

Shedding (infrared) light on the septic brain

Jai N Darvall

The brain in sepsis

Intensive care clinicians will be familiar with the acute brain syndrome observed in patients with sepsis, variously described as “septic encephalopathy” or “sepsis-associated brain dysfunction”.¹ Less well appreciated are the long-term morbidity and mortality associated with this condition. Enduring, new-onset, moderate-to-severe cognitive impairment is seen in at least 10% of survivors of severe sepsis, with a corresponding increase in new, significant, functional limitations.²

A variety of pathophysiological processes may contribute to brain injury in sepsis. These include the direct effects of inflammation, oedema and cellular dysfunction on the brain — the “neuro-inflammatory response” — as well as the indirect effects of systemic hypotension, hypoxaemia and metabolic derangement.³ The net result includes microglial activation, disruption of the blood–brain barrier, deficit in cholinergic function and ultimately neuronal apoptosis.⁴

Monitoring the septic brain

Traditional imaging modalities are limited in the diagnosis and monitoring of septic encephalopathy. As a consequence, interest has arisen in applying emerging technologies to this area (Table 1). For example, positron emission tomography (PET) studies of sepsis in primates have shown the ability to diagnose very early microglial activation in the brain (within hours).¹² PET can also reveal changes in neurotransmitter function in sepsis, with the potential for development of specific treatment targets.⁷ Changes seen on electroencephalography (EEG) may precede clinical encephalopathy and can predict outcome in septic patients, including mortality.^{8,9} Non-convulsive seizures have a prevalence of 10%–20% in severe sepsis, and continuous EEG monitoring may facilitate rapid diagnosis.¹ Brain injury biomarkers, such as neuron-specific enolase and S100 β , have potential predictive and prognostic value in septic encephalopathy.^{10,13} More recently, transcranial Doppler (TCD) ultrasound has shown promise, with cerebral vasoconstriction diagnosed by a high pulsatility correlating with clinical encephalopathy. TCD ultrasound also provides the ability to examine cerebrovascular autoregulation.¹¹

Near-infrared spectroscopy

It is relevant to this issue of the *Journal* that recent advances have been made in applying near-infrared spectroscopy (NIRS) to cerebral monitoring. This technique is non-invasive, easy to apply and offers continuous patient monitoring. Properties of the near-infrared light spectrum that are advantageous to cerebral monitoring include increased tissue penetration and absorbance by cytochrome c oxidase, which can provide

information on cerebral oxygen consumption.¹⁴ There are considerable challenges in applying NIRS, however, including scattering (not all optical attenuation is due to tissue absorption), influence of the extracranial circulation and reliance on algorithms (some are proprietary). There is also considerable variation in cerebral tissue oxygen saturation within and between individuals.¹⁵ Therefore, NIRS has been recommended as a trend monitor for cerebral oxygenation, rather than for use with absolute thresholds.¹⁵

NIRS in sepsis

The ability of NIRS to monitor cerebrovascular autoregulation (CVAR) in sepsis is a promising new area of research. Recent studies of CVAR in the brains of septic patients, mainly using TCD ultrasound, have generated conflicting results. Although much research points to impaired autoregulation as a consequence of sepsis, it is probable that other factors (such as time course, severity of sepsis and alterations in PaCO₂) confound this association.^{16–19} Once disordered CVAR is present in the septic patient, however, there is a clear association with encephalopathy.^{11,16} Bindra and colleagues, in this issue of the *Journal*, increase our understanding of this relationship.²⁰ In a single-centre study of 28 septic patients, they show an association between NIRS-derived high tissue oxygenation reactivity index (TOx) (a validated indicator of impaired CVAR) and mortality (odds ratio for survival, 0.13 [95% CI, 0.01–0.69]; $P < 0.05$). Given the very high mortality in this cohort (64% at 3 months), the single-centre design and the small sample size, their results must be interpreted with caution, but nonetheless provide further evidence for the deleterious effects of impaired CVAR in sepsis and perhaps offer insights into potential treatment targets.

Future directions

Given the implications of persisting disability due to septic encephalopathy, there is a pressing need to identify targets for its prevention or treatment. Further research is required to determine whether manipulation of CVAR can modify patient outcomes, perhaps with respect to optimising autoregulatory capacity along the lines of the optimal TOx target described by Bindra and colleagues. Developing NIRS technology towards continuous monitoring is also an important next step, as the results of the median 85 minutes per day monitoring period in this study may not accurately reflect the haemodynamic complexity, over time, of the septic, critically ill patient. As these and other issues are addressed, NIRS offers significant potential to illuminate our understanding and treatment of sepsis.

Table 1. Brain monitoring modalities in patients with sepsis

Modality	Features in sepsis	Prognostic value	Advantages; disadvantages
CT	Diffuse white matter change, ischaemic/haemorrhagic stroke	Diffuse and severe white matter lesions associated with poor outcome ⁵	Widely available, useful for exclusion of differential diagnoses; poorly sensitive, intermittent only
MRI	Cytotoxic/vasogenic oedema, posterior reversible encephalopathy syndrome	Severity of white matter lesions correlated with Glasgow Outcome Score ⁶	Earlier diagnosis than CT possible; logistical/availability constraints, intermittent only
PET	Microglial activation	Potential for very early diagnosis	Potential for treatments targeting neurotransmitter pathways; ⁷ pre-clinical data only
EEG	Periodic discharges, non-convulsive status epilepticus, absent EEG reactivity	Absent EEG reactivity, delta-predominant background, periodic discharges associated with mortality ^{8,9}	Continuous recording possible, diagnosis of non-convulsive seizures allows early treatment
Biomarkers	Elevated S100 β /neuron-specific enolase	S100 β more discriminatory for mortality, extent of brain damage ¹⁰	Convenient, repeated samples possible; poorly specific
TCD ultrasound	High pulsatility index, high mean autoregulatory index	Cerebral vasoconstriction \pm disordered cerebrovascular autoregulation correlated with encephalopathy ¹¹	Non-invasive, continuous recording possible; operator dependent

CT = computed tomography. MRI = magnetic resonance imaging. PET = positron emission tomography. EEG = electroencephalography. TCD = transcranial Doppler.

Competing interests

None declared.

Author details

Jai N Darvall, Intensive Care Specialist and Anaesthetist,¹ and Senior Lecturer in Critical Care²

- Intensive Care Unit and Department of Anaesthesia and Pain Management, Royal Melbourne Hospital, Melbourne, VIC, Australia.
- Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, VIC, Australia.

Correspondence: jai.darvall@mh.org.au

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