α reinforces its role as a predictor of SAE [107].

Neurodegeneration-associated biomarkers

Neuroinflammation and BBB dysfunction in the late phase of sepsis may result in the production of biomarkers linked to degenerative processes, such as amyloid-β (Aβ), tau protein, glycogen synthase kinase-3 beta (GSK3β), and receptors for advanced glycation end products (RAGE). Identifying these biomarkers can help understand the underlying mechanisms of sepsis-associated brain injury and prevent long-term cognitive impairments in patients with SAE. Sepsis and neurodegenerative diseases, such as AD, share similarities in the molecular patterns of brain lesions [108]. For example, Aβ and phosphorylated tau (p-tau) accumulation were observed in sepsis-surviving rats 30 days after sepsis induction by CLP [109]. Another study found that animals exposed to LPS showed hippocampal accumulation of Aβ plaques and intracellular p-tau [110]. Sepsis-surviving animals showed deposition of amyloid aggregates and p-tau in the prefrontal cortex and hippocampus 10 days after sepsis induction. In all these studies, the animals exhibited memory-related cognitive deficits [28]. Another interesting clinical data showed that serum tau levels in patients with sepsis were independently correlated with SAE [111].

GSK3β is an essential kinase associated with the up-regulation of tau protein [112]. Furthermore, GSK3β participates in the RAGE-dependent signalling pathway that regulates the β- and -secretase cleavage of APP for generating Aβ [113]. A mouse model study of AD showed that the RAGE-dependent signalling in microglia contributes to neuroinflammation, Aβ accumulation, and memory impairment [114]. The injection of RAGE antibodies into the hippocampus of sepsis-surviving animals reduced Aβ and p-tau accumulation, reinforcing

the involvement of RAGE in cognitive impairment during the recovery of animals from sepsis [109].

Targeting of neuroinflammation for sepsis-associated cognitive decline

To date, no specific pharmacological strategy exists for the treatment or prevention of long-term cognitive decline in sepsis survivors. Clinicians should be aware of this as early as possible and respond appropriately in order to enhance patients' quality of life and decrease the economic burden. Current treatment strategies include directing patients to long-term care homes and cognitive behavioural therapy [115]. In experimental animal models, sepsis survivors showed improved cognitive performance after administration of HMGB1 [116], NLRP3 [98], and RAGE inhibitors [109]. Additionally, reversing mitochondrial dysfunction via mitochondrial biogenesis also improved cognition [64]. However, preclinical and clinical studies are required to provide detailed understanding of the pathophysiology of postsepsis sequelae in order to identify specific treatment strategies and prevent and treat long-term cognitive impairment after sepsis.

Effect of sepsis on different brain regions

Brainstem dysfunction and SAE

The brainstem has a variety of functions, such as controlling reflexes and the circadian clock, maintaining vitals, and modulating immune responses [115]. After sepsis, irregular signals from the brainstem affect alertness, leading to cardiovascular complications and immune dysfunction [117]. A systematic review reported that haemorrhagic and necrotic lesions, gliosis, hypoplasia, oedema, and calcification were observed in the postmortem brainstem samples of patients with sepsis [79]. Similarly, another review showed that an experimental model of LPS-induced sepsis increased oxidative stress in the brainstem and exacerbated apoptosis of autonomic centres [118]. Additionally, altered heart rate, impaired sympathetic activity, and absence of EEG reactivity are the main predictors of organ dysfunction and mortality in critically ill patients [119].

Amygdala and psychological disorders in sepsis survivors

Sepsis survivors often suffer from long-lasting mental health problems. Postsepsis psychiatric consequences include post-traumatic stress disorder (PTSD), depression, and anxiety [120]. Furthermore, sepsis involving the limbic system has been reported to cause unique psychiatric complications [118]. Although behavioural changes have been reported in sepsis survivors, the neuroanatomical changes have not been well described in the literature. However, recent studies have explored neuroanatomical abnormalities using computed tomography or magnetic resonance imaging (MRI). In one prospective observational study, brain MRI revealed volumetric changes in patients with sepsis, wherein the most volume reduction was found in the cerebral and cerebellar white matter, cerebral cortex, hippocampus, and amygdala [121].

The amygdala, which is composed of two nuclei, i.e. the basolateral region and central region (CeA), is a key node in the fear and anxiety circuitry in humans and rodents [122,123]. Several brain functions depend on the amygdala nuclei, including fear expression,

memory formation, anxiety, and depression. In terms of microglial activation, the amygdala is particularly affected during sepsis. The CeA is composed of two inhibitory neurons that express protein kinase Cδ PKCδ+) or somatostatin (SOM+), leading to expression, extinction, and generalisation of fear. Furthermore, PKCδ+ neurons play a crucial role in the fear memory network. Studies have reported that the inhibition of PKCδ+ neurons drives the formation of artificial aversive memories and that the optogenetic activation of PKCδ+ neurons promotes anxiogenic and anorexic effects. These findings indicate the diversity of subcircuits within the PKCδ+ neuron population [124]. Considering that acute adaptive defensive behaviour is controlled by the CeA and amygdala dysfunction has been frequently highlighted in psychiatric disorders, prolonged maladaptive behaviour that involves an overlapping circuit centred on the amygdala can develop [122]. Experimental evidence has demonstrated a link between the pathological activation of extended amygdala neurons during the acute phase of sepsis and subsequent development of PTSD-like behaviours [125]. Specifically, transient activation in CeA neurons that primarily express PKCδ and project to the ventral bed nucleus of the striata terminals has been reported. Furthermore, the administration of the antiepileptic drug, levetiracetam, suppressed this transient activation of the amygdala and prevented long-term increase in anxiety-related behaviours and exaggerated conditioned fear responses in sepsis survivors [126]. Considering these reports, the amygdala might be involved in the psychiatric consequences in sepsis survivors.

Changes in hippocampus, frontal cortex, and white matter and cognitive decline in sepsis survivors

The frontal cortex and hippocampus are known to play a primary role in cognition and executive function [127]. Significant postsepsis sequelae can include cognitive impairment, attention deficiency, lack of verbal fluency, and functional disability, with approximately half of sepsis survivors exhibiting cognitive decline [128]. A brain MRI study revealed volumetric changes in patients with sepsis, with the most noticeable volume reduction found in the cerebral and cerebellar white matter, cerebral cortex, and hippocampus [121]. Results from a systematic review revealed glial activation, neuronal hypoxia, demyelination, axonal injury, and atrophy in the hippocampus and haemorrhagic and ischaemic lesions, gliosis, necrosis, and neuronal apoptosis in the cortex in the postmortem brain samples of patients with sepsis [79].

In an experimental model of sepsis, *in vivo* glial activation and oxidative stress were reported mainly in the cortex and hippocampus [129]. The levels of the proinflammatory markers, TNF-α, IL-6, and IL-1β, significantly increased after sepsis in both the hippocampus and cortex [109]. Notably, Aβ and tau markers associated with AD pathology were significantly elevated in the frontal cortex and hippocampus after sepsis induction [109]. Furthermore, RAGE inhibitors have been demonstrated to inhibit sepsis-associated damage to the hippocampus and frontal cortex and improve memory in mouse models via the Akt/mTOR signalling pathway [109]. Additionally, increased glial activation and elevated levels of proinflammatory content in the hippocampus and cortex showed impaired spatial and long-term memory in septic mice, as evaluated by the Morris water maze and novel object recognition tasks [109,130].

Recent reports have shown that polymicrobial sepsis induced by CLP increases fibrillar amyloid plaque load in the hippocampus and neuroinflammation in APP/PS1 mice, an AD mouse model [131]. Sepsis enhances plaque-related astrocyte activation and C4b gene expression in the hippocampus [131]. Additionally, sepsis negatively modulates the gut microbiome of APP/PS1 mice, which is associated with a proamyloidogenic and neuroinflammatory state [129]. Apart from the hippocampus and frontal cortex, the white matter is also affected in patients with sepsis. Patients with sepsis have demonstrated white matter lesions in MRI studies [132] and white matter axonal injury in postmortem brain studies [133]. All these clinical and preclinical evidence demonstrate the association of the frontal cortex, hippocampus, and white matter with cognitive decline in sepsis survivors.

Conclusions

The World Health Organization has designated sepsis as a primary global health concern. However, no specific guidelines exist for the pharmacological therapy of sepsis-related brain dysfunction, and treatment options for sepsis are generally limited to antibiotics and supportive therapy. Early mobility of the patient, discontinuation of sedation, rehydration, management of physical and psychological distress, and avoidance of prodelirious medicines are non-pharmacological measures that can be considered to prevent or treat delirium and decrease neuroinflammation in SAE.

Further studies should be conducted for unravelling what happens in the brains of patients with sepsis and identifying the mechanisms underlying the host's immune response that trigger neuroinflammation. This could be a new avenue to prevent cognitive sequelae and provide a better quality of life for sepsis survivors.

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Data Availability

NA

Abbreviations

Aβ	amyloid-β
AD	Alzheimer's disease
AQP4	aquaporin-4
BBB	blood–brain barrier
CLP	cecal ligation and puncture
CNS	central nervous system

CR	complement receptor
CRP	C-reactive protein
CSF	cerebrospinal fluid
CytC	cytochrome C
DAMP	damage-associated molecular pattern molecule
Drp1	dynamin-related protein 1
GSDMD	gasdermin-D
GSK3β	glycogen synthase kinase-3 beta
ICU	intensive care unit
IL	interleukin
iNOS	inducible NO synthase
LPS	lipopolysaccharide
Mfn2	Mitofusin-2
MMP	matrix metalloproteinase
MPO	myeloperoxidase
MRI	magnetic resonance imaging
NE	neutrophil elastase
NET	neutrophil extracellular trap
NF-κB	nuclear factor-kappa B
NO	nitric oxide
NSE	neuron-specific enolase
NT-proCNP	propeptide of the C-type natriuretic peptide
p-tau	phosphorylated tau
PAMP	pathogen-associated molecular pattern
PGE2	prostaglandin
PKCδ+	protein kinase Cδ
PRR	Pattern recognition receptor
PTSD	post-traumatic stress disorder
RAGE	receptors for advanced glycation end product

ROS	reactive oxygen species
SAA	serum amyloid A
SAE	sepsis-associated encephalopathy
sofA	sequential organ failure assessment
SOM+	somatostatin
TJ	tight junction
TLR	toll-like receptor
TNF-α	tumour necrosis factor α
ZO-1	zonula occludens-1

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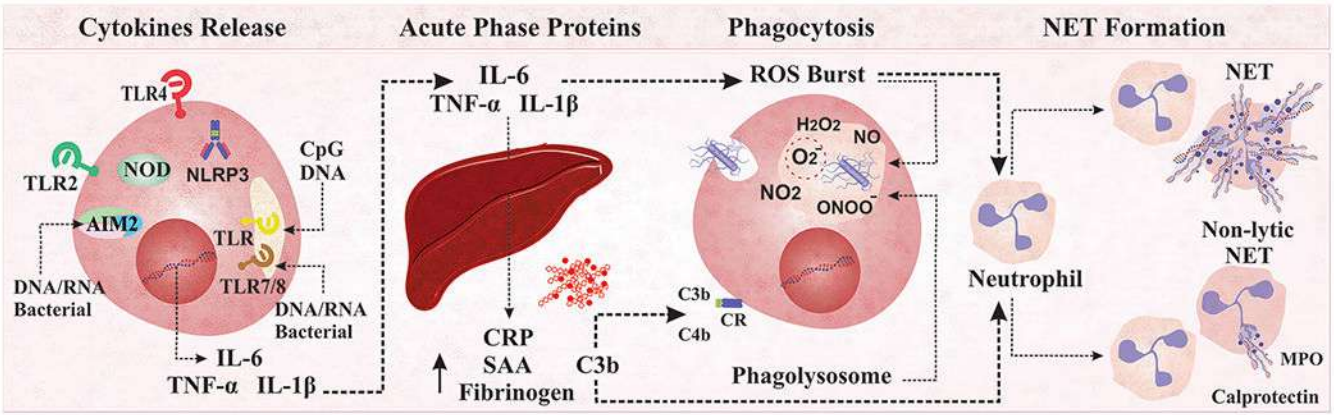

Figure 1. Sepsis triggers the innate immune response

Cytokine release: PAMPs and DAMPs activate PPRs, including TLR, thus initiating cell signaling through activation of the NF-κB for the production and release of TNF-α, IL-1β, and IL-6. *Acute phase protein*: Cytokines are liver inductors of CRP, SAA, haptoglobin, complement system, and fibrinogen. *Phagocytosis:* CR1, CR3, and CR4, among other receptors, activate the phagocyte cells to internalise microorganisms, dead or dying cells into the phagolysosomes producing an oxidative burst. *NET formation:* ROS can stimulate the neutrophils to produce MPO, NE, and calprotectin to trigger cell depolarisation and chromatin decondensation to release the NET. Abbreviations: CR1, CR3, and CR4, complement receptors; C3b and C4b, complement protein; IL, interleukin; LCF, lactoferrin; MPO, myeloperoxidase; NE, neutrophil elastase; NETs, neutrophil extracellular traps; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species; SAA, serum amyloid A; TLR, Toll-like receptor.

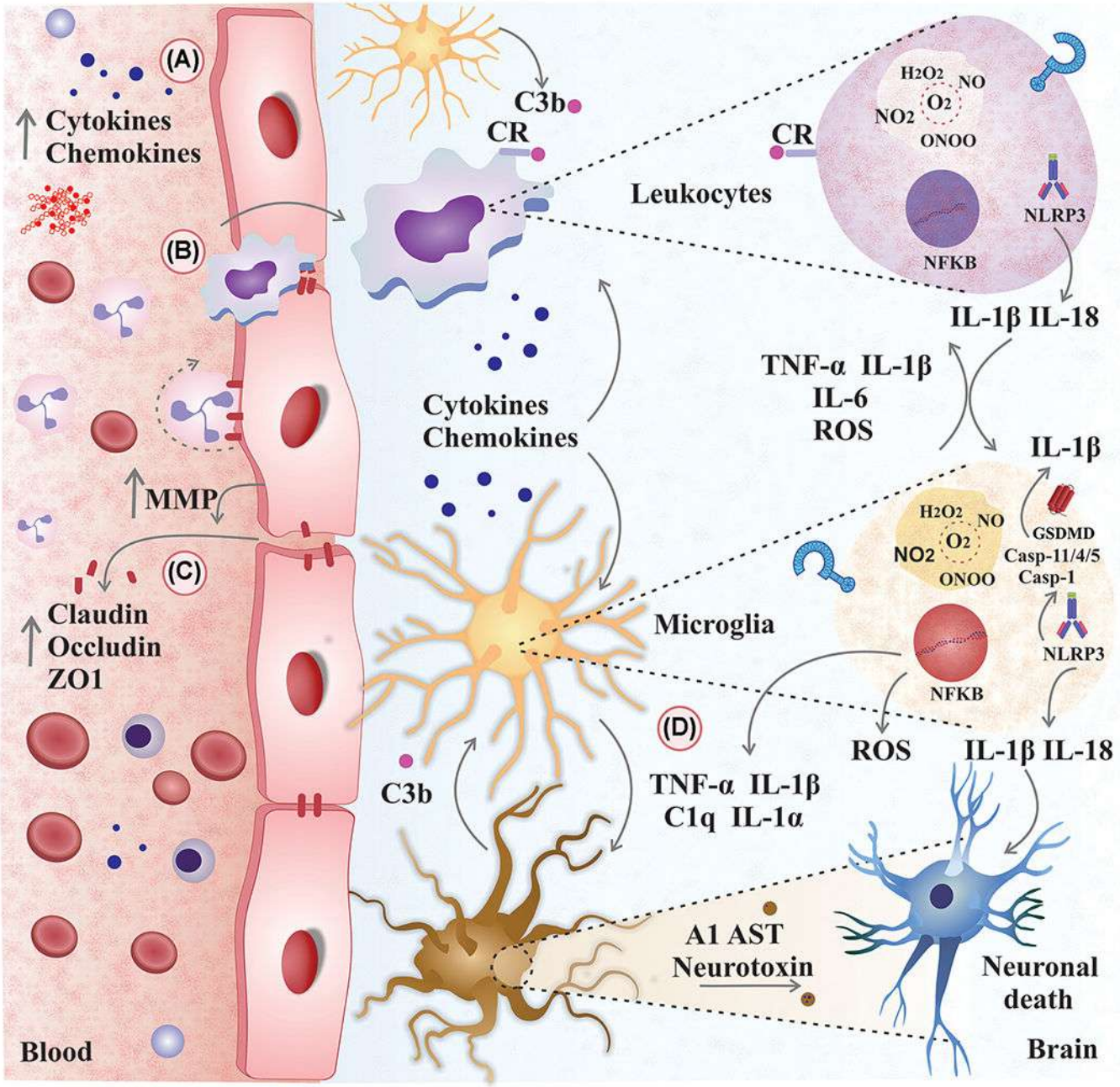

Figure 2. Sepsis triggers neuroinflammation

(**A**) Sepsis-triggered systemic inflammation increases the levels of inflammatory mediators in the bloodstream. (**B**) Increased leukocyte rolling on the BBB facilitates its entry into the brain. (**C**) Enhanced permeability of the BBB occurs due to endothelial damage and altered TJ protein levels. (**D**) Microglial cells are activated to maintain brain homeostasis. However, activated microglia release more inflammatory mediators and activated astrocytes to produce increased cytokine/chemokines leading to neuroinflammation and neuronal death in the septic brain. Abbreviations: CR1, CR3, and CR4, complement receptors; C3b and C4b, complement protein; IL, interleukin; LCF, lactoferrin; MPO, myeloperoxidase; NE,

neutrophil elastase; NETs, neutrophil extracellular traps; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species; SAA, serum amyloid A; TLR, Toll-like receptor.