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The brain and systemic organ systems: when essential interactions become toxic relationships

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Acute brain injury outcomes are driven not only by the underlying neurologic pathology, but also by non-neurological (systemic) complications [1;2]. Conversely, systemic illness as the primary process can have deleterious effects on the brain [1;3]. Cross-talk between brain and systemic organ systems is a well-known mechanism [4;5], but the impact of treatment on these interactions is equally important. For example, while status epilepticus (SE) may lead to permanent neuronal injury and catecholamine-related systemic complications, its treatment may also affect morbidity and mortality. Despite aggressive first-line (benzodiazepines) and second-line (phenytoin/fosphenytoin, levetiracetam) interventions, more than 40% of these patients will progress to refractory SE [6]. This requires treatment with general anesthetics which may lead to systemic complications, including hypotension requiring vasopressors, immunosuppression and ileus [7]. An algorithmic approach to the management of refractory SE designed to terminate seizures rapidly while minimizing the risk of both neurologic and systemic complications has recently been described [6].

The brain interacts with the heart and lungs via a complex interplay between humoral, neural and cellular pathways [4;5]. Acute lung injury (ALI) develops in more than 20% of traumatic brain injury (TBI) patients and increases their in-hospital mortality [8]. In experimental models, TBI increases the vulnerability of the lungs to mechanical injury and also to non-mechanical injury such as inflammation or ischemia-reperfusion [9]. In patients with previously normal neurologic function, primary ALI can lead to brain damage through release of inflammatory mediators following stimulation of mechanical and chemical receptors in the lungs, airway and respiratory muscles [4]. Importantly, even in healthy lungs, mechanical ventilation (MV) can cause or worsen brain injury secondary to a deleterious inflammatory response [10]. While lung-protective ventilation strategies might mitigate these adverse effects, they may conflict with recommended therapeutic targets for brain injured

patients [11]. For example, permissive hypercarbia might not be appropriate because even modest increases in $PaCO_2$ can result in intractable rises in intracranial pressure if brain compliance is reduced. Conversely, protective MV could be beneficial for pulmonary and neurological outcomes by reducing the inflammation associated with ventilator-induced lung injury [12]. However, the outcome benefits of implementing respiratory care bundles in TBI patients remain unclear in the absence of large randomized controlled trials [13]. In the French BI-VILI project, a multi-faceted approach combining lung-protective ventilation and an early extubation strategy in brain-injured patients was implemented in 20 ICU's [14]. Using a prospective before-after study design, a benefit on ventilator-free days and 90-day-mortality could not be demonstrated, but overall compliance with the ventilation care bundle was low. Of note, the small subgroup of patients whose care complied with the entire set of bundle recommendations did have better 90-day-outcomes and higher number of ventilator-free days.

Brain-heart interconnections have been recognized for decades [5]. Neurocardiogenic injury is associated with increased all-cause and cardiac mortality after SAH [15]. Like for the lungs, primary cardiac injury can also adversely impact the normal brain [16]. Brain injury-related cardiac complications (neurogenic stunned myocardium and stress cardiomyopathy) are often temporary and reversible, so treatment is generally focused on supportive care and management of the underlying brain injury [17]. However, optimal management strategies for failing systemic organ systems, including blood pressure, fluid balance, blood gas and hemoglobin targets, can conflict with what is recommended in brain-injured patients [11].

Neurologic disease, and particularly TBI, is a risk factor for venous thromboembolism (VTE). Both physical and pharmacological (low molecular weight heparin or low dose

unfractionated heparin) prophylaxis methods are recommended. Pharmacological VTE prophylaxis should be started after 48 h in those at low risk of hematoma expansion and after 72 h in patients at medium or high risk, based on evidence from over 5,000 TBI patients [18]. However, a post-hoc analysis of 603 patients in the erythropoietin in TBI trial demonstrated that such practice is not widespread [19]. While the early use of mechanical prophylaxis was almost universal in this study (91% of patients on day 1 and 97% by day 3), pharmacological prophylaxis was delayed until day 3 in 30% of patients and had been implemented in only 57% by day 7. One third of VTE events (in almost 20% of patients) developed within the first 3 days, but the impact of the delay in chemoprophylaxis on this finding is unclear. Risk factors for VTE included worse TBI severity, highlighting the need for further studies in this high risk group.

The impact of general critical illness on the brain can be substantial. Sepsis is frequently complicated by encephalopathy which is associated with worse short- and long-term outcomes, including permanent cognitive and other neurologic impairments [3]. A recent retrospective analysis of a prospective, multi-center database including 2,513 patients with sepsis at ICU admission, demonstrated that even mild alterations in mental status (GCS of 13–14) were independently associated with mortality [20]. Overall, the development of encephalopathy was associated with higher use of ICU resources, longer hospital stay, and higher mortality. Acute renal failure, hypo- as well as hyperglycemia, hypercapnea, hypernatremia and *S. aureus* infection were independent risk factors for sepsis-related encephalopathy. Although a causal relationship could not be proven in this observational trial, these risk factors are potentially modifiable.

In summary, the critical care management of acute brain injury should take into account the complex interactions between the brain and systemic organ systems. On the other hand, the potential for systemic illness to cause acute brain dysfunction is ever-present, and strategies that protect the brain as well as systemic organ systems should be incorporated into general critical care management. In some situations, therapeutic dilemmas or double-edged sword choices cannot be avoided. Therapy may then be a compromise on an individual basis, balancing the potential for adverse effects on the injured brain of treatment for failing systemic organ systems, and *vice versa*. While the epidemiology and mechanisms of these complex brain-systemic inter-relationships are increasingly understood, well-designed studies investigating therapeutic approaches to recognize and manage systemic complications in primary brain injury, or brain-oriented interventions in general critical care patients, are crucial to improve clinical outcomes [1].

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Legend to Figure 1

Schematic representation of some of the pathways involved in brain-injury related systemic organ failure, and critical illness-related brain dysfunction

Ach, acetylcholine; AKI, acute kidney injury; DAMP, damage-associated molecular patterns; HMGB1,high mobility group B1; HPA, hypothalamic-pituitary axis; IL, interleukin; LCOS, low cardiac output syndrome; MOF, multi-organ failure; TNF, tumor necrosis factor; VTE, venous-thromboembolism.