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FOCUS ON

Focus on delirium, sedation and neuro critical care 2019: towards a more brain-friendly environment?

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The brain is always 'at risk' in critically ill patients, regardless of the underlying condition that precipitated their admission to an intensive care unit (ICU) [1]. Clinically, this may manifest in many ways: reduced consciousness, coma, or delirium, are all prevalent symptoms in critically ill patients [2]. The pathophysiology can be conceptualized as a complex interplay between predisposing risk factors, disease-related processes, and issues related to the ICU environment or therapies (Fig. 1). Such a brain dysfunction is associated with worse outcomes and long-lasting cognitive and psychological consequences in ICU survivors [3]. The Improving Care of Acute lung injury Patients (ICAP) trial [4] was a prospective 5-year follow-up of 520 acute respiratory distress syndrome (ARDS) patients. Hospital Anxiety and Depression Scale and Impact of Event Scale-Revised were obtained in 186 of the 196 patients who survived to 3 months. More than half of these patients suffered from prolonged symptoms of anxiety (in 38%), depression (in 32%), and post-traumatic stress disorder (in 23%) with overlap between these symptoms and a median symptom duration of 33–39 months. Antecedents of mental health problems, especially recent anxiety and depression preceding the ARDS, and a lower level of education were the most important pre-ARDS risk factors for prolonged psychiatric morbidity. A similar association was found in a Dutch retrospective study of 1090 patients admitted to a mixed medical/surgical ICU [5] in which pre-ICU psychopathology increased the incidence of delirium by 30%. Perhaps screening for these risk factors might allow for more directed interventions in the recovery phase after critical illness?

Psychotropic drugs are often used to treat ICU delirium, even though the evidence for short- and long-term benefits of many of these drugs is not very strong. Haloperidol is amongst the most frequently used agents. The Agents Intervening against Delirium in Intensive Care Unit (AID-ICU) international, prospective, 2-week prevalence study recruited 1260 patients from 99 ICUs in 13 countries and found that the incidence of delirium was 25% [6]. This incidence is relatively low compared to other studies [2]. Roughly half of the delirium in AID-ICU was of the mixed type, whereas the other half was equally divided between hypo-active and hyper-active subtypes (each approximately 25%) [6]; haloperidol was the main agent used in delirious patients; delirium and the use of circulatory support were the main independent predictors of haloperidol use. There was no association between haloperidol use and increased 90-day mortality, although the study was likely underpowered to detect such an effect. Interestingly, haloperidol use was independent of the delirium subtype, and almost 10% of the patients received a fixed dose. The Prophylactic Haloperidol Use for Delirium in ICU Patients at High Risk for Delirium (REDUCE) study [7], a large ($n = 1789$) randomized controlled trial (RCT), provided evidence against such practice; there was no effect of prophylactic fixed doses of haloperidol on mortality, or on the incidence or duration of ICU delirium. Moreover, in a post hoc analysis of these data, haloperidol serum levels were lower than expected and did not correlate with the number of delirium-free days [8]. Of note, benzodiazepines were the second most

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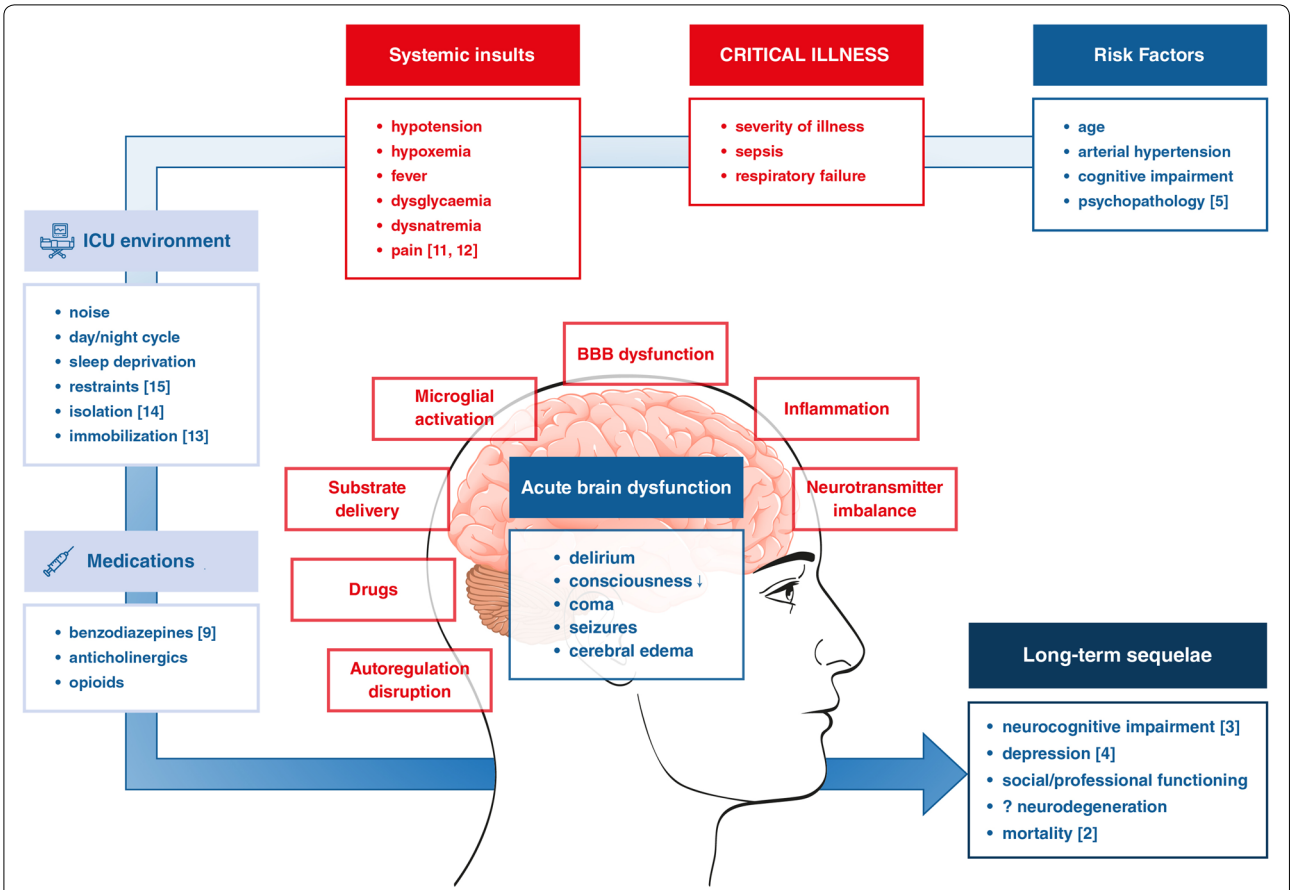

Fig. 1 Risk factors and contributors to critical-illness-acquired brain dysfunction. Following the arrow counter-clockwise: risk factors pre-critical illness; critical-illness-related risk factors; potentially mitigatable risk factors related to the ICU environment or treatment. Pathophysiological mechanisms of acute brain dysfunction are presented around the brain, and long-term sequelae at the end of the arrow. Numbers between square brackets refer to the references in the text. (Adapted, with permission, from [1])

commonly used agents against delirium in AID-ICU, followed by dexmedetomidine, and quetiapine. Continuous infusions of benzodiazepines have well-known pro-delirogenic effects, in addition to other side effects [9]. The evidence for using dexmedetomidine for delirium was recently challenged by the SPICE III RCT [10]; open-label dexmedetomidine had no effect on coma-free or delirium-free days, or 90-day mortality, but caused a higher rate of hypotension and bradycardia. It is clear that the conundrum of the optimal treatment of ICU delirium is far from solved, and that evidence for the exact role and indications of different therapeutic agents is equally opaque.

Pain, as well as indiscriminate opioid use, is a well-known contributor to the development of ICU delirium. Pain is difficult to assess in the critically ill, and a gold standard test is lacking. In a small observational study in 20 ICU patients, there were discordant results for the same painful procedure when pain was assessed using the behavioral pain scale compared to an electrophysiological tool (the Analgesia Nocioception Index) [11]. The Europain®study [12] was a large prospective international multicenter observational study, which investigated the pain associated with commonly performed ICU procedures (4812 procedures in 3815 patients). All the 12 investigated procedures, except for wound care, significantly increased patient-reported pain intensity. Procedures associated with the highest increases in pain were (endo)tracheal suctioning, chest tube or wound drain removal, turning, and insertion of an arterial line. Surprising, and difficult to interpret, was the observation that pre-procedural opioids (pethidine/meperidine) and haloperidol increased the reported pain distress during the procedure.

Non-pharmacological measures are an inherent part of the collective efforts to improve patient comfort in the ICU. Mobilization of patients has well-known beneficial effects on outcome and reduced delirium incidence, especially when started early. However, the implementation of early mobilization protocols remains a challenge. A systematic multi-level team approach is necessary to overcome barriers to early mobilization [13], such as lack of staffing, lack of training, or lack of financial support. In a before–after study performed in a Brazilian hospital [14], extended visiting times reduced the incidence of delirium from 12.1 to 6.7%. Physical restraints are commonly used in some countries to avoid patients harming themselves or their environment. However, restraints have well-known detrimental psychological effects and evidence that they actually prevent self-harm is lacking. Therefore, it seems that the current widespread use of restraints should be re-evaluated [15].

Brain dysfunction in critically ill patients is increasingly recognized as one of the major clinical and scientific challenges. The 'hostile' ICU environment is itself an important contributor to ICU-acquired brain dysfunction and, as such, interventions to humanize critical care should be embraced and studied in a systematic way. The evidence against pharmacological prophylaxis of delirium is accumulating, but the exact timing, indications, and preferred agents for pharmacological treatment remain unclear. A complex challenge never has a simple solution, and future efforts should focus on multimodal interventions for the prevention and treatment of ICU-acquired brain dysfunction.

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