Cerebral Monitoring in Sepsis

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Cerebral Monitoring in Sepsis: *SAE* definition

- **Sepsis** is a life-threatening condition that is often revealed or complicated by an acute brain dysfunction, defined by changes in consciousness, ranging from confusion (i.e., delirium) to coma.
  

- **Sepsis-associated encephalopathy** (*SAE*) is characterised by electrophysiological changes that have been associated with poor prognosis with increased morbidity, mortality and long-term cognitive disability.
  

- **Diagnosis of SAE** is crucial for avoiding potentially devastating effects and is based on neurological examination that guides further investigations and monitoring.
  
Cerebral Monitoring in Sepsis: SAE pathophysiology

Sepsis-associated encephalopathy

**Neural pathway** » activation of primary afferent nerves, such as the vagal or the trigeminal nerves, by involving peripherally produced pathogen-associated molecular patterns (PAMPs) and cytokines » cholinergic activity

**Humoral pathway** » involves circulating cytokines sensed the brain at the level of the choroid plexus and the circumventricular organs that lie outside the BBB » behavioral, neuroendocrine, and neurovegetative dysfunction (β-adrenergic system)

**BBB pathway** » endothelial barrier disruption with induced permeability leads to brain overexpression of NOS, production of ROS, microglia activation, cerebral hypoperfusion and mitochondrial cytophatic hypoxia » ultimately neuronal damage.

Sepsis-induced encephalopathy

Circulatory failure » systemic hypotension and hypoperfusion, cerebral autoregulation impairment

Systemic organ failure » hepatic, renal, metabolic and energetic failure contribute to brain severity dysfunction

Drugs side-effects » direct or indirect CNS toxicity, due to delayed clearance of sedative drugs, opioids, antibiotics, fluid overload and sodium/osmotic disorders

Environmental factors » physical restraints, light and noise exposure

Sepsis-associated encephalopathy

Cerebral Monitoring in Sepsis: \textit{SAE} diagnosis

- \textbf{SAE diagnosis:} recognition of brain dysfunction using clinical, EEG and chemical criteria


\checkmark \textbf{Clinical neurologic evaluation and tools to determine mental state}
- Delirium: disturbances of consciousness, impaired cognitive function, personality changes, inattention, lack of concentration, confusion, alteration of sleep/wake cycle, or considerable excitation, which may evolve from agitation to stupor and coma.
- convulsions, myoclonus, focal or generalized seizures, although less frequently than in other encephalopathies.
- Glasgow Coma Scale, Richmond Agitation–Sedation Scale, Confusion Assessment Method for the ICU (CAM-ICU), Intensive Care Delirium Screening checklist (ICDSC), Assessment to Intensive Care Environment (ATICE)

\checkmark \textbf{EEG patterns of brain dysfunction, electrographic seizures and chemical criteria}
- EEG abnormalities include increased theta rhythms, predominant delta, triphasic waves and, less often but more pejorative, burst suppression patterns (high sensitivity, low specificity)
- periodic epileptiform discharges with nonconvulsive seizures.
- Serum levels of NSE and S-100b protein have been shown to correlate with poor outcome in septic shock.
Cerebral Monitoring in Sepsis: *SAE* diagnosis

**SAE diagnosis: brain imaging**


- **CT scan**
  - rule out structural brain lesions

- **Cerebral MRI**

  **Acute changes**
  - variable degrees of vasogenic edema, related to BBB breakdown
  - posterior reversible encephalopathy syndrome (PRES)
  - cytotoxic edema, related to perfusion deficits in watershed areas
  - ischemic lesions surrounding the Virchow-Robin spaces

  **Chronic changes**
  - white matter disruption
  - bilateral lesions of basal ganglia, hypothalamus and thalamus
  - leukoencephalopathy and brain atrophy (frontal cortex, hippocampus)
• Faced to such complex scenario, adequate monitoring of the septic brain would potentially be of great help for prevention, management and prognostication and – ideally – to attenuate the harm of sepsis-related cerebral complications on outcome.

Cerebral Monitoring in Sepsis: brain perfusion monitoring

• **Brain Perfusion:** several studies have evaluated the link between cerebral perfusion abnormalities and brain dysfunction in sepsis. Accordingly, it could be speculated that the cerebral effects of vasopressors may be unpredictable depending on the degree of BBB dysfunction.


• **ICP and CPP:** septic patients may present moderate elevations of ICP > 15 and CPP < 50 mmHg mainly related to low MAP.


• **CBF:** is early reduced in patients with sepsis and delirium, independent from changes in ABP or CO. One study evaluated the presence of cerebral vasoconstriction, using TCD and the pulsatility index (PI) on the MCA in septic patients; a PI >1.3 on the first day of sepsis diagnosis was associated with the development of neurological symptoms, independently from age and APACHE II score.


Cerebral Monitoring in Sepsis: autoregulation monitoring

- **Cerebral Autoregulation**: as cerebral blood flow (CBF) is dependent on several confounders, it is more important to monitor the integrity of **CBF autoregulation** than absolute CBF values, in order to adjust blood pressure levels and to avoid the secondary brain ischemic events.

- Cerebral autoregulation was more altered in patients with brain dysfunction and with the highest levels of inflammation and of brain injury biomarkers.


Example of rapid worsening of cerebral autoregulation in response to spontaneous arterial hypotension in septic patients. Flow velocity (FV) and the tissue oxygenation index (TOI) decrease around 12:05, and the indices Tox and Mx both increase toward values close to +1.
**Cerebral Monitoring in Sepsis:** vasoreactivity monitoring

- **Cerebral Vasoreactivity:** results of studies of CO2-reactivity in sepsis are non-concordant. Albeit, alterations in autoregulation may be largely influenced by CO2 levels, with the highest risk of impaired autoregulation for PaCO2 > 38 mmHg.


Example of autoregulation impairment recovery documented with PRx index after manipulation of CO2. Clinicians should not systematically aim to correct hypocapnia in septic patients.
• Brain Oxygenation: brain hypoxia in sepsis may be related to **hypoperfusion**

Taccone FS et al. Sepsis is associated with altered cerebral microcirculation and tissue hypoxia in experimental peritonitis. Crit Care Med. 2014 Feb;42(2).

However, other types of hypoxia have to be considered, namely **dysperfusion and cytopathic hypoxia**.

Example of PbtO2 and CPP nonlinear relationship.
Cerebral Monitoring in Sepsis: *brain oxygenation* monitoring

Interplay between brain hypoxia, MAP and respiratory rate

Example of bedside brain monitoring in a septic patient:

- FiO2: 50%
- P/F ratio 280
- PaO2 - 140 mmHg
- PaCO2 – 36 mmHg (ETCO2 32mmHg)
- MAP – 100 mmHg
- Cerebral Oximetry (NIRS) < 30%
Brain Microdialysis: energy metabolism alterations, by their nature, are clinically silent until their late stages, at which point patients may suffer significant irreversible brain damage; early detection is important.

The decrease in pyruvate levels, associated with the increased LPR, glutamate, and glycerol levels, strongly suggests tissue ischemia.

It is possible that these metabolic alterations were secondary to other mechanisms inducing cellular injury:
- mitochondrial dysfunction
- insufficient glucose supply
- increased glycolytic response in cerebral cells
- oxidative glutamate toxicity

Figure 5. Differences in cerebral lactate/pyruvate ratio, cerebral glutamate, and cerebral glycerol between those animals with mean arterial pressure (MAP) of 65-70 mm Hg (n = 4) and those with MAP less than 65 mm Hg at 18 hours since sepsis induction, p value of less than 0.05 (*)

Teconne FS et al. Sepsis is associated with altered cerebral microcirculation and tissue hypoxia in experimental peritonitis. Crit Care Med. 2014 Feb;42(2).
Cerebral Monitoring in Sepsis: *brain electric activity*

EEG tracing and power is correlated with CBF and brain metabolism

<table>
<thead>
<tr>
<th>CBF (ml/100 g-min)</th>
<th>EEG Change</th>
<th>Cellular Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>35-50</td>
<td>Normal</td>
<td>Decreased Protein Synthesis</td>
</tr>
<tr>
<td>25-35</td>
<td>Loss of Faster Frequencies (8-14 Hz)</td>
<td>Anaerobic Metabolism • Neurotransmitter Release (i.e. glutamate)</td>
</tr>
<tr>
<td>18-25</td>
<td>Increasing Slower Frequencies (4-7 Hz)</td>
<td>Lactic Acidosis • Declining ATP</td>
</tr>
<tr>
<td>12-18</td>
<td>Increasing Slower Frequencies (1-4 Hz)</td>
<td>Sodium-Potassium Pump Failure • Increased Intracellular Water Content</td>
</tr>
<tr>
<td>&lt;10-12</td>
<td>Suppression</td>
<td>Calcium Accumulation • Anoxic Depolarization • Cell Death</td>
</tr>
</tbody>
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• EEG monitoring in sepsis:

- predominant **theta-activity** was associated with a 19% mortality in septic patients (compared to 0% in those with normal EEG).

- predominant **delta-activity** had a 36% mortality rate.

- triphasic waves and periodic epileptiform discharges were associated with a greater degree of cerebral dysfunction and greater mortality.


- time in burst-suppression during coma was an independent predictor of prevalence and time to resolution of postcoma/postdeep sedation ICU delirium.

Cerebral Monitoring in Sepsis: *brain electric activity*

- Continuous EEG monitoring and bilateral BIS EEG tracing.
  
  a) frontal intermittent generalized rhythmic delta activity (GRDA)
  b) generalized periodic discharges (GPDs) with triphasic waves
  c) nonconvulsive status epilepticus
  d) moderate generalized slowing
Cerebral Monitoring in Sepsis: *brain electric activity*

- CDSA (compressed density spectral array) and aEEG (amplitude EEG) are useful screening tools for nonconvulsive seizures in the ICU.

**Evoked potentials**

- **SSEP** peak latencies were significantly prolonged in patients with sepsis compared to controls. Cortical responses (N70 and the N20-N70 latency, both dependent on intracortical conduction), were more frequently prolonged and to a greater extent. The delay was related to the severity of sepsis but unaffected by sedation. The relationship of SSEP prolongation to outcome was not assessed.

Cerebral Monitoring in Sepsis: **heart rate variability**

**• HRV monitoring in sepsis:**

- **low HRV** (SD of RR intervals) and **sympathovagal balance** (LF/HF) during septic shock are associated with both an increased hyperinflammatory and antiinflammatory response.


- **reduction in HRV indices** is associated with hypercytokinemia, indicating that the autonomic nervous system and the inflammatory response mediated by the cytokine network affect each other. ... Thus, heart rate variability indices are associated with both the severity and poor outcome of sepsis.


- **HRV analysis revealed early information** about the onset of sepsis about 60 hours (median value) before of sepsis diagnosis.


- **HRV**, as reflected in LFnu and the LF/HF ratio and measured with a single brief (5-minute) period of monitoring while in the ED, **may provide** the emergency physician with a **readily available, noninvasive, early marker of illness** severity among patients with sepsis.

Key messages

- Brain dysfunction is frequent in septic patients and has a high risk of increased morbidity and mortality.

- Brain injury is often heterogeneous; there is no specific therapy of sepsis-related brain injury and the management is multi-factorial, aiming to maintain adequate cerebral perfusion and oxygenation, and avoid secondary systemic insults and over-sedation.

- Brain monitoring - including TCD, NIRS, EEG, EP, HRV, CT, and MRI of septic patients may be helpful for the diagnosis, the management and the prognostication of sepsis.