CRITICAL CARE

COMMENTARY

Pathophysiology of septic encephalopathy - an unsolved puzzle

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See related research by van der Boogaard *et al.*, http://ccforum.com/content/14/3/R81

Abstract

The exact cellular and molecular mechanisms of sepsis-induced encephalopathy remain elusive. The breakdown of the blood-brain barrier (BBB) is considered a focal point in the development of sepsis-induced brain damage. Contributing factors for the compromise of the BBB include cytokines and chemokines, activation of the complement cascade, phagocyte-derived toxic mediators, and bacterial products. To date, we are far from fully understanding the neuropathology that develops as a secondary remote organ injury as a consequence of sepsis. Howver, recent studies suggest that bacterial proteins may readily cross the functional BBB and trigger an inflammatory response in the subarachnoid space, in absence of a bacterial invasion. A better understanding of the pathophysiological events leading to septic encephalopathy appears crucial to advance the clinical care for this vulnerable patient population.

The clinical study by van der Boogaard and colleagues recently published in *Critical Care* [1] was designed to unravel some of the open questions regarding the pathophysiology of septic encephalopathy. The authors mimicked inflammation-associated encephalopathy by induction of experimental endotoxemia using *Escheria coli*-derived lipopolysaccharides (LPSs) in 15 healthy young volunteers. Outcome parameters were serum levels of cytokines, cortisol, neuron specific enolase, S100-β, as well as electroencephalographic changes and cognitive function in comparison to a healthy cohort of ten control volunteers. Interestingly, van der Boogaard and colleagues described that the endotoxin-induced 'cytokine storm' and cortisol release failed to provoke any signs of septic encephalopathy [1]. No clinically relevant electroencephalographic changes occurred, and markers of neuronal damage (neuron specific enolase, S100-β) were found to be slightly reduced following LPS challenge. Endotoxemia even resulted in a higher state of alertness and improved cognitive function in comparison to the healthy cohort. The authors concluded that temporary systemic inflammation caused by endotoxemia cannot provoke the development of septic encephalopathy. Nonetheless, their present study shed some further light towards our understanding of the immunological pathophysiology of septic encephalopathy, as it appears unlikely that bacterial LPS is a driving force in the development of septic encephalopathy. Noteworthy, the spectrum of responsible microorganisms has shifted from predominantly Gram-negative bacteria in the late 1970s and 1980s to predominantly Gram-positive bacteria and fungal infections at present [2].

The authors' findings underscore the complexity and ambiguity of septic encephalopathy, which continues to be a puzzling complication of the sepsis syndrome. This is of particular concern, as up to 70% of all septic patients develop signs of such brain damage [3]. Traditionally, septic encephalopathy was thought to occur due to inflammatory breakdown of the blood-brain barrier (BBB) as a 'key' causative factor of sepsis-associated delirium [3]. A dysfunction of the BBB has been shown to be induced by various inflammatory mediators, such as IL-1β, TNF-α, complement, and bradykinin, which can cause a 'sterile meningitis' in the absence of a bacterial pathogen [4,5]. Moreover, complement C3 and C5a have been linked to sepsis-induced compromise of the BBB [6]. Of note, direct contact between blood and cerebrospinal fluid leads to complement activation, as may be the case in severe BBB dysfunction [7]. The disruption of this physical barrier then allows circulating neurotoxic substances to extravasate into the brain parenchyma and promote an inflammatory response. However, this traditional notion of initial BBB compromise prior to development of septic encephalopathy has recently been challenged [8]. In their experimental study, Londoño and

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Cadavid [8] injected mice intraperitoneally with labeled outer membrane lipoproteins of *Borellia turicatae* and monitored their localization in the brain. Surprisingly, two of the lipoproteins studied (LVsp1 and LVsp2) were capable of disseminating from the periphery into the brain and caused intracerebral inflammation without intracerebral spirochete accumulation [8]. These findings provide novel insights into the potential development of septic encephalopathy. Another piece of the complex puzzle of septic encephalopathy may be the extensive communication between the nervous and the immune system. Interestingly, this interaction is bi-directional, as cytokines can trigger the release of glucocorticoids via the hypothalamic-pituitary axis, and, in turn, glucocorticoids suppress cytokine synthesis of leukocytes [9]. Moreover, both systems use a common biochemical language of hormones, ligands and receptors to communicate with each other [10,11]. In the setting of sepsis, the majority of work in neuroimmunology has focused on the anti-inflammatory properties of the vagus nerve, popularized by the term 'the inflammatory reflex' [12]. While these interactions are likely to be involved in the development of septic encephalopathy, the exact mechanisms remain inadequately understood.

One of the dilemmas in current sepsis research is the poor transferability of promising experimental findings. Many pharmacological research strategies have failed a successful translation from 'bench to bedside'. This predicament is likely caused by an obvious disconnect between controlled animal models and the heterogeneous clinical sepsis syndrome observed in humans [13]. Experimental human studies, such as the study by van der Boogaard and colleagues, are limited by several factors. Endotoxemia is usually induced in a young, healthy population, and may rather present an acute intoxication model than the multi-microbial or fungal infections observed in the sepsis syndrome. In such an experimental setting, the timing and dosage of LPS has to be limited based on safety issues, and therefore might not reach the threshold for the development of a significant BBB damage. Moreover, sepsis results from various causative etiologies, and susceptibility is influenced by premorbid factors, including ethnicity, gender, age, genetic defects and environmental factors.

The advancement of clinical care for the septic patient will be an enormous challenge. The belief that a single key mediator causes sepsis, and that its neutralization could be a cure for all patients with sepsis, seems erroneous [14]. In particular, pre-existing genetic and epigenetic changes, mutations in genes that encode pattern-recognition receptors or inflammatory mediators, may have an enormous impact on the host's susceptibility to sepsis. Interdisciplinary approaches involving both clinicians and basic scientists will be necessary to improve our knowledge of the underlying pathophysiology of sepsis and septic encephalopathy. Such interdisciplinary, large-scale programs involving surgery, genomics, proteomics, biostatistics, bioinformatics, computational biology and genetics are currently underway [15].

Abbreviations

BBB = blood-brain barrier; IL = interleukin; LPS = lipopolysaccharide; TNF = tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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