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Neuroinflammation in Sepsis: Sepsis Associated Delirium

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Abstract: Sepsis-associated delirium (SAD) is a clinical manifestation of the involvement of the central nervous system (CNS) during sepsis. The purpose of this review is to provide a concise overview of SAD including the epidemiology and current diagnostic criteria for SAD. We present in detail the pathophysiology with regards to blood-brain-barrier breakdown, cytokine activation and neurotransmitter deregulation. Treatment and prognosis for SAD are also briefly discussed. SAD is the most common form of delirium acquired in the ICU (Intensive Care Unit), and is described in about 50% of septic patients. Clinical features include altered level of consciousness, reduced attention, change in cognition and perceptual disturbances. Symptoms can reversible, but prolonged deficits can be observed in older patients. Pathophysiology of SAD is poorly understood, but involves microvascular, metabolic and, not least, inflammatory mechanisms leading to CNS dysfunction. These mechanisms can be different in SAD compared to ICU delirium associated with other conditions. SAD is diagnosed clinically using validated tools such as CAM-ICU (Confusion Assessment Method for the Intensive Care Medicine) or ICDSC (The Intensive Care Delirium Screening Checklist), which have good specificity but low sensitivity. Neuroimaging studies and EEG (Electroencephalography) can be useful complement to clinical evaluation to define the severity of the condition. Prompt diagnosis and eradication of septic foci whenever possible is vital. Preventive measures for SAD in the critically ill patient requiring long-term sedation include maintaining light levels of sedation using non-benzodiazepine sedatives (either propofol or dexmedetomidine). Early mobilization of patients in the ICU is also recommended. Antipsychotic drugs (haloperidol and atypical antipsychotics) are widely used to treat SAD, but firm evidence of their efficacy is lacking.

Keywords: Brain diseases, delirium, encephalopathy, neuroinflammation, sepsis, sepsis associated delirium, sepsis associated encephalopathy, septic shock.

INTRODUCTION

Confusional states are a major clinical problem in several areas of clinical medicine, from psychiatry to geriatrics and neurology, and, in modern times, in intensive care medicine. Encephalopathy, delirium, agitation, irritation, confusion, disorientation are commonly used terms to describe the patient [1]. In the intensive care unit (ICU), sepsis and septic shock (SS) are frequently associated with confusional states characterized by acute and potentially reversible cerebral dysfunction, affecting alertness, awareness, cognition and behavior. Different denominations have been used to identify the central nervous system (CNS) involvement during sepsis: sepsis-associated encephalopathy (SAE), sepsis-associated delirium (SAD) or sepsis-related brain dysfunction. The term septic encephalopathy is not recommended, because it suggests an active infection within the CNS. SAE is defined as a diffuse cerebral dysfunction that accompanies sepsis in the absence of direct central nervous system (CNS) infection, structural abnormality or other types of encephalopathy (for example, hepatic or renal encephalopathy), as detected by clinical or standard laboratory test [2, 3].

SAD is diagnosed in patients with sepsis according to the Diagnostic and Statistical Manual of Mental Disorders IV edition (DSM-IV) criteria for delirium as in (Table **1**).

In addition to sepsis, preexisting dementia, history of hypertension and/or alcoholism, a high severity of illness at admission and coma are risk factors for the development of SAD. SAD is associated with an increased mortality [4, 5] mainly due to increased metabolic, inflammatory and hemodynamic demand caused by SIRS (Systemic Inflammatory Response Syndrome), rather than a direct central nervous system injury.

The interest in SAD has been growing over the past decade as the sepsis community now recognizes that SAD is an early event in the acute stage of critical illness, and is associated with increased mortality and long-term morbidity. The purpose of this review is to summarize the current knowledge on the most relevant clinical, pathophysiological, diagnostic and therapeutic aspects of SAD.

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Table 1. Diagnostic and statistical manual of mental disorders IV edition (DSM-IV) criteria for delirium diagnosis.

DSM-IV Criteria
1. Disturbance of consciousness with reduced ability to focus, sustain, or shift attention
2. A change in cognition (memory, language, or orientation) or the development of a perceptual disturbance not better accounted for by a dementia
3. Disturbance develops over hours or days and fluctuates during course of day
4. There is evidence from the history, physical examination, and laboratory findings that: (i) the disturbance is caused by the direct physiological consequences of a general medical condition (ii) the symptoms in criterion (i) developed during substance intoxication, or during or shortly after, a Withdrawal syndrome (iii) the delirium has more than one aetiology".

DEFINITION AND CLINICAL MANIFESTATION

SAD is characterized by an altered level of consciousness with a reduced ability to focus, sustain, or shift attention associated with either a change in cognition (i.e., memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance (i.e., hallucinations, delusions) [6].

In contrast to dementia that develops slowly, delirium develops over a short period of time, usually hours to days, and fluctuates during the day. There may be associated alterations in sleep patterns, e.g., day-night reversal, emotional states, nonspecific neurological abnormalities and a sudden and significant decline in functional ability.

While delirium presents with psychiatric symptoms, it is important to emphasize that these symptoms are manifestations of medical abnormalities and not primary psychiatric illnesses.

Delirium is classified according to *motoric* (psychomotor) subtypes as hyperactive, hypoactive, and mixed delirium [7]. The hypoactive subtype of delirium is characterized by a flat affect, withdrawal, apathy, or lethargy, and is the most prevalent form in medical and surgical critically ill patients. The hyperactive delirious patient is described as agitated, restless, violent, or emotionally labile. Although challenging to manage clinically, the weight of evidence suggests a better overall prognosis for the hyperactive patient compared to the hypoactive delirious patient [8].

Motor signs are rarely observed in patients with SAD. Asterixis, myoclonus, and tremors, which are relatively frequent in metabolic encephalopathies, are rarely seen in SAD. 'Paratonic rigidity' (defined as velocity dependent resistance to passive movements, less evident when limbs are moved slowly) can be present in SAD [9]. Conversely, up to 70% of severe cases of SAD develop an associated intensive care unit acquired weakness (ICU-AW) [5].

EPIDEMIOLOGY

The incidence of SAD is poorly defined, because the diagnostic criteria are not well established, the diagnosis is based on exclusion criteria, and only few studies with a heterogeneous cohort of patients have addressed the question directly [10, 11]. Despite these limitations, since sepsis is the leading cause of ICU admission [5] and 20 to 50% of septic patients have some degree of encephalopathy, SAD is estimated to be the most common form of delirium acquired in the ICU [12]. ICU delirium is present in one third of patients according to the multinational Delirium Epidemiology in Critical Care (DECCA) study [13]. In this study of 497 patients admitted to 104 ICUs from 11 countries in South and North America and Spain, sepsis was the leading cause of ICU admission.

SAD is more frequent in patients with biliary tract or gastrointestinal infection as source of sepsis especially when caused by Staphylococcus Aureus, Enterococcus Feacium, Acinetobacter spp., Pseudomonas Aeruginosa and Stenotrophomonas Maltophilia. Septic patients with higher disease severity have an increased risk of developing SAD [10].

Taken together, these factors suggest that patients with a higher burden of systemic illness are more likely to develop SAD, and that the source of infection and causative organism are important in the development of SAD.

DIAGNOSIS

Diagnosis of SAD is clinical, and is a diagnosis of exclusion. In a febrile, delirious patient, it is mandatory to first exclude direct CNS infections such as meningitis, brain abscess, subdural empyema or encephalitis. Sepsis is an essential pre-requisite for diagnosis, as is the exclusion of other causes of encephalopathy, neuroleptic malignant syndrome, malignant hyperthermia, nonconvulsive status epilepticus, endocrine disorders, acute CNS vascular events such as stroke and vasculitis, several drugs, or alcohol withdrawal [2]. Commonly used screening tools for SAD are the Confusion Assessment Method for Intensive Care Medicine (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC). Both require that the patient is awake. The CAM was developed in 1990 by Inouye *et al*. to aid in delirium assessment by non-psychiatric personnel [14]. It was modified to the CAM-ICU by Ely *et al*. in 2001 [15] for use in mechanically ventilated ICU patients not able to verbalize. CAM-ICU has a sensitivity of 47%, a specificity of 98% and a positive predictive value of 95% (9) when applied daily by nurses, compared to the diagnosis made by a team of three delirium experts including psychiatrist,

geriatrician and neurologist. Diagnostic features include an acute change or fluctuation in mental status (feature 1) and inattention (feature 2), and one of the following: (a) disorganized thinking (feature 3) or (b) altered level of consciousness (feature 4) (Fig. **1**). The diagnosis of delirium using the CAM-ICU requires a non-sedated patient with a Richmond Agitation-Sedation scale (RASS) score of -3 or lighter; however, recent evidence suggests that even patients moderate sedation may lead to inflated diagnosis of delirium. The proportion of patients diagnosed with delirium can be decreased by 40%, if only patients with light sedation (RASS -1) are considered [16]. Rapidly reversible, sedation-related delirium does not have the same poor prognosis as persistent delirium [17]; misdiagnosis of persistent sedation as delirium can be dangerous as demonstrated by a recent trial on the use of rivastigmine that was prematurely stopped because of increased mortality in the treatment group [18].

The ICDSC was developed in 2001 by Bergeron *et al*. to assess critically ill ICU patients for delirium based on DSM criteria [19]. It includes assessment of consciousness, attentiveness, orientation, the presence of hallucinations or delusions, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and overall symptom fluctuation (Table **2**). In the original paper, a score of 4 or higher was considered positive for diagnosis of delirium with a sensitivity of 99% and a specificity of 64%.

In a recent systematic review [20], the pooled sensitivity of the CAM-ICU was 80.0% (95% confidence interval (CI): 77.1 to 82.6%), and the pooled specificity was 95.9% (95% CI: 94.8 to 96.8%). The pooled sensitivity of the ICDSC was 74% (95% CI: 65.3 to 81.5%), and the pooled specificity was 81.9% (95% CI: 76.7 to 86.4%), demonstrating a slight improvement in delirium diagnosis when ICAM-ICU is used. However, as for CAM_ICU, the level of sedation can be a confounding factor, and evaluation of delirium should consider the level of sedation using appropriate scores [16].

Biomarkers of SAD

Although screening tools currently serve as the foundation for SAD detection, serum biomarkers might improve diagnostic sensitivity and specificity, and may provide insights into pathophysiological mechanisms. Elevated serum levels of the S-100ß protein and Neuron-Specific Enolase (NSE) have been demonstrated in patients with SAD. Association of S-100ß serum levels with the severity of encephalopathy has provided uncertain results [13, 21, 22]. Other markers, such as the glial fibrillary acidic protein [GFAP], have been demonstrated to be elevated in septic children [23].

The pro-inflammatory cytokine IL-8 is mostly prevalent in patients with SAD, whereas the anti-inflammatory

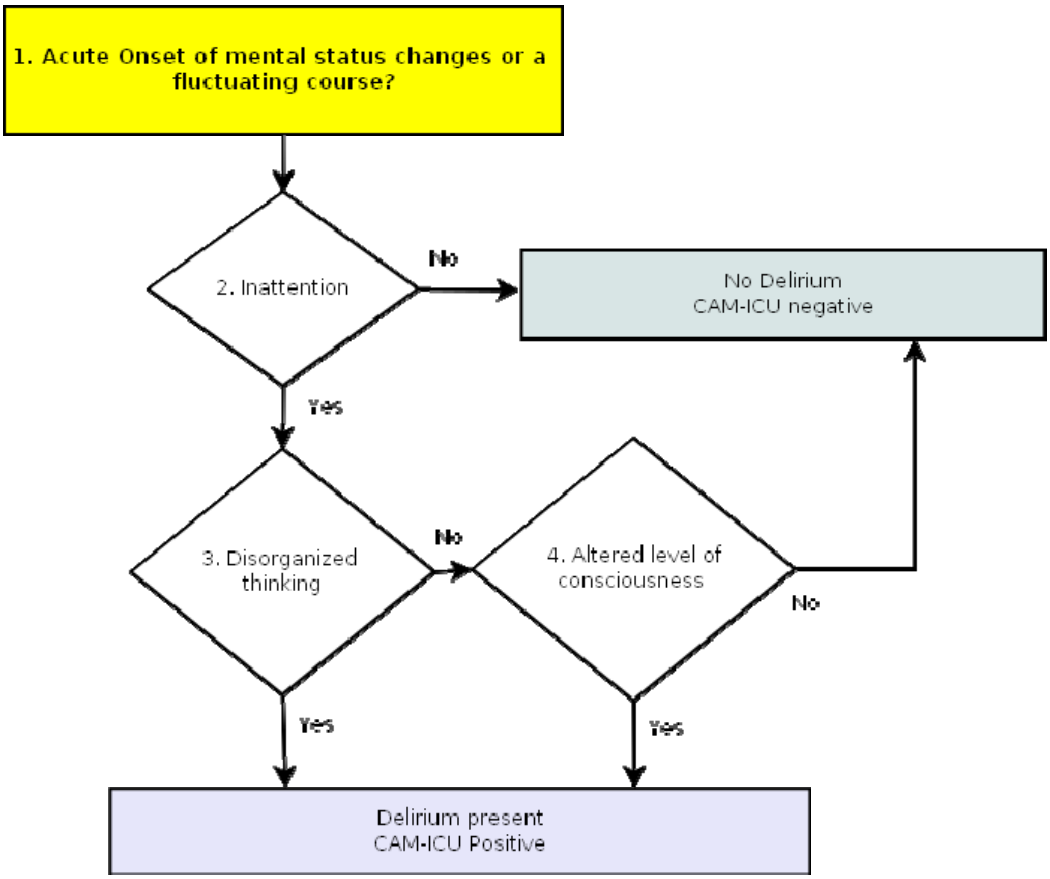

Fig. (1). Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Diagnostic algorithm for the Intensive Care Acquired Delirium.

Table 2. Intensive care delirium screening checklist (ICDSC).

Intensive Care Delirium Screening Checklist (ICDSC)	Score (1 Point for Each Item if Present)
Altered level of consciousness	-
Inattention	-
Disorientation	-
Hallucinations or delusions	-
Psychomotor agitation or retardation	-
Inappropriate speech or mood	-
Sleep-wake cycle disturbance	-
Symptom fluctuation	-
Total Score	

ICDSC is a checklist based on data for the previous 24 hours. Total score 8 points. Scoring position of each item is equal to 1 point. A score of 4 or greater is a positive screen for delirium.

cytokines IL-10 and Ab1-42/40in are preferentially expressed in patients with non-septic delirium [24].

Taken together, the increased serum level of neuronal and glial biomarkers in SAD supports the idea that the brain is a key target of mediators of sepsis. Increased serum inflammatory levels of cytokines in SAD suggest that the underlying mechanisms causing delirium may be different in various disease states. Clinical usefulness of serum biomarkers in SAD warrants further studies.

Neuroimaging Studies

Magnetic resonance imaging (MRI) of the brain has been used in diagnosing patients with SAD. In one of the first published studies [25], Fluid Attenuated Inversion Recovery (FLAIR) MRI showed widespread ischemia-related hyper-intensity alterations of bilateral basal ganglia, thalamus, cerebellum and brainstem. Studies in humans and animals have demonstrated a great variety of brain MRI abnormalities including white matter alterations and vasogenic edema [26, 27]. Vasogenic edema with hyper-intense signal on FLAIR sequences and hypo-intense signal on diffusion weighted imaging (DWI) and increased apparent diffusion coefficient (ADC) sequences probably reflects the breakdown of the blood-brain barrier. The extension of lesions detected by brain MRI is associated with severity of SAD and outcome [28]. In septic-shock patients with acute neurologic changes, brain MRI can reveal leukoencephalopathy or ischemic stroke, which is associated with increased ICU mortality and long-term morbidity [29].

Electrophysiological Investigations

SAD is thought to be associated with a degree of brain electrical activity derangement. These alterations are not specific for SAD, and EEG is not particularly useful for differentiating between etiologies, because several different encephalopathies present with the same EEG patterns. Nonetheless, EEG alterations during sepsis are early, revealing that SAE is an early feature of infection, which might appear before other systemic features of sepsis become obvious showing diffuse slowing at the time the neurological examination is still normal [9]. EEG may also assist the clinician in defining the severity of SAD, and serial measurements may help in defining the evolution of SAE. With increasing severity of SAE, the EEG may shows a progressive slowing of electrical brain activity from mild slowing in the theta range (>4 to <8Hz) to diffuse delta waves (≤4Hz), generalized triphasic waves, generalized burst-suppression pattern (alternating diffuse reductions in voltage with burst of higher voltage waves) or EEG suppression [30]. Flat EEG in absence of sedation is strongly related to the severity of encephalopathy, and may serve as a useful tool in those patients in whom the neurological assessment is not feasible.

Somatosensory evoked potentials (SSEP), particular a decrease in P1 amplitude and increased duration of S-P1 and N1-P2 latencies, can be altered at a very early stage of sepsis [31-33]. These alterations are not influenced by sedative, and are associated with severity of SAD [34].

PATHOPHYSIOLOGY

The pathophysiology of SEA is multifactorial (Fig. **2**). Direct microbial invasion of the brain is a rare event [35], while alterations of cerebral microcirculation, neuro-transmission and metabolism are key events and probably interact with each other in causing SAD.

Cerebral Endothelial Activation and Blood-Brain-Barrier Breakdown (BBB)

The brain has a tightly regulated microenvironment maintained primarily by the BBB, which is constituted by an intricated network between astrocyte foot processes, pericytes and the endothelial cells. The tight junctions between the endothelial cells limit the passage of plasma constituents into the brain. Specialized carriers regulate the

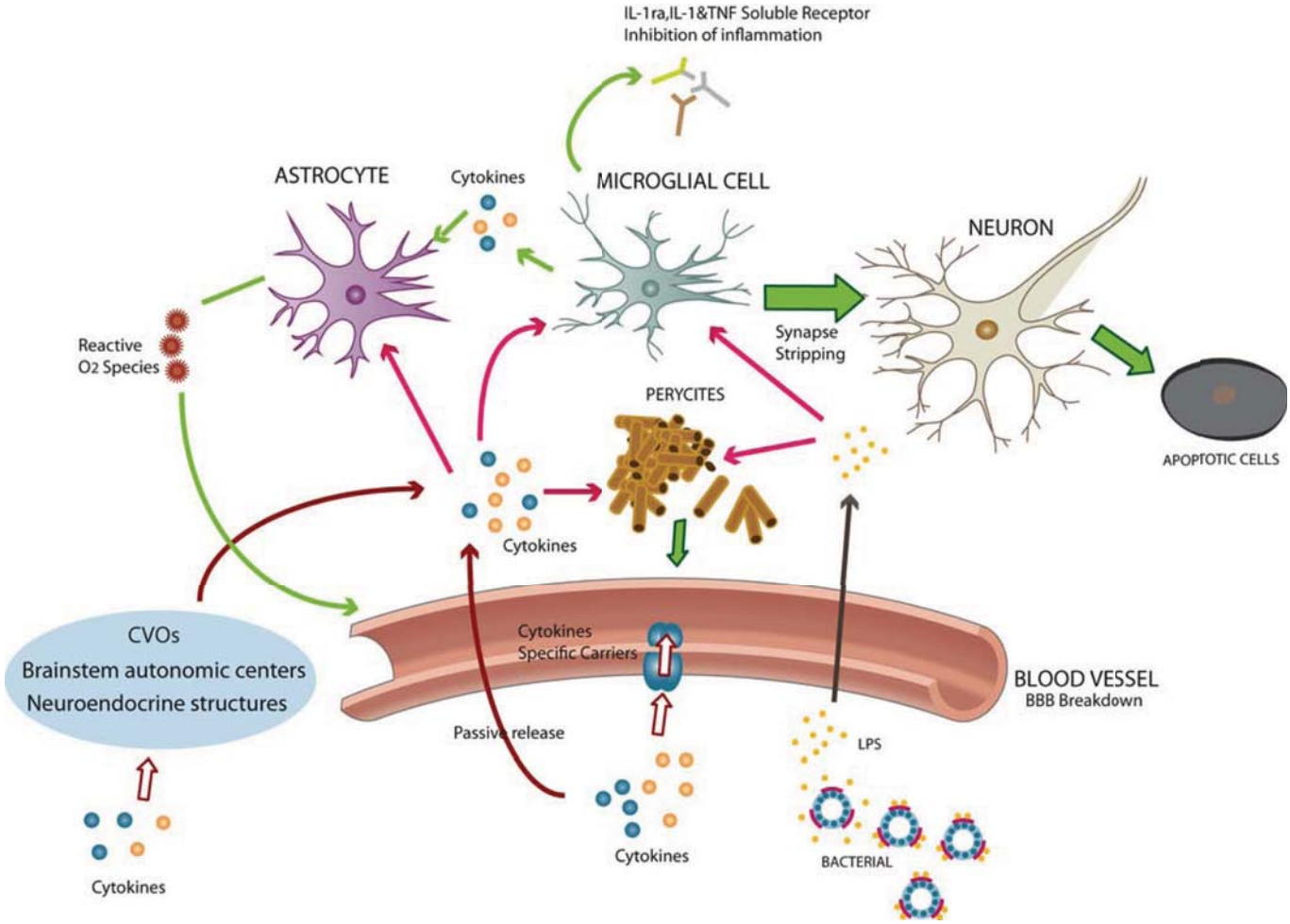

Fig. (2). Pathophysiology of sepsis-associated delirium. Blood native cytokines (IL-1, IL-6, TNF-α) can penetrate the central nervous system (CNS) through different mechanisms: disruption of the damaged blood brain barrier (BBB) permits the cytokines to pass from the blood into the CNS; the BBB is absent in the circumventricular organs (CVOs) that are located nearby the midline ventricular system; this allows the cytokines to directly interact with neuroendocrine structures; finally, cytochines may use of specific carriers. Cytokines in turn activate perycites, macroglial cells and astrocytes inducing neuroinflammation and neuronal damage (synapse stripping). Lipopolysaccharide (LPS) can penetrate passively into CNS inducing perycites and microglial cells activation.

influx and efflux of specific substances into and outside the brain [36, 37].

Although the exact pathophysiology of SAD remains poorly understood, the alterations of the BBB have been documented both *in vivo* and *in vitro* animal models of the septic brain. Animal research has demonstrated a breakdown of the BBB during sepsis caused by pericyte detachment and microglial activation, which are induced by a direct effect of lipopolysaccharides (Fig. **2**) [38]. Moreover, septic animals exhibit high cerebro-spinal fluid levels of substances that are normally selectively excluded by BBB, such as proteins, colloidal iron oxide [39], ^{14}C-amino acids [40] and N in the ^{125}I-albumin [41], pointing to disruption of BBB permeability.

Recently, there has been a growing interest on the possible rule of metalloproteinases (MMP) and caspases in BBB breakdown during sepsis. MMP, which are regulated by cytokines, are able to clive occluding, a main constituent of tight junction proteins, leading to detachment of endothelial cells from the extracellular matrix [42, 43]. Caspase expression induced by cytokines can induce apoptosis in cerebral endothelial cells contributing to BBB breakdown.

BBB breakdown can be associated with altered brain microcirculation. Recently, Taccone *et al*. [44] demonstrated a progressive decrease in total cerebral perfused vessel density, functional capillary density and the total number of perfused capillaries in a sheep model of septic shock. Altered brain microcirculation may explain the disturbances of the cerebro-vascular autoregulation and reactivity observed in septic patients [45]. The association of altered brain micro-circulation and BBB breakdown has profound effects on the brain function, and is a key contributor to the generation of brain edema [26, 46].

Cytokines and Cellular Activation

In normal conditions, the brain is protected from cytokines and inflammatory cell accumulation. BBB is

impermeable to cytokines, although specific carriers for these molecules exist that allow blood-borne cytokines to reach the hypothalamic nuclei [47]. CNS cells express low levels of the major histocompatibility complex antigens thereby inhibiting leukocytes activation. CNS endothelial cells also express low levels of adhesion molecules such as VCAM-1 and ICAM-1 compared to the peripheral vascular endothelium [48, 49], reducing leukocyte rolling and adhesion.

Although protective mechanisms exist, two main mechanisms are responsible for the interaction between the CNS and the immune system during sepsis, resulting in brain inflammation: 1) the cytokine trafficking into the brain and 2) the vagal system.

Cytokines can penetrate into the CNS through different mechanisms (Fig. **2**). BBB disruption permits the cytokines to pass from the blood into the CNS. In addition, the BBB is absent in the circumventricular organs (CVOs) that are located nearby the midline ventricular system. This allows the cytokines to directly interact with neuroendocrine structures (e.g., organum subfornicale, organum subcommisurale, corpus pineale, neurohyphysis and organum vasculosum laminae terminalis) and brainstem autonomic centers (area postrema) [47]. Furthermore, some cytokines such as IL1 [50], IL-1 receptor antagonist (IL-1ra), IL-6 [51], and tumor necrosis factor-alpha (TNFα) [52, 53] have specific transport systems. Finally, CNS cells including macrophages, microglial cells [54], astrocytes [55, 56] and cerebral endothelial cells [57] can produce cytokines upon activation. Once cytokines have penetrated the CNS, they activate microglial cells to evolve into proliferating, migrating and neuron-damaging cells, causing the so-called synapse stripping (Fig. **2**). Recently, Van Gool *et al*. proposed that blood-native cytokines, such as TNFα, activate the cerebral microglia to release active inflammatory mediators within the CNS, altering the neuronal function and causing delirium [58]. Astrocytes are important components of the CNS immune network and their disruption is thought to be a key mechanism leading to BBB breakdown [59, 60]. In particular, these cells possess receptors for inflammatory mediators that are able to induce the production of reactive oxygen species [61]. Moreover, activated astrocytes are able to induce neuron dysfunction trough different mechanisms, including potassium channel inhibition with alteration of regional blood flow [62] and impairment of transport of energy substrates [63] that all contributes to the BBB breakdown [64, 65].

IL-1 activates the vagal fibers terminating in the nucleus tractus solitarius. The afferent branches stimulate the hypothalamic-pituitary-adrenal axis [66] and inhibit the macrophage activity, the so-called "cholinergic anti-inflammatory pathway". Pre-existing cholinergic dysfunction or cholinergic inhibition increases the severity of delirium; however, rivastigmine, a cholinesterase inhibitor, has no effect on mortality or delirium [67].

Neurotransmitter Deregulation and Cerebral Metabolism

SIRS is able to evoke a derangement in the neuro-transmitter system. The serum levels of amino acids such as tyrosine, tryptophan, and phenylalanine that are essential for neurotransmitter synthesis are increased during sepsis [68]. Moreover, patients with sepsis have an increased ratio of aromatic to branched-chain amino acids in the serum [69-71], which can be related to the decreased level of norepinephrine, dopamine and serotonin concentrations found in the brains of septic rats. Glutamate also plays an important role in neuroinflammation during sepsis. Riluzole, which limits the synaptic release of glutamate, reduces the neurological effects of experimental sepsis in rats, and improves survival [72].

Sepsis is associated with mitochondrial derangement [73, 74], decreased ATP synthesis [75] and increased nitric oxide production [76], although these mechanisms have not been extensively studied in the septic brain. Interestingly, a recent study using proteomics showed an alteration in the brain protein composition during SAD [77]. Proteins related to cell structure (chaperonins), energy production (78 kDa glucose-regulated proteins), cell signaling and cell death (GFAP) can all be down-regulated 24 hours after the onset of sepsis.

TREATMENT

Prompt diagnosis and eradication of infection is the mainstay of SAD prevention and treatment. Preventive measures require that delirium management be part of an integrated Pain-Analgesia-Delirium (PAD) protocol. A protocol could be useful in many ways: facilitate the transfer of evidence-based "best practices" to the bedside, reduce the delay in treatment and could uniform the clinical. Moreover, a protocolized approach could significantly improve patient outcomes and serve as a guide for quality improvement [78]. Since the sedatives over-usage, especially benzodiazepines, has been related to delirium development [79-81], maintaining light sedation level with non benzodiazepine drugs is recommended.

The 'ABCDE' bundle is a multicomponent process that is designed to prevent and monitor delirium, especially in the ICU setting [82, 83]. The first step of the bundle ('A' for Awake the patients daily) aims to break the cycle of over sedation-prolonged mechanical ventilation. Daily interruption of sedatives allows clinicians to evaluate the patient's readiness to wean from mechanical ventilation ('B' for breathing) and to perform trials of spontaneous breathing (SBT). Protocolized interruptions of sedation and mechanical ventilation should be coordinated ('C') [84]. Once awakened, patients should be routinely evaluated for the presence of delirium ('D'), using validated screening tools (CAM-ICU, ICDSC). Moreover, early mobilization ('E') of ICU patients reduces acute cognitive and physical dysfunction.

Reversible causes that may precipitate or exacerbate delirium such as hypoxia, hypercapnia, hypoglycemia, metabolic derangements, infection, or shock should be actively investigated and treated before engaging in antipsychotic treatments. Despite antipsychotic medications are endorsed by various international guidelines [78, 85, 86],

and are widely used to treat delirious ICU patients, no randomized, placebo-controlled trial has established the efficacy or safety of any antipsychotic agent in the management of ICU delirium, and no approved medications exist for the treatment of ICU delirium. Recent guidelines suggest that the use of atypical antipsychotic medications such as quietiapine may reduce the duration of delirium (Level of recommendation C); however, recommendation is based on a single-center, small (36 patients) randomized control trial [87].

Haloperidol is the most common empirical therapeutic choice for ICU delirium; however, there is no evidence that haloperidol reduces the duration of delirium in adult ICU patients. Recent guidelines for the management of pain, agitation, and delirium in adult ICU patients provide no recommendation for the use of haloperidol to prevent or treat ICU delirium [78]. In a recent randomized controlled trial, patients in the haloperidol group spent about the same number of days alive, without delirium, and without coma as did patients in the placebo group [88]. In patients with delirium who require continuous infusion of sedatives, the choice of dexmedetomidine rather than benzodiazepine is strongly recommended (Level of evidence 2B). SCCM guidelines suggest that the use of atypical antipsychotic medications (quietiapine, Level of recommendation C) may reduce the duration of delirium; however, recommendation is based on a single-center, small (36 patients) randomized control trial [87]. In patients with delirium who require continuous infusion of sedatives, the choice of dexmedetomidine rather than benzodiazepine is strongly recommended (Level of evidence 2B).

PROGNOSIS

Establishing a prognosis for patients with SAD is challenging. Sepsis and septic shock are one of the leading causes of mortality in the ICU [89], and delirium is associated with an increased mortality rate [90]. Although SAD has been shown to be an independent predictor of hospital mortality [5], it is not clear if a true causal relationship exists or the association between SAD and mortality merely reflects the severity of critical illness.

The clinical manifestations of SAD may be completely reversible with the resolution of sepsis [91]; however, in the older population neurocognitive and functional disability can persist for years [92]. Longer delirium duration is independently associated with increased odds of disability in daily life activities and worse motor-sensory function in the following year [93].

SUMMARY

SAD is a clinical manifestation of the involvement of the central nervous system (CNS) during sepsis and it is described in about 50% of septic patients. Clinical features include altered level of consciousness, reduced attention, change in cognition and perceptual disturbances. This altered mental status may be present in the early stage of sepsis, even before other more clear signs of sepsis ensue. Pathophysiology of SAD is poorly understood, but involves microvascular, metabolic and, not least, inflammatory mechanisms leading to CNS dysfunction. SAD is diagnosed clinically using validated tools such as CAM-ICU or ICDSC, associated with neuroimaging studies, EEG and SSEP. Prompt diagnosis and eradication of septic foci whenever possible is vital. Addressing modifiable risk factors such as sedation management, delirium related medications, immobility, sleep disruption could help to prevent and reduce the duration of this deadly syndrome. The ABCDE bundle is an approach that clinicians can implement for their patients in ICU to prevent the adverse outcomes associated with delirium and critical illness. Antipsychotic drugs (haloperidol and atypical antipsychotics) are widely used to treat SAD, but firm evidence of their efficacy is lacking.

SAE is potentially reversible, but the presence of central nervous system involvement always worsens the prognosis of septic patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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