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Septic-associated encephalopathy - everything starts at a microlevel

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See related research by Taccone et al., http://ccforum.com/content/14/4/R140

Abstract

Sepsis-associated encephalopathy is associated with increased mortality and morbidity. Its pathophysiology remains insufficiently elucidated, although there is evidence for a neuroinflammatory process sequentially involving endothelial activation, blood-brain barrier alteration and cellular dysfunction and alteration in neurotransmission. Experimental studies have shown that microcirculatory dysfunction, a consequence of endothelial activation, is an early pathogenic step. To date, we do not know whether it is present in septic patients, whether it accounts for clinical features and whether it is treatable.

The experimental study by Taccone and colleagues recently published in *Critical Care* [1] aims to determine whether sepsis is associated with early cerebral micro-circulatory failure, which is believed to play a role in the pathophysiology of sepsis-associated encephalopathy (SAE). SAE is a frequent and severe complication of sepsis as it is associated with increased mortality, morbidity and plausibly with diminished long-term cognitive performance [2,3]. Evidence suggests that SAE results from an alteration of neurotransmission, the mechanisms of which are insufficiently elucidated.

One pathophysiologic scenario is an inflammatory process that starts by cerebral endothelial activation [3], which directly releases or, through alteration of the blood-brain barrier, facilitates the passage of inflammatory mediators (that is, cytokines, chemokines) into the parenchyma. Increased permeability of the blood-brain barrier has been extensively documented in experimental models of sepsis, has been linked to complement activation [4], and has been observed in septic patients using magnetic resonance imaging (MRI) [5]. In turn, these inflammatory mediators will affect all brain cells. Van Gool and colleagues [6] proposed that sepsis-induced microglial activation plays a role in delirium. Inflammatory mediators are able to alter cellular metabolism by inducing oxidative stress and mitochondrial dysfunction [7], resulting in pathologic abnormalities that range from alterations of neurotransmission to apoptosis [8]. It has been shown that experimental sepsis, via inflammatory mediators, alters brain cholinergic [9], beta-adrenergic, gamma-aminobutyric acid and serotoninergic signalling, predominately in the neocortex and hippocampus [10]. This feature may account for the electroencephalographic disturbances reported in septic patients [11]. Additional factors that compound this neuroinflammatory process include the release of excitatory amino acids, hyperglycemia, exposure to neurotoxic pharmacologic agents, hemodynamic alterations, coagulopathy, and hypoxemia [3].

One major consequence of endothelial activation is that it may compromise regional brain tissue perfusion by altering microcirculation. Microcirculatory dysfunction (MD) has previously been experimentally assessed, notably by measuring neurovascular coupling. This consists of assessing changes in cortical flow velocity during somatosensory activation [12]. Interestingly, this MD preceded both neurophysiologic and macrocirculatory alterations, indicating that it is an early step in the pathogenesis of SAE. Taccone and colleagues [1] provide a convincing visual demonstration of this phenomenon. Using cortical videomicroscopy in an ovine peritonitis model, they found evidence of a reduced density of perfused and functional capillaries. But if the

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occurrence of MD during experimental sepsis is established, it remains to be seen whether this phenomenon is present in septic patients, whether it accounts for clinical features of SAE and whether it is treatable. The microcirculation has not been evaluated in septic patients; in contrast, several studies have examined macrocirculatory changes with inconsistent results [3]. One argument may be the impairment of autoregulation reported in some studies of septic patients [13], although autoregulation is primarily determined by arterioles, which lie outside micro-circulation. Neuropathologic findings of diffuse ischemic damages and micro-haemorrhages support this hypothesis [14]. Recent advances in MRI are enabling important inferences regarding the cerebral microcirculation; however, simpler techniques are needed to directly assess and monitor cerebral microcirculation or correlated markers at the bedside. It would be of interest to determine whether cerebral MD is correlated with micro-circulatory disturbances in other organs that are more easily amenable to direct assessment. The neurological consequence of MD is unknown, although one study interestingly showed that delirium in septic patients is associated with disturbed autoregulation rather than with altered cerebral blood flow or tissue oxygenation [13].

The clinical importance of cerebral microcirculatory impairment in sepsis might be confirmed by assessing the effects of therapeutic intervention. Prominent micro-circulatory effects of various agents have been tested in septic animals, including curcumin, bradykinin, inducible nitric oxide synthase (iNOS) inhibitors, anticytokines or complement antibodies and glucocorticoids [15]. The effects of glucocorticoids and that of other therapeutic agents used in sepsis (that is, activated protein C) on SAE are unknown. One other major unanswered issue is whether targeting higher systemic blood pressures will improve cerebral perfusion and oxygenation in the presence of MD.

One may argue that MD is merely one feature in the complex pathogenesis of SAE. In the experimental setting it will be important to develop agents or strategies that modulate what ostensibly is an early pathogenic phenomenon rather than targeting later events that may not be reversible. In patients, we need more evidence of the role of microcirculation in SAE. This will require techniques to measure and monitor the cerebral microcirculation at the bedside.

Abbreviations

MS: microcirculatory dysfunction; MRI: magnetic resonance imaging; SAE: sepsis-associated encephalopathy.

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Competing interests

The authors declare that they have no competing interests.

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