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EDITORIAL

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Studying septic encephalopathy: what animal models can predict

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Impaired mental function, delirium, and the development of deep coma is often seen in patients with systemic inflammation, typically as an early symptom [1]. The concept of early or septic encephalopathy as an entity that cannot be explained by hepatic or renal dysfunction, hypotension, or hypoxia is relatively new and has been reported to occur in a range of 8–70% of septic patients [2], usually associated with a poor outcome [3]. In a prospective study in 50 patients, which examined the relationship between the degree of encephalopathy, bacteremia, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and survival, the authors could demonstrate a clear relationship between decreasing Glasgow Coma Scale score and increasing mortality [4]. The underlying mechanisms have only been defined in parts. As neither microorganisms nor their products can be isolated from the blood of many septic patients, septic encephalopathy probably arises from the action of inflammatory mediators on the brain or a cytotoxic response of brain cells to these mediators, namely leukocytes, endothelial cells, astrocytes, and neurons [5].

In an ideal world one would suggest that more than 2500 years after the first description of an association between generalized infection and impaired brain function by Hippocrates [6] our current insight and knowledge about inflammatory diseases has led to the development of a simple and easy-to-use screening tool to identify those patients who, for multiple reasons, subsequently will develop systemic inflammatory response syndrome (SIRS); however, things are not so simple!

A logical approach to overcome this diagnostic gap is to create a window to the brain. The electroencephalogram (EEG) has been shown to be a sensitive indicator of septic encephalopathy and offers the advantage of being used even in patients who otherwise are not able to be assessed clinically. The degree of changes in the EEG correlates with the severity of the clinical course [7]. In general, an increase in slower frequencies can be observed, and, in more severe cases, additional triphasic waves, theta pattern, and burst suppression may occur. Persistent cortical lesions may induce multifocal epileptiform potentials [8], although some patients may recover completely both clinically and with respect to EEG [2]. However, the EEG provides a large amount of data that are often difficult to assess; hence, it has not achieved much enthusiasm in the study of septic encephalopathy. On the other hand, in this condition somatosensory evoked potentials (SEP), usually in response to median nerve stimulation, show a deteriorated cortical signal with increased latencies and suppressed amplitudes [9]. Similar to the EEG, the magnitude of pathological changes in the SEP is found to be more pronounced in patients with severe or prolonged septic encephalopathy [10].

In this issue of "Intensive Care Medicine", Ohnesorge and colleagues [11] present the results of an animal study in which they evaluated the predictive value of somatosensory evoked potentials (SEP) as an early indicator of cerebral dysfunction associated with inflammatory disease. They tried to relate early changes in SEP morphology with subsequent development of SIRS, induced experimentally in mini pigs by injection of Na-Taurocholate and enterokinase in the pancreatic duct with the consecutive development of pancreatitis. The SIRS was defined as a 33% decrease in systemic vascular resistance (SVR). In the pre-septic period the investigators found a decrease in SEP amplitudes in six of eight animals to a

median value of 47% compared with baseline. The major strength in their study design was the fact that measurements were obtained in 2-h intervals until the appearance of pre-defined SIRS criteria in every individual animal, which actually differed between 4 and 18 h; however, there were no changes in SEP latencies at any point of measurement.

Impairment of mental state suggests, as in the EEG, a general slowing and prolongation of the SEP signal. A recent study in medical ICU patients by Zauner and colleagues [12] demonstrated, by utilizing subcortical and cortical SEP analysis, that septic encephalopathy occurs more frequently than generally assumed, and that its severity is associated with the severity of illness. Prolongation of the subcortical SEP pathway (N13–N20 interpeak latency) was found in 34% of patients, whereas up to 84% of all patients showed a prolongation of the cortical SEP pathway (N20–N70 interpeak latency). It is remarkable that this particular study did not report any changes in SEP amplitudes, which was the main finding in the study by Ohnesorge and colleagues [11].

So we are back to the crucial question: What animal models can predict when their results are put into perspective of decision making in real patients? The major problem remains to establish an animal model which mimics pathophysiology of SIRS in humans and is sensitive to related EEG changes at the same time. It may be questionable whether Ohnesorge and colleagues [11] really investigated sepsis-related encephalopathy. Although septic complications of acute pancreatitis do arise, these are usually late features. The observed loss of vascular resistance and the increase in body temperature and heart rate within the described time interval after pancreatitis was induced are well-known systemic cytokine-induced symptoms, which also occur without evidence of sepsis [13]. Another finding which deserves explanation is the fact that two animals did not show any decrease in SEP amplitude and another, after an initial decrease, showed a subsequent increase prior to the time point where SIRS was defined. This heterogeneous pattern in the time course of SEP amplitudes and the uncontrolled nature of the study imply that the data obtained from the animal model in general probably show a trend rather than convincingly demonstrate the predictive value of SEP amplitudes to assess the early stage of septic encephalopathy; however, this study turned out to be one of the first to associate the modulation of SEP amplitudes with the possible development of septic encephalopathy in an individual time link. It has shown that changes in SEP even precede the general suppression seen in the EEG. Although the results are maybe less uniform than expected, this pilot approach should encourage the investigators to proceed to a more controlled animal model which considers the multifactorial nature of the underlying pathologic entity.

In essence, SEP appears to be a promising candidate for early tracking septic encephalopathy, and the work by Ohnesorge et al. [11] is undoubtedly a valuable contribution to the evaluation of the technique for this indication; however, we have to be aware of the large variability of individual responses, the limitation of an animal model, and the need for more consistent data in ICU patients. Meanwhile, our primary focus should be to clinically assess the mental status of every critically ill patient equally seriously as we monitor other organ dysfunctions. This is not a trivial task.

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