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Biomarker panel to differentiate brain injury from brain dysfunction in patients with sepsis-associated encephalopathy

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Biomarker panel to differentiate brain injury from brain dysfunction in patients with sepsis-associated encephalopathy

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Dear Editor,

We agree with Ehlenbach et al. that microvascular brain injury in sepsis represents one of several important mechanisms for the development of long-term neurocognitive deficits (1, 2). But despite mounting evidence about the common scenario of acute and long-term mortality and long-term cognitive implications predicted by duration of sepsis-associated encephalopathy (SAE), most clinicians still do not factor acute brain dysfunction (diagnosed as delirium) into prognostic considerations unless there is sustained coma (3). Endothelial activation and blood brain barrier injury induce a great degree of morbidity to septic patients that contributes to excess death and disability among survivors (4). Magnetic resonance imaging (MRI) reveals brain injury by displaying white matter hyperintensities (WMH), but the clinical situation of septic patients prevents repeated examinations (5). While bedside clinical examinations are helpful overall to provide day-to-day patient care and blunt estimates of overall “dose” of brain dysfunction sustained during a patient’s

1 septic course, there is a driving unmet need to develop a biomarker for SAE to aid in
2 prognostication and ultimately for prevention/treatment paradigms. A single ideal
3 biomarker is unlikely to fulfil all diagnostic and prognostic needs. Hence, a panel of
4 validated biomarkers might be superior to detect and monitor SAE by targeting
5 different steps that are involved in the pathophysiological process of SAE in terms of
6 pattern recognition. We propose a three step approach to SAE.
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15 **First step**, systemic inflammation alters endothelial function including the cerebral
16 vasculature allowing for the development of endothelial dysfunction (4). Validated
17 biomarkers targeting endothelial dysfunction indicate vascular changes in sepsis and
18 blood-brain barrier (BBB) impairment (4). C-type natriuretic peptide is dominantly
19 expressed in the central nervous system (CNS) and released during encephalopathy
20 from endothelial cells (5). Thus, its N-terminal propeptide (NT-proCNP) was recently
21 validated as predictor of SAE (5).
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33 **Second step**, the evolution of SAE is the activation of microglia cells, supposed to be
34 imminent for the induction of neuroinflammation in the CNS (5). Unfortunately, no
35 body fluid biomarkers of microglia activation are available in vivo. In contrast, S100B
36 is a marker of glial cell damage. Currently S100B is the best validated choice among
37 available biomarker candidates for this purpose (5).
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46 **Third step**, the most striking importance in SAE is the development of structural
47 brain injury, apparent as subsequent neurocognitive deficit (6). Specific validated
48 CNS biomarkers for the neuroaxonal compartment are neurofilament proteins (Nf)
49 (6). Nf give the opportunity to sensitively indicate structural brain injury in the course
50 of SAE (6).
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1 Based on pioneering work, NT-proCNP, S100B and Nf represent a robust biomarker
2 signature panel to detect both brain dysfunction (as indicated by elevated NT-
3 proCNP and S100B) and brain injury (represented by increasing Nf levels) in SAE
4 with the potential to differentiate between both entities. We encourage further studies
5 to evaluate these validated and other candidate body fluid biomarkers in SAE. This
6 might enable clinicians to identify, among septic patients with delirium, the extent of
7 brain injury via timely brain imaging and to determine who will benefit from
8 neurocognitive rehabilitation to improve long-term neurocognitive outcome.
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23 **Conflicts of interest**

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26 E Wesley Ely reports having been a consultant with Masimo in the past. On behalf of
27 all authors, the corresponding author states that there is no other conflict of interest.
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36 **References**

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