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What's new in post-ICU cognitive impairment?

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Prevalence of post-ICU cognitive impairment

As ICU survivorship has increased, long-term cognitive impairment affects the recovery of our patients, often shifts care toward institutionalization, and represents a significant public health problem. Cognitive impairment is typically marked by deficits in neuropsychological function, as measured by the domains of memory, attention, processing speed, visuospatial ability, and executive function. Prior epidemiologic data on post-ICU long-term cognitive impairment have been based on small cohort studies, restricted to single pathophysiologic states or ICU type (e.g., acute lung injury, acute respiratory distress syndrome, medical ICU), have reported wide ranges of cognitive impairment in 4–62 % patients, and have been measured from 2–156 months post-ICU discharge [1].

The BRAIN-ICU study (bringing to light the risk factors and incidence of neuropsychological dysfunction in ICU survivors) is the largest multicenter cohort examining post-ICU cognitive impairment. This prospective cohort consisted of 821 medical and surgical ICU patients, who were tested at 3 and 12 months after hospital discharge for long-term cognitive impairment. Only 6 % of this population had mild to moderate cognitive impairment pre-ICU admission. Global cognition was measured using the repeatable battery for the assessment of neuropsychological status, where scores below 1.5 standard deviations below the age-adjusted population means were comparable to patients with moderate traumatic brain injury, and scores below 2 standard deviations below the age-adjusted population means were comparable to patients with mild Alzheimer's disease. The investigators found that, at 3 months, 40 and 26 % of ICU patients had global cognition scores lower than 1.5 and 2 standard deviations, respectively. This effect persisted at 12 months with 34 and 24 % having cognition scores similarly affected. The domain of executive function was also measured, using the trail-making test part B, and found to be similarly depressed at 3 and 12 months [2].

Another study examining long-term cognitive impairment, also rigorously accounting for pre-morbid cognitive functioning, utilized data from the group health cooperative and evaluated 2,929 subjects over the age of 65 without dementia at baseline. Screening for cognitive impairment was accomplished using the cognitive

abilities screening instrument every 2 years, followed by an evaluation for dementia for those with lower scores. The major finding was that acute care and critical illness hospitalizations were associated with a higher likelihood of abrupt cognitive decline, compared to those not hospitalized. There was some suggestion that critical illness may have a large effect on incident dementia (hazard ratio = 2.3, 95 % CI, 0.9–5.7; $P = 0.09$); however, the study was underpowered to detect this difference [3].

Critical illness is also associated with sepsis and it has been suspected that post-ICU impairments of cognitive and functional status may be long lasting. Using data from 1998–2006, a prospective cohort was constructed from the health and retirement study to determine the change in cognitive and physical functioning among survivors of severe sepsis, where 516 survived sepsis and 4,517 survived a non-sepsis hospitalization to complete at least one follow-up interview. Severe sepsis was independently associated with three-fold the odds of moderate to severe cognitive impairment, and sepsis was independently associated with 1.5 new functional limitations [4]. Even in the broader BRAIN-ICU population study, it is suggested that functional-oriented and physical-targeted therapies may help those surviving critical illness, as at least one-third of the study patients had persistent symptoms of mild depression driven by somatic symptoms, rather than solely cognitive [1, 5]. Other than mood-related disorders, acute in-hospital stress symptoms may also be associated with impairment in cognition 1 year after a critical illness [2, 6]. It is important to understand that there is a complex intertwined interaction between emotional and cognitive states; however, these studies treated these entities discretely.

Risk factors, mechanisms, and prediction of post-ICU cognitive impairment

In the BRAIN-ICU study, duration of in-hospital delirium, or acute brain dysfunction, was an independent risk factor for worse global cognition scores and executive function at 3 and 12 months; this was independent of sedative or analgesic medication use, age, preexisting cognitive impairment, baseline comorbidities, or ICU organ failures [2, 3]. The mechanism behind delirium and long-term cognitive impairment after critical illness is not well understood and is complex (Fig. 1). Peripheral cytokine production may prime centrally located microglia and produce cholingeric dysfunction, alter tryptophan metabolism (kynurenine pathway), induce neuronal apotosis, and lead to brain atrophy [4, 7]. This neuroinflammation may be ameliorated by neuroprotectants such as statin medications [8]. Among those with a systemic inflammatory response syndrome, biomarker studies have found an association of proinflammatory cytokine IL-8 with delirium but not long-term cognitive impairment [9]. Other candidate biomarkers associated with delirium are inflammatory markers STNFR1, STNFR2, adiponectin, and IL-1β, which appear to be unmodified by the presence of sepsis [10].

Sepsis-induced cognitive impairment may represent a unique subset of ICU neuroinflammation, and the cytokine-based responses have parallels to Alzheimer's disease. In sepsis, there is evidence of brain function desynchronization as measured by magnetoencephalography (MEG). This desynchronization may be associated with impaired cognitive function due to altered functional connectivity between brain regions. In a group of 25 sepsis survivors, there is ongoing work testing the neurophysiologic mechanisms of cognitive impairment (German Clinical Trials Register, DRKS00005484) [11]. Other ICU risk-modifying factors for long-term cognitive impairment may be episodes of hypoxia or hypotension, medication usage (e.g., sedative, opioids, analgesics, antipsychotics), and/or alteration in glucose control [1].

Predicting long-term cognitive impairment has been challenging and restricts the ability of providers to risk stratify individual rehabilitation needs. Quantitative EEG may improve delirium detection, delirium severity, and deficits in learning and memory. Biomarkers, such as C-reactive protein, interleukin-6, amyloid-β, and APOE4 allele, may reflect both acute and long-term brain

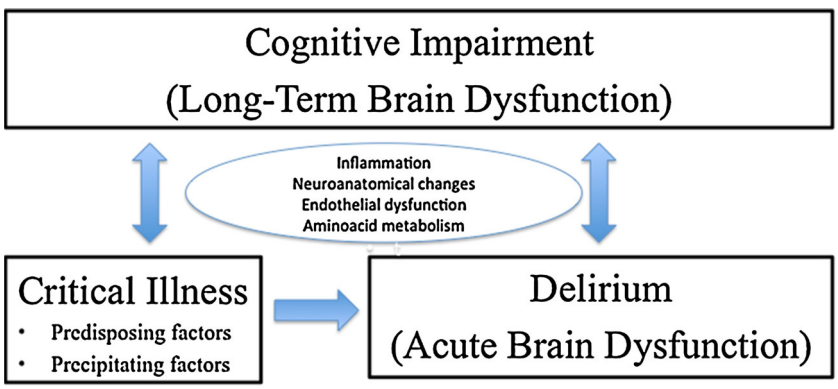

Fig. 1 Complex relationships between cognitive impairment, delirium, and critical illness

inflammation and might add power for predicting future cognitive impairment [9, 12].

Rehabilitation of post-ICU cognitive impairment

There is some promise and feasibility in using early cognitive rehabilitation to improve cognitive outcomes in ICU survivors. The returning to everyday tasks utilizing rehabilitation networks (RETURN) study used cognitive functioning as a primary outcome in a single-center, pilot randomized control trial of general medical and surgical ICU survivors. Of 21 ICU survivors with cognitive or functional deficits measured at hospital discharge over a 3-month period, 8 received usual care, and 13 received intervention of in-home cognitive, physical, and functional rehabilitation. Specifically, the cognitive training consisted of goal-management training (GMT), a stepwise and targeted approach to the rehabilitation of executive function. At the end of the time period, the group receiving intervention had significantly improved executive functioning ($P < 0.01$), as measured by the Tower test for planning and strategy, as well as functional status, as measured by the functional activities questionnaire [13].

Improved cerebrovascular function may be an effect of exercise and also result in improved cognition. The activity and cognitive therapy in an ICU (ACT-ICU) trial [14] evaluated the feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients. Within 24 h of enrollment, including when on mechanical ventilation, and until hospital discharge, inpatient cognitive therapy was provided to 41 of 43 (95 %) patients randomized to the cognitive plus physical therapy arm and consisted of two 20-min daily sessions that targeted orientation, memory, attention, delayed memory, problem-solving, and processing speed. At hospital discharge, for those patients manifesting impaired executive function or functional mobility, a GMT cognitive therapy program was assigned for 6 sessions over 12 weeks. Of the 18 eligible patients in the cognitive plus physical therapy arm, 17 (94 %) received at least one GMT session. Although both the RETURN study and ACT-ICU study used similar GMT cognitive therapy, the ACT-ICU study did not find an improvement in executive functioning [15]. Although the ACT-ICU trial was a feasibility study, there is a recently completed Chilean study powered to evaluate the effects of early and intensive occupational therapy for delirium prevention in critically ill non-ventilated patients (ClinicalTrials.gov Identifier: NCT01555996; results pending)

Conclusion

The care of the critically ill patient does not end upon ICU discharge, and there are long-term cognitive effects altering the quality of survivorship. Future work should attempt to unravel the complex relationship between emotional and cognitive impairments through quantitative but also qualitative studies. There is still much to be learned about the downstream impacts of our in-hospital decisions on the lives of critically ill survivors.

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Conflicts of interest The authors declare that they have no conflict of interest.

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