

Executive Dysfunction Following Critical Illness: Exploring Risk Factors and Management Options in Geriatric Populations

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Abstract Cognitive impairment is a common occurrence that has been shown to occur in over 50 % of patients following critical illness. This impairment occurs across a range of domains including attention, memory, processing speed, and executive dysfunction. In this article, we will discuss the pathophysiology behind cognitive impairment including hypoxemia and cytokines. Secondly, we will describe the risk factors for cognitive impairment including age, length of stay, and delirium. Lastly, we will review emerging data related to the use of cognitive rehabilitation, formation of postintensive care clinics in qualifying patients, and potential neuropharmacologic therapy. While our chapter focuses on cognitive impairment generally, it places a particular emphasis on executive dysfunction, not because impairment occurs solely in this domain but because impairments of an executive nature may be uniquely debilitating.

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Introduction

America, as well as the industrialized world, is aging rapidly [1]. The population of elderly Americans nearly doubled from 19.1 million in 1966 to nearly 34 million in 1998, with this number expected to double by the year 2030 [2]. The “oldest old” (≥85 years) accounted for a mere 7 % of the population three decades ago yet now constitutes nearly 15 % by 2010 [3]. Older Americans consume health-care resources at a rate two to three times greater than younger adults due to the increasing prevalence of chronic disease among those of advanced age and other factors. The aforementioned trends are predictably impacting intensive care unit (ICU)s, as increasing numbers of elderly patients are admitted for both the exacerbation of chronic illnesses as well as the development of acute illnesses such as severe sepsis [3]. Currently, more than 75 % of all ICU days are incurred by elderly patients, and a typical ICU length of stay is 7 times greater for patients >75 than for those <65 [4]. While potentially debilitating to patients of all ages, the effects of critical illness and ICU hospitalization on elderly individuals may be particularly profound, with recent evidence suggesting that older patients are more likely than their younger counterparts to experience prolonged disability following hospitalization while also experiencing greater quality of life decrements [5–7]. Studies of acutely ill elderly suggest that cognitively intact patients may experience accelerated cognitive decline after general hospital treatment and that those with mild forms of cognitive impairment are at greater risk for adverse outcomes including increased mortality and permanent institutionalization [8, 9]. Consequently, the effort to understand cognitive impairment following critical

illness as well as the degree to which functional disability is mediated by deficits in certain neuropsychological domains is a critically important goal and one with far-reaching public health implications. This goal can be facilitated through investigation of a particular type of cognitive dysfunction, widely known as executive dysfunction. In the view of thought leaders in the fields of geriatric medicine and neuropsychology, executive function is uniquely related to an array of functional disabilities in both elderly and nonelderly and which may be caused by specific mechanisms of injury common to critical illness as well as patients cared for in the ICU [10, 11]. In this article, we will discuss the risk factors, clinical outcomes, and potential treatment of cognitive impairment, with a particular focus on executive dysfunction, one of the many domains impacted by critical illness.

Definition

Executive dysfunction is a particularly debilitating form of cognitive impairment that is widespread in survivors of critical illness, highlighting the importance of a definition of executive functioning. Our point in focusing on executive dysfunction in this review *is not to suggest that it is the only domain impacted after critical illness or the domain impacted most commonly* but because—for reasons explained in this manuscript—deficits in this area are significantly problematic for functioning. While acknowledging the presence of ongoing questions regarding the conceptual boundaries of executive functioning [11–13], a general consensus regarding this construct exists and is reflected in the following definition: *executive functions are those involved in complex cognitions such as planning, initiating, shifting/sequencing, monitoring and inhibiting which enable individuals to engage in purposeful, goal directed behaviors* [6, 13–17]. When globally or elementally impaired, this condition is referred to as executive dysfunction [18–22]. While referred to as an “umbrella” construct [23], as it encompasses multiple cognitive components, the conceptualization of executive functioning is guided by two primary themes: (1) that the higher order cognitive functions related to executive functioning are primarily (but not entirely) dependent on frontal and subcortical systems and (2) that executive functions control the execution of complex activities essential for successful higher order functioning [10]. These activities could include but are not limited to tasks such as balancing a checkbook and managing money, driving or map reading, following instructions and engaging in hobbies, working outside of the home, and understanding social cues [10, 24••].

Despite its obvious importance as a construct, executive functioning has been outside of the purview of physicians and researchers in nonpsychiatric specialties until very recently, as evidenced by two examples [25]. First, the definitive

internal medicine textbook, the voluminous Harrison’s Principles of Internal Medicine did not index “executive function” until the 16th edition (2005) [26]. Second, a MEDLINE search from 1966 to October 2004 combining the three leading North American general medical journals, *Journal of the American Medical Association*, the *New England Journal of Medicine*, and the *Annals of Internal Medicine*, yielded a total of 119,009 articles [25]. When researchers combined this search with the key word “executive functioning,” it yielded only one result. This state of affairs is changing dramatically in both research and clinical arenas, perhaps owing in part to the increased recognition that executive dysfunction is common and that it may more powerfully contribute to functional decrements and problems in living than deficits in memory and other domains. Consider, for example, that a total of 155 articles containing the term “executive dysfunction” were indexed in MEDLINE in 2003. A mere 3 years later, this number had risen to 421, representing a 172 % increase in 3 years and reflecting a burgeoning interest in this subject. Thus, executive functioning is both a widely underinvestigated construct as well as the focus of greatly increasing attention, due to a dawning awareness that executive dysfunction is common in geriatric and medical cohorts, as well as potentially extremely detrimental [25, 27].

Biological Mechanisms of Executive Dysfunction

The mechanisms of long-term cognitive impairment (LTCI) following critical illness are complex and multifaceted yet remain largely unelucidated. This is particularly the case with regard to the mechanisms of executive dysfunction, which have been extensively explored in other populations but never studied among ICU cohorts. While the existence of a “common pathway” to explain all executive dysfunction in survivors of critical illness is unlikely due to the heterogeneity of ICU populations and the differing etiologies underlying their illnesses, a number of prominent and biologically plausible mechanisms exist.

Hypoxemia

The presence of sustained respiratory distress of a severity typically requiring mechanical ventilation is one of the more universal experiences associated with critical illness [28••]. Indeed, the incidence of mechanical ventilation is increasing, with patients ≥ 65 having the highest age-specific incidence [29]. Among mechanically ventilated patients, particularly those suffering from conditions such as sepsis and acute respiratory distress syndrome (ARDS), prolonged periods of hypoxemia and hypotension are common, with the most definitive study to date reporting that ARDS patients have an average of 25 episodes of desaturation < 90 and 1 episode < 85 , for a duration of more than 2 h during a typical hospital stay

[28••]. Tyrosine hydroxylase, the rate-limiting enzyme for dopamine synthesis, is oxygen dependent, and decreased dopamine levels have been observed in brain tissue during prolonged periods of hypoxia [30]. As the brain engages in the process of adapting to hypoxia, *N*-methyl-D-aspartate (NMDA) glutamate receptors become more excitable, in turn leading to oxidative cell death [31]. In patients with conditions that include prominent symptoms due to hypoxemia, such as those with chronic obstructive pulmonary disease (COPD) as well as obstructive sleep apnea (OSA), executive deficits are prominent and include poor problem solving skills, impaired concept formation, and limited cognitive flexibility [12, 32–35]. These findings make sense in light of evidence that suggests that structures within the frontal circuits are particularly sensitive to hypoxia [35].

Cytokine-Mediated Executive Impairment

It is now recognized that the brain is in fact an “immunologically active organ” vulnerable to and influenced by systemic inflammatory reactions and responses, such as those that result from septic shock and sepsis [36, 37]. These inflammatory responses are mediated by cytokines that penetrate the blood-brain barrier and directly or indirectly modulate brain activity, potentially altering neurotransmission [38]. While human investigations are ongoing, much of the evidence for an association between cytokines and neurocognitive function is derived from animal models, which demonstrate that high interleukin-1 (IL-1) and interleukin-6 (IL-6) levels occur in brain regions such as the hippocampus and the prefrontal cortex [38, 39]. Neuropsychological dysfunction associated with inflammation includes impairments in elements of executive functioning including working memory, cognitive flexibility, and set shifting [40, 41]. Wide-ranging and persistent deficits in executive functioning, including abnormalities on tasks of working memory, verbal fluency, and planning/organization, have been observed in patients receiving interferon treatment and thus experiencing significant neuroinflammation, for conditions such as melanoma, leukemia, amyotrophic lateral sclerosis, cancer, and chronic hepatitis [42–44].

Risk Factors

The reasons for the specific development and progression of executive dysfunction in ICU survivors are unknown, although a limited number of risk factors have been evaluated that contribute to cognitive impairment generally [28••, 45••] (Table 1).

Table 1 Risk factors for executive dysfunction

Characteristic
Age
Hospital length of stay
ICU length of stay
Delirium

Age and Length of Stay in the ICU and Hospital

A prospective study of 30 long-stay, nondelirious, tracheal intubated ICU patients was tested with the Cambridge Neuropsychological Test Automated Battery (CANTAB) in the ICU, 1 week after ICU discharge, and 2 months after ICU discharge. Significant problems with strategic thinking and problem solving—problems broadly considered to be “executive” in nature—were found in all 30 patients while in the ICU. Additionally, 20 of these patients had problems with memory. The amount of difficulty with problem solving while in the ICU correlated with length of ICU stay ($p=0.011$), age ($p=0.036$), and length of hospital stay following the ICU ($p=0.004$) [45••]. Further, the finding by Jones and colleagues regarding age and executive dysfunction in ICU survivors is supported by substantial data from studies of humans and nonhuman primates alike that demonstrates that advanced age is a risk factor, with evidence suggesting that healthy subjects in their 70s and 80s, as well as even younger cohorts, frequently display executive deficits [46–49].

Delirium

There is emerging evidence to suggest that delirium may be characterized by distinct anatomic patterns and processes although this remains to be studied [50]. Recent investigations employing sophisticated scanning technologies have demonstrated that delirium is associated with significant cerebral hypoperfusion in particular brain regions, including frontal, temporal, and subcortical regions [51]. Subcortical structures, which appear to mediate key elements of executive functioning, are particularly susceptible to even slight alternations in blood flow because of the small perforating vessels feeding these structures [52]. Evidence from clinical investigations suggests that executive dysfunction commonly develops secondary to reduced blood flow to vulnerable subcortical structures implicated in frontal-subcortical circuitry, even in the absence of frank ischemic injury [53].

The Awakening and Breathing Controlled (ABC) [54] trial, a multicenter, prospective study which randomized 336 ventilated patients to a spontaneous awakening trial (SAT) coordinated with spontaneous breathing trial (SBT) (ABC group) versus SBTs plus sedation via usual care, found that the ABC

group spent three fewer days on mechanical ventilation, three fewer days in the ICU, and five fewer days in the hospital. The ABC group also had a 14 % improvement in 1-year survival (hazard ratio 0.68, 95 % confidence interval 0.5 to 0.92; $p=0.01$). During the ABC trial, 180 medical intensive care unit (MICU) patients were included in an a priori analysis assessing cognitive function following discharge at both 3 and 12 months. The ABC group experienced less cognitive impairment as compared to the control group at 3 months postdischarge (absolute risk reduction 20.2 %, 95 % CI 1.5 to 36.1 %, $p=0.03$). However, no difference in cognitive impairment was found between groups at the 12-month follow-up period [54]. Deficits of an executive nature, including problems in planning, were extremely common among ABC trial patients.

A prospective cohort study of 77 mechanically ventilated patients evaluated the duration of delirium during hospitalization to determine association with long-term cognitive impairment. The median duration of delirium was found to be 2 days. Cognitive impairment was found in 79 % of patients and severe cognitive impairment was found in 62 % of these patients 3 months after discharge. Deficits in executive abilities such as set shifting and planning were common. Cognitive impairment was found in 71 % of patients, while 35 % of patients were classified as having severe cognitive impairment 1 year following discharge. Following adjustment for age, education, baseline cognition, severity of illness, and utilization of sedatives in the ICU, the duration of delirium was found to be an independent risk factor for worse cognition by averaging T scores from nine cognitive assessment tests [55].

In addition, a large, multicenter, prospective observational cohort study of 821 adult medical ICU and surgical ICU patients, Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU study), was conducted to estimate the prevalence of long-term cognitive impairment following critical illness secondary to respiratory failure, cardiogenic shock, or septic shock. Delirium was the strongest independent predictor of cognitive impairment in 50 % of patients in this complication following critical illness. A Repeatable Battery for Neuropsychological Status (RBANS) score similar to Alzheimer's disease (2 standard deviations below the population mean) was found in 26 % of patients, and a score similar to moderate traumatic brain injury (TBI) (1.5 standard deviations below the population mean) was found in 40 % of patients 3 months after discharge. The RBANS has relatively little coverage of executive functioning, but on tests that involved executive abilities—e.g., tests of fluency and tests of planning—difficulties were frequently observed. Both young and older adults, with and without comorbidities, experienced these deficits which persisted at 12 months in 24 and 34 % of these individuals having RBANS scores similar to Alzheimer's disease and moderate traumatic brain injury, respectively [56••].

Clinical Outcomes Associated with Executive Dysfunction

Among many non-ICU medical, geriatric, and psychiatric populations, the functional correlates of executive dysfunction have been widely studied, with evidence documenting often robust associations between executive dysfunction, quality of life, and functional decrements. Such findings are logically consistent in light of the fact that, at their most elemental level, higher order activities of daily living require capacities in areas such as planning, organization, and generation of flexible and efficient strategies, all of which are limited by executive dysfunction. A brief review of the literature pertaining to executive functioning and domain-specific outcomes is instructive, as it offers potential insights into the adverse effects of executive dysfunction in patients following critical illness.

Independent Living/Functioning

Executive dysfunction is associated with deficits in the performance of instrumental activities of daily living among community-dwelling elderly, assisted-living residents, vascular dementia sufferers, and patients with Alzheimer's disease [57–62]. In otherwise healthy elderly, executive dysfunction is a harbinger of decreasing personal independence and is a risk factor for needing formal health care [63, 64]. It contributes to an inability to effectively solve everyday problems [65] and effectively manage financial tasks and appears to be a more significant predictor of financial mismanagement than overall cognitive impairment [66, 67].

Health-Care Management

Executive dysfunction explains over 50 % of the variance in the ability to provide informed consent for medical care in certain populations and is a robust predictor of poor medication adherence, even in the absence of complex medication regimes [68–70]. Among medical inpatients with dementia, it is associated with resistance to care [71]. Executive dysfunction is related to the inability to successfully utilize certain medical devices, such as inhalers [72].

Employment

Executive dysfunction has consistently been identified as the most reliable neuropsychological indicator of poor employment outcome after both TBI and mild TBI and has been strongly associated with reduced occupational attainment and an inability to engage in complex workplace tasks [73, 74]. In psychiatric and specific chronically ill populations, executive dysfunction is associated with problematic work behaviors as well as unemployment [69, 75, 76].

Social Functioning

Executive dysfunction has been linked to marked impairment in social functioning among cohorts with schizophrenia and bipolar disorder, as well as among community controls [77–80].

Quality of Life (QoL)

Executive dysfunction has been shown to be predictive of poor QoL among a diverse array of patient populations including individuals with epilepsy, human immunodeficiency virus (HIV), multiple sclerosis, and chronic mental illness [21, 81–84].

Treatment

Cognitive Rehabilitation

Cognitive rehabilitation has been evaluated in two small studies to determine outcomes in critically ill patients, and this area is still in the very early phases of investigation. A randomized, single-center feasibility study (ACT-ICU) was conducted in 87 medical or surgical ICU patients with shock or respiratory failure. Patients were randomized in a 1:1:2 ratio to usual care, early once-daily physical therapy, or early once-daily physical therapy in addition to twice-daily cognitive therapy [85]. In noncomatose patients, cognitive therapy included orientation, memory, and attention exercises. Ninety five percent of patients randomized to the physical and cognitive therapy group received early, cognitive therapy. No significant difference was found between groups in measures of executive function (Tower Test and Dysexecutive Questionnaire), global cognition (Mini-Mental Status Exam), functional mobility (Timed Up-And-Go Test), activities of daily living (Katz Activities of Daily Living), instrumental activities of daily living (Functional Activities Questionnaire), or health-related quality of life (European Quality of Life-5 Dimensions Visual Analog Scale) at 3-month follow-up. No difference was found between groups in delirium/coma-free days, ventilator-free days, ICU length of stay, or hospital length of stay. Larger studies need to be performed to get a better representation of the benefits of combination physical and cognitive therapy on long-term outcomes in critically ill patients.

Twenty-one MICU and SICU patients with cognitive or functional impairment were randomized at hospital discharge in randomized, single-center feasibility study (RETURN) to assess usual care as compared to in-home combination therapy (cognitive, physical, and functional therapy). At 3 months, cognitive, executive functioning was improved in the intervention group as assessed by the Tower Test (median 13, IQR 11.5–14) versus the usual care group (median 7.5, IQR

4–8.5, $p < 0.01$). Better scores on the Functional Activities Questionnaire were obtained at 3 months in the intervention group (median 1, IQR 0–3) as compared to the usual care group (median 8, IQR 6–11.9, $p = 0.04$). Large, randomized studies need to be conducted to further assess the validity of these results [86].

Post-ICU Follow-Up Clinics

The Society of Critical Care Medicine (SCCM) has coined the term postintensive care syndrome (PICS) to describe the constellation of the following symptoms following stay in the intensive care unit: new or worsening problems in physical, cognitive, or mental health status arising after a critical illness and persisting beyond acute care hospitalization [87]. The establishment of ICU survivor clinics is one method to care for the long-term complications of these patients, and these clinics may have the potential to impact cognitive functioning, including executive functioning, via early identification and treatment including cognitive rehabilitation.

There are two PICS clinics currently in the UK. The first ICU follow-up clinic was established in the UK in 1993 [88]. The clinic is run by a nurse, an ICU consultant, for half a day twice monthly. Criteria for the clinic include an ICU stay of 2 least days. These patients are seen at 2, 6, and 12 months following discharge. Following the addition of several more clinics in the UK in subsequent years, a survey was conducted in 2006. ICUs were surveyed to determine the state of ICU follow-up clinics [89]. Thirty percent of the 266 ICUs that responded to the survey in the UK had a PICS clinic. The majority was nurse-led (55 %) and required an ICU length of stay of at least 3 to 4 days (77 %). Psychological and physical therapy was available in one third of the clinics surveyed. Australia also first established PICS clinics in the early 1990s as well [90].

Neuropharmacologic Therapy

Currently, there is a lack of evidence evaluating neuropharmacologic therapy for the treatment of cognitive impairment following critical illness (Table 2) and conflicting evidence evaluating the benefit of acetylcholinesterase inhibitors in patients

Table 2 Potential neuropharmacologic therapies for executive dysfunction

Medication class
Acetylcholinesterase inhibitors
Stimulants
Testosterone
Dopamine receptor agonists
Anti-inflammatory agents

with mild cognitive impairment. Four clinical trials have shown improvement on assessment scales evaluating memory and attention with utilization of donepezil [91]. However, these benefits are thought to be minor, short-lived, and linked to substantial side effects [92]. In general, these studies have pertained to individuals with mild cognitive impairment and early manifestations of dementia and have focused more on the remediation of memory deficits than executive dysfunction.

Stimulants such as methylphenidate and modafinil have shown benefit in patients with cognitive impairment, patients with traumatic brain injury requiring an ICU stay, those with various tumors including primary brain and breast tumors, and patients who have received cancer-related treatment [91, 93, 94]. The Working Memory Task Test and Distraction Task Test, a test that ostensibly evaluates executive abilities, improved following administration of methylphenidate in ICU survivors following TBI. Also, modafinil showed significant improvement in cognitive testing and psychomotor speech compared to placebo [94].

Testosterone, dopamine receptor agonists, and anti-inflammatory agents are other therapies that have been considered for the treatment of cognitive impairment. Testosterone has shown favorable outcomes in patients with mild cognitive impairment, while estrogens with and without progestin have not shown benefit as compared to placebo [92]. It is hypothesized that improved spatial memory is seen in patients with cognitive impairment with a deficiency of testosterone only. Piribedil is a dopamine receptor agonist that has shown benefit in cognitive impairment. However, this agent is not currently available in the USA. Anti-inflammatory agents are also thought to potentially provide benefit in cognitive impairment. However, rofecoxib, the agent evaluated for this indication, has been removed from the market in the USA due to concerns about safety. Larger, more rigorously designed studies need to be conducted to further determine the efficacy of the utilization of neuropharmacotherapy in the treatment of cognitive impairment.

Conclusions

Cognitive impairment is common following critical illness. Executive dysfunction is a specific form of cognitive impairment that is problematic following critical illness and which contributes to the inability to successfully engage in and master complex tasks and challenges essential to independent functioning.

Identification of risk factors for and the clinical manifestations associated with executive dysfunction are key in prevention and treatment. Further studies need to be conducted to evaluate the effects of cognitive rehabilitation both in the

hospital and postdischarge on patient outcomes, the effects of post-ICU follow-up clinics, and neuropharmacotherapy on executive dysfunction.

Compliance with Ethical Standards

Conflict of Interest Dr. Jo Ellen Wilson and Dr. James C. Jackson declare that they have no conflicts of interest.

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