The Brain in Sepsis

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When microorganisms invade a host, signals are transmitted to the brain through a systematic pathway that mainly involves circulating proinflammatory cytokines and the activation of afferent nerve fibers at the site of infection. The brain then orchestrates a host response by triggering the synthesis of various hormones and by activating autonomic nervous centers. This review article will discuss our current knowledge of the underlying mechanisms of sepsis-induced brain dysfunction, including direct infestation of the brain by pathogens, direct or indirect effects of endotoxin and other bacterial products, the role of metabolic disturbances, abnormal circulation and oxygen metabolism, and the role of inflammation. It will also summarize the main clinical features of sepsis-induced brain dysfunction.

The stress concept of Hans Selye is primarily based on physical stressors. He noted that physical stress induces a general and stereotyped response, called the ‘General Adaptation Syndrome’ [1]. It is now recognized that the brain and the immune system are the two main adaptive systems of the body. When a host is subjected to a stress stimulus, the cross-talk between the brain and the immune system is fundamental to maintaining homeostasis. The two major pathways involved in the interaction between the brain and the immune system are the hypothalamic–pituitary–adrenal (HPA) axis and the autonomic nervous system [2].

Severe sepsis is a critical situation that triggers a cascade of immune and neurological events. As early as the beginning of the 20th century, physicians noted that endotoxin is capable of altering the central nervous system (CNS) [3,4], and that numerous consequences of endotoxin challenges could be mediated through the brain [5]. So-called septic encephalopathy is the most widely known of the brain dysfunctions that may complicate the course of sepsis [6]. However, there is also a body of evidence for abnormal neuroendocrine [7,8] and autonomic nervous responses to sepsis [9,10].

This review aims to summarize the current knowledge of the mechanisms and the various clinical features of brain dysfunction in severe sepsis. We will not consider the manifestations of direct infestation of the CNS, e.g. meningitis, encephalitis, or brain abscess.

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Brain response to sepsis
The two major elements of the brain involved in the stress response are the corticotropin-releasing hormone/arginine-vasopressin (CRH)/(AVP) system and the locus ceruleus–noradrenergic (LC–NA) system. The two systems are strongly interconnected, and activation of one system results automatically in activation of the other [11]. At the site of pathogenic invasion, the sensory afferent fibers of the peripheral nervous system ‘sense’ the local threat and send signals to the CNS, allowing it to localize the stressor. Activation of the brain is also mediated through circulating proinflammatory cytokines, mainly tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and IL-6 [12]. However, signaling to the brain is obviously more complex and involves numerous other circulating mediators of inflammation, e.g. macrophage migrating inhibiting factor, IL-8, interferon-α and -γ, IL-2, IL-12, epidermal growth factor, transforming growth factor-β, prostanoïds, and platelet activating factor. In addition, cytokines produced locally in the brain or in the adrenal glands may also activate the CRH/AVP system or the LC–NA system [13,14]. Activation of these systems results in the release of corticosteroids and catecholamines, which act in concert to maintain homeostasis. The various consequences of the hormonal responses to sepsis have been described previously [15]. Ex vivo experiments on human whole blood cultures stimulated by lipopolysaccharide (LPS) show that catecholamines inhibit the production of type 1/proinflammatory cytokines such as TNF-α, IL-12, and interferon-γ by antigen-presenting cells and T helper 1 cells, and stimulate the production of type 2/anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β [2,16]. These effects are mediated through β2-adrenergic receptor stimulation. Through these
mechanisms, catecholamines may suppress cellular immunity and enhance humoral immunity [2]. In addition, efferent vagus nerve signaling opposes LPS-induced TNF synthesis and prevents shock [17]. Although major advances have been made in the understanding of brain signaling and the generation of the brain's response to stress, little is known about the precise regulation of the CRH/AVP and LC-NA systems in response to sepsis.

Possible mechanisms underlying brain dysfunction in sepsis
The exact mechanisms of brain dysfunction in sepsis are unknown, but are likely to be multiple. Theoretically, brain dysfunction may result from direct infestation by pathogens, toxins released by microorganisms located in the periphery, metabolic disorders, vascular abnormalities, or inflammation.

Direct infestation by microorganisms
Disseminated microabscesses may be observed in septic patients but are not a predominant feature (Fig. 1) [18]. Moreover, brain dysfunction has been described in sepsis relating to various types of microorganisms, and also in patients where no pathogen could be isolated [19,20]. Thus, it seems very unlikely that direct infestation by pathogens explains sepsis-related CNS dysfunction.

Role of endotoxin and other bacterial toxins
Bacterial toxins have long been recognized as a cause of brain dysfunction [3,4,19]; however, endotoxin cannot cross the blood–brain barrier [21]. Therefore, whether central nervous effects induced by intravenous injection of endotoxin result from the endotoxin itself, or from the subsequent inflammatory processes, remains unclear.

Role of metabolic derangements
Animal studies
Extensive muscle proteolysis in sepsis may lead to an accumulation of aromatic and sulfur-containing amino acids. Concomitant alteration in the blood–brain barrier may favor the transport of these toxic amino acids to the brain. Indeed, in rats exposed to cecal ligature and puncture-induced sepsis, decreased catecholaminergic and serotoninergic brain neurotransmitter levels parallel the severity of encephalopathy [22], and can be restored by the infusion of branched chain amino acid-enriched formulas [23]. In addition, studies using the 14C-2-deoxyglucose autoradiographic method show altered local glucose utilization in discrete brain regions strongly related to the serotoninergic or noradrenergic system [24]. Alterations in the brain adrenergic system have been consistently observed in various experimental models of sepsis [25]. In contrast, levels of gamma-aminobutyric acid (GABA) have been found to increase in the plasma but remain unchanged in various brain areas, although all animals demonstrated clinical signs of encephalopathy [26]. Therefore, GABA is very unlikely to mediate sepsis-related brain dysfunction.

Clinical studies
Since renal and hepatic dysfunctions are common in sepsis, one can assume that the subsequent systemic metabolic derangements cause septic encephalopathy. In a study of 55 patients with severe sepsis, encephalopathy was associated with higher serum levels of urea, a higher incidence rate of renal failure, and higher levels of bilirubin [27]. Numerous patients, despite having normal renal and hepatic functions, presented with altered mental status, suggesting that sepsis-related brain dysfunction does not follow renal or hepatic failure. In patients with severe sepsis, altered mental status may be associated with increased plasma levels of aromatic amino acids and ammonia, and decreased plasma levels of branched-chain amino acid.
Acids [28,29], which can be normalized by perfusion of amino acid formulas enriched with branched-chain amino acids [28]. The increased levels of amino acids in the cerebrospinal fluid (CSF) are also in keeping with their potential role in the genesis of septic encephalopathy [30,31].

Altered noradrenergic and serotoninergic transmission is consistently found in data obtained in experimental models of sepsis and in septic patients, although whether these derangements are the cause, or simply a marker, of cerebral dysfunction remains unclear [32].

The role of abnormal circulation and oxygen metabolism

Animal studies

Cerebral blood flow (CBF) and oxygen delivery have been studied in various experimental models of sepsis [33–39]. In anesthetized animals, the injection of endotoxin or infusion of group B streptococci resulted in a rapid decrease in global [35,39] and regional [35] CBF. In addition, the streptococcal infusion fully inhibited an increase in CBF during hypercarbia, and this effect was independent of systemic hemodynamic compromise and prostanoids [39]. However, studies in conscious rats challenged with Escherichia coli endotoxin showed unchanged global and regional CBF, both before and after blockade of opioids [36]. Similarly, studies in a canine model of endotoxin shock showed no evidence of altered cerebral vascular reactivity [34,40]. Using phosphorus-31 nuclear magnetic resonance imaging (MRI) in septic rats, Hotchkiss et al. failed to demonstrate any alteration in brain energy metabolism [37,38]. Law et al. also failed to demonstrate any decrease in oxygen delivery to the brain during endotoxin shock in conscious rats [41].

Clinical studies

In a retrospective study of 84 patients with severe sepsis and multiple organ dysfunction, multivariate analyses showed that persistent cardiovascular collapse was the only factor associated with encephalopathy, suggesting that brain dysfunction is, at least partly, secondary to hypoxia and ischemia [20,42]. In a prospective, case-controlled, postmortem study, compared with non-septic shock or extracranial-related sudden deaths, septic shock presented with diffuse severe ischemic and hemorrhagic lesions of the brain, which were correlated with persistent hypotension and severe coagulation disorders, respectively [43]. Cerebrovascular events may occur in severe sepsis and may be related to the use of exogenous catecholamines [44]. In a cohort of six patients with septic encephalopathy and multiple organ failure, CBF and cerebral rate of oxygen metabolism were found to be significantly lower (46±2 vs. 28±3 mL/100 g/min, and 3.1±0.2 vs.1.2±0.2 mL/100 g/min, respectively) and cerebral vascular resistance significantly higher (2.0±0.1 vs. 3.0±0.4 mm Hg/mL/100 g/min), compared with normal, conscious subjects [45]. In this study, at the time of cerebral circulation and metabolic assessment, all patients were comatose (Glasgow Coma Scale 4–10), and had diffuse slow-wave activity on electroencephalogram (EEG) and increased latency of the auditory brain stem response. However, other studies in anesthetized septic patients reported normal autoregulation of CBF [46–48].

The role of cytokines and inflammation

Animal studies

In pigs, prolonged bacteremia induced profound brain damage consistent with inflammation, e.g. perivascular edema, spongiform degeneration, hyperemia, and purpura [49]. Simultaneously, high levels of TNF-α and IL-6 were found in the CSF of the animals. Similarly, in Wistar rats, intravenous injection of LPS induced a rapid increase in TNF-α in the CSF and blood [50]. TNF-α was preferentially observed in the tight junctional area of the ependymal cell layer and the vessels, suggesting that TNF-α contributes to the breakdown of the blood–brain barrier and to cerebral edema. The brain TNF-α response to intravenous injection of LPS involved local expression of TNF-α, and is independent of systemic levels of TNF-α [51].

Clinical studies

In patients deceased from septic shock, typical lesions of multifocal necrotizing leukoencephalopathy have been found, confirming that proinflammatory cytokines like TNF-α and IL-1β may be involved in the pathogenesis of sepsis-related brain dysfunction [52].

Clinical features of brain dysfunction in sepsis

Septic encephalopathy

The prevalence of encephalopathy in severe sepsis varies from 9–71%, depending on its definition [6,18,20,27,32]. Encephalopathy is simply defined by impaired mental state. The problem is that patients with severe sepsis are often sedated, precluding accurate assessment of mental status. In the absence of sedation, septic encephalopathy may include various stages of altered consciousness, from reduced awareness and reduced concentration, to unresponsive coma [27]. The severity of the impairment in mental status usually correlates with the global severity of illness as assessed by Acute Physiology and Chronic Health Evaluation II or organ failure scores [27]. In contrast to metabolic causes of encephalopathy, motor deficits such as asterixis, tremor, and myoclonus are rarely observed in sepsis [53]. Brain electrophysiology recordings are useful to establish the diagnosis of encephalopathy in patients with severe sepsis.
EEG recordings usually show diffuse abnormalities like slowing, triphasic waves, or burst-suppression pattern (Fig. 2) [53]. Impaired subcortical and cortical evoked potential pathways have been reported in 34% and 84% of all patients, respectively [54]. Interestingly, the degree of EEG or evoked potential abnormality parallels the degree of the clinical severity of the encephalopathy. Nevertheless, up to 50% of patients with an apparently clinically normal mental status may have abnormal EEG recordings [53]. A CSF is usually normal but sometimes shows a slight increase in protein content. Similarly, CT scans or MRIs are not helpful. Finally, it has been suggested that brain dysfunction is an independent prognostic factor in sepsis [32]; however, it is more likely that encephalopathy is only a marker of the severity of the disease, rather than a cause of death.

**Neuroendocrine dysfunction**

The endocrine response to sepsis is complex. The role of the HPA axis in the pathophysiology of septic shock has been described previously [15]. Briefly, severe sepsis may be associated with blunted HPA axis responses [8] and relative vasopressin deficiency [7]. In sepsis, it is now recognized that the clinical feature of hormonal insufficiency includes hemodynamic instability and reduced responsiveness to vasopressor, uncontrolled inflammation, metabolic disturbances, and death [8,55,56]. The exact prevalence and the underlying mechanisms for the hormone deficiency remain unclear, although impaired pituitary function is likely [57]. Moreover, correcting the disorder by hormone replacement therapy improves cardiovascular function and may improve survival from septic shock [56,58].

**Autonomic failure**

In sepsis, autonomic failure is a commonly unrecognized manifestation of brain dysfunction. Damage to areas of the brain related to autonomic functions (e.g. locus ceruleus, hypothalamic nuclei), results in specific symptoms such as an increase or drop in blood pressure and heart rate, arrhythmia, irregular respiration, apnea, myocardial injury, and neurogenic pulmonary edema [59]. All of these features...
are commonly observed in patients with severe sepsis. Indeed, in animals [9] and healthy volunteers [60] challenged with LPS, and in septic patients [10,61–63], spectral analyses of cardiovascular signals consistently demonstrated a blunted sympathetic modulation of the heart and the vessels that preceded hemodynamic compromise. In addition, autonomic failure increased the risk of death from critical illness [61,64]. The mechanism of this sepsis-related autonomic failure probably involved damage within autonomic centers in the brain [10,43]. Whether modulating autonomic function has an impact on survival from septic shock requires further investigation.

In summary, the brain plays a major role in host defense against sepsis, acting mainly through neuroendocrine pathways and the autonomic nervous system. Data from both experimental models of sepsis and patients have provided a body of evidence that suggests that septic encephalopathy, neuroendocrine dysfunction, and autonomic failure occur commonly in severe sepsis, and that neuroendocrine dysfunction and autonomic failure may be responsible, at least in part, for circulatory shock and organ dysfunction.

Disclosure
David Orlikowski, Tarek Sharshar, and Djillali Annane have no relevant financial interest in this manuscript.

References


