Coma, Delirium, and Cognitive Dysfunction in Critical Illness

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Syndromes of global cerebral dysfunction associated with critical illness include acute disorders such as coma and delirium, and chronic processes namely cognitive impairment. These syndromes can result from direct cerebral injury, but in many instances develop as a complication of a systemic insult such as cardiac arrest, hypoxemia, sepsis, metabolic derangements, and pharmacological exposures. Coma frequently evolves into phenomenologically distinct disorders of consciousness such as the vegetative state and the minimally conscious state, and it must be differentiated from conditions in which consciousness is preserved, as in the locked-in state. Coma and delirium are independently associated with increased short-term mortality, while cognitive impairment has been linked to the poor long term functional status and quality of life observed in critical illness survivors. Advances have been made in defining, scoring, and delineating the epidemiology of cerebral dysfunction in the intensive care unit, but research is needed to elucidate underlying mechanisms, with the goal of identifying targets for prevention and therapy.

Acute brain dysfunction

A high proportion of patients who are admitted to the ICU develops a global alteration in cognitive function that is associated with an underlying cerebral process that can be structural or metabolic [1,2]. Terms that are used commonly to describe these disturbances include coma, delirium, encephalopathy, acute confusional state, organic brain syndrome, acute organic reaction,

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cerebral insufficiency, brain failure, and ICU psychosis; etiology-specific terms, such as "septic encephalopathy" or "hepatic encephalopathy," have been used when there is a strong presumption regarding the causative mechanism. It has been proposed that many of these disorders are clinical expressions of a pathophysiologic spectrum, collectively defined as "critical illness brain syndrome" [3], "critical illness–associated cognitive dysfunction" [4], or "critical illness encephalopathy" [1]. This discussion is centered on two of the most common forms of acute brain dysfunction that are encountered in the ICU: coma and delirium.

Coma

Clinical descriptions of consciousness identify two interrelated domains of neurologic function: arousal or wakefulness, and awareness, often termed "the content of consciousness" [5]. Awareness, in turn, has many components, including perception, attention, memory, executive function, and motivation. The anatomic substrate of arousal is the ascending reticular activating system, a network of neurons extending from the pontine and midbrain tegmentum and projecting to the cerebral hemispheres through the thalamus [6,7]. The different components of awareness are linked to discrete neuronal networks that are distributed throughout the cerebral cortices [8].

Coma is characterized by a severe disruption in arousal and awareness. It is differentiated from transient states, such as syncope or concussion, by a duration of greater than 1 hour. Coma is a transitional state, which, in most cases, evolves toward recovery of consciousness, the vegetative or minimally conscious state, or brain death [9,10]. Plum and Posner [5] proposed a simple, four-part neurologic evaluation of comatose patients, including an assessment of the level of consciousness, brainstem function, motor activity, and respiratory pattern. Coma is characterized by absent or limited vocal or muscle activity and a severely reduced or abnormal response to noxious stimuli, an absence of sleep wake cycles, slowed electroencephalographic (EEG) activity, and decreased cerebral metabolism [9].

The level of consciousness has been described with terms such as somnolence, stupor, lethargy, and obtundation; however, these terms are not defined reliably in the literature, and should be discarded in favor of more objective scoring systems, such as the Glasgow Coma Scale (GCS) [11]. Notwithstanding, the GCS has limitations, including a low sensitivity to subtle changes in arousal; a failure to assess brainstem function; and the difficulty with obtaining a verbal score in patients who are endotracheally intubated, sedated, or aphasic. Alternative scoring systems that integrate brainstem findings include the Glasgow Liege Score [12] and the recently proposed Full Outline of UnResponsiveness (FOUR) score [13]. Additional scales have been developed to provide a more detailed description of cognitive function in patients who have consciousness disorders; however, the validity

and reliability of these scales, and their bedside usefulness, have not been established [14].

Coma is associated with structural or functional disruption of bilateral hemispheric or brainstem structures, inactivating key elements of the ascending reticular activating system. Common causes of coma include direct or primary cerebral disorders resulting from trauma, cerebrovascular disease, neuroinfectious or neuroinflammatory diseases, seizures, and brain tumors. Systemic alterations that are associated with coma include cardiopulmonary arrest, pharmacologic and toxic exposures, sepsis, severe metabolic and physiologic derangements, and endocrine insufficiency [5]. Several neurotransmitter systems have been implicated in the generation of consciousness, including cholinergic, glutamatergic, adrenergic, serotoninergic, and histaminergic neurons [15]. Pharmacologic agents, toxins, or metabolic processes that interfere with these neurotransmitters can impair arousal and attention.

Although coma is reported frequently in studies of patients who have primary neurologic or neurosurgical disorders, fewer reports have evaluated the epidemiology and impact of coma in the general ICU. Among survivors of cardiac arrest, 80% to 90% are comatose for varying lengths of time, and 5% to 30% are comatose at discharge [16]. In large-scale studies of critically ill patients receiving mechanical ventilation, 15% to 20% are comatose [17,18], and coma has been implicated in up to one quarter of patients who fail to separate from mechanical ventilation [19]. In a cohort of elderly patients (>65 years) admitted to the medical ICU, nearly one third were comatose on admission, and 8% subsequently developed coma [20]. In a study of sepsis-associated encephalopathy, 16% of patients who had sepsis were comatose (ie, GCS $\leq$ 8); the level of consciousness was linked closely to mortality [21]. Among 203 patients who had chronic critical illness and were admitted to a respiratory care unit, 61 (30%) were comatose [22].

Coma has prognostic significance in patients who have primary and secondary mechanisms of brain injury. Coma has been identified as a powerful predictor of death and functional outcomes in patients who have stroke [23,24], traumatic brain injury [11,25], or cardiac arrest [26,27]. Among 558 patients who were admitted to the ICU, coma was the strongest independent predictor of death and length of stay [28]. In a cohort of 15,973 medical and surgical ICU patients, admission GCS was a leading predictor of mortality [29]; of note, coma developing in the setting of sepsis was linked to worse survival than was posttraumatic coma [29]. The GCS is an integral component in several intensive care prognostic scoring systems [30–36].

Differential diagnosis of coma

Coma must be differentiated from brain death, the VS, minimally conscious state (MCS), akinetic mutism, pharmacologically induced states of decreased arousal, and the locked-in syndrome (LIS).

Brain death

Brain death represents a complete and irreversible loss of brain and brainstem function. It is recognized clinically by the abolition of consciousness, cranial nerve activity, motor reflexes, and spontaneous breathing [5,37]. Before a diagnosis of brain death can be made, conditions that can confound neurologic assessment must be ruled out, in particular physiologic or metabolic derangements, severe hypothermia (temperature $<32°C$), and recent exposure to toxic or pharmacologic agents that might impair consciousness or neuromuscular transmission. Although not necessary for the clinical diagnosis, the EEG in brain death is silent [38], and cerebral metabolism is absent [39]. In patients who meet criteria for brain death but are receiving organ-support therapies, cardiovascular activity, renal and hepatic function, and passive pulmonary gas exchange may be sustained for a limited time. It is widely accepted that a clinical diagnosis of brain death is necessary and sufficient to diagnose death of the organism; however, there are differences in diagnostic methodology between countries, states, and even institutions, and critical care providers should familiarize themselves with local policies and norms [37].

Vegetative state

In contrast to comatose patients in whom there is an absence of arousal and awareness, patients in a VS present with a global impairment in consciousness, in which awareness of self or of the environment is absent, but signs of arousal are retained [40]. Patients who are in a VS open their eyes spontaneously, but do not react in any meaningful way to environmental cues; in particular, they are unable to visually follow a moving person nor can they fixate on these objects or persons, and they do not follow any commands. The VS is the result of extensive damage to the cerebral cortex with relative sparing of the brainstem; its most frequent causes are traumatic brain injury and cardiac arrest. Emerging data from functional neuroimaging and electrophysiologic studies indicate that variable degrees of cortical activation may occur in patients who meet clinical criteria for the VS [41–43]. Patients who remain in a VS for longer than 1 month are classified as having a "persistent vegetative state" [44,45].

Minimally conscious state

Patients in a minimally conscious state (MCS) have a global alteration in consciousness with elements of arousal, but are differentiated from VS because they present intermittent evidence of self or environmental awareness [46]. The subject in an MCS might sporadically follow commands, attend to recognizable objects or voices, initiate meaningful speech, or engage in purposeful movement; however, these behaviors are never obtained in a reliable fashion. Like the VS, the MCS occurs in the setting of catastrophic hemispheric brain injury; however, recent investigations with functional

imaging and evoked potentials suggest that the MCS involves a lesser degree of cortical impairment than does the VS, perhaps as a result of preservation of corticocortical and corticothalamic circuits with activation of associative cortical regions [47–49]. The long-term outcomes of patients in an MCS have not been studied well; however, significant recovery of neurologic function has been reported [50].

Akinetic mutism

Typically, akinetic mutism is seen with injury to bilateral frontal lobes as might result from traumatic contusions or anterior cerebral artery vasospasm following aneurysmal subarachnoid hemorrhage. The result is a profound deficiency in executive function [51]. Patients in this state are unable to initiate movement or speech; they seem on the verge of initiating activity, yet this is never accomplished. Unlike patients in an MCS, patients who have akinetic mutism do not exhibit any motor or verbal response to verbal or noxious stimulus; unlike VS, they do not have spasticity or hyperreflexia, which suggests relative sparing of corticospinal fibers [52]. Neurologic recovery has been reported in patients who have akinetic mutism [53].

Pharmacologically induced coma

The treatment of neurologic emergencies, such as refractory status epilepticus or intractable intracranial hypertension, can involve the deliberate induction of a comalike state with sedative or anesthetic agents [54,55]. Agents that are used commonly for pharmacologically induced coma include barbiturates [56], propofol [57], and midazolam [58], all of which are responsible for a dramatic decrease in neuronal activity, with concomitant reductions in cerebral metabolism and cerebral blood flow. Pharmacologically induced coma can abolish virtually all clinical evidence of brain or brainstem activity, and confounds the clinician's ability to diagnose coma or even brain death.

Locked-in syndrome

The locked-in syndrome (LIS) 2006 is caused by focal injury to the ventral pons, which leads to quadriplegia and anarthria, but preserved arousal and awareness [59]. The most common etiologies include brainstem infarction or hemorrhage, multiple sclerosis, or central pontine myelinolysis. In its classic presentation, patients who have LIS can express themselves only by blinking and by vertical eye movements [60]. Alternative presentations may occur in patients who have injuries of the rostral pons and midbrain, in whom even eye movements are lost ("total LIS") [61]. States analogous to LIS may occur in patients who have Guillain-Barré syndrome and those receiving neuromuscular blocking drugs without appropriate sedation.

It is imperative to consider the possibility of LIS in patients who present acutely with an unexplained alteration in consciousness. If a total LIS is suspected based on the presence of midbrain or diencephalic injury, the diagnosis can be substantiated with the help of EEG or functional neuroimaging [9,60].

Management of coma

The acute onset of coma should be viewed as a life-threatening emergency that requires a swift and structured management approach incorporating concurrent and carefully prioritized resuscitative, diagnostic, and therapeutic efforts [10]. Initial resuscitation should assess and treat airway, breathing, and circulatory dysfunction; in the setting of trauma, the cervical spine should be immobilized. During and immediately following initial stabilization, attention should be directed to diagnosing and treating common and rapidly reversible metabolic and pharmacologic causes of coma, including hypoglycemia and intoxication with opioids or benzodiazepines; systemic derangements, such as hypertension, hypotension, hypoxemia, anemia, acidosis, hypothermia and hyperthermia, should be identified and corrective measures should be instituted.

Resuscitative measures should be accompanied by a focused diagnostic evaluation to identify the underlying etiology or precipitating factor leading to coma. This includes a structured neurologic assessment, serum chemistries and complete blood count, arterial blood gas, and toxicology screens [10]. In nearly all instances of acute coma, an emergent brain CT is mandated. CT has high sensitivity for acute intracranial hemorrhage, hydrocephalus, and brain edema, and moderate sensitivity for abscess or tumor. Frequently, CT is unrevealing in hyperacute ischemic stroke and toxic–metabolic or hypoxic–ischemic coma. Moreover, some investigators have questioned the value of CT in the diagnostic work-up of comatose patients in the ICU who do not have focal neurologic deficits or seizures [62].

Patients who have unexplained coma and normal or equivocal CT findings should undergo MRI, which detects acute ischemic stroke, cerebral venous sinus thrombosis, brain edema, brain tumor, inflammatory processes, cerebral abscess, and diffuse axonal injury. Studies in patients in the ICU who have sepsis or after cardiac surgery suggested that MRI can detect lesions that are not suspected by clinical examination or CT [63,64]. When central nervous system infection or inflammation is suspected, or if a diagnosis of intracranial aneurysm rupture is being entertained and CT is unrevealing, lumbar puncture should be obtained, although the diagnostic yield for infectious causes is low in patients who do not have immune compromise and have not had a neurosurgical procedure [65]. Finally, an EEG should be sought if clinical examination is suggestive of ongoing seizure activity or when occult seizure activity—in particular, nonconvulsive status epilepticus—is suspected, as it may be diagnosed in up to 20% of patients in the ICU who have unexplained alterations in consciousness [66,67].

Delirium

Delirium is a global disturbance in cognitive function that is characterized by impaired attention associated with changes in the level of consciousness, disorganized thinking, and a fluctuating course; contrary to coma,

elements of arousal and awareness are retained [68–70]. Delirium frequently precedes or follows comatose states, and is linked to the same types of global cerebral or systemic physiologic and metabolic insults that have been associated with coma [5,69]. Alternatively, delirium has been associated with focal brain injury involving, in particular, frontal, right parietal, and basal ganglia structures [71,72].

Diagnosis

Historically, accounts of delirium in the medical and lay press have been inconsistent, which explains some of the misconceptions regarding this syndrome that persist to this day [69]. Delirium may be unrecognized or misdiagnosed as another disorder, such as depression or dementia, in up to 84% of cases [73]. In the ICU, failure to diagnose delirium may occur because of infrequent neurologic assessments, the fluctuating nature of delirium, and a perception that alterations in mental status are a normal response to acute illness [74].

A consensus has emerged around the clinical definition of delirium proposed in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) of the American Psychiatric Association [70]. The *DSM* criteria for delirium include a disturbance of consciousness with impaired attention; a change in cognitive function (eg, memory impairment, disorientation, or language disturbance) or a perceptual disturbance; the disturbance develops over a short period of time (hours to days) and fluctuates; and the history, physical examination, or laboratory data suggest that the abnormalities are caused by a general medical condition and are not better accounted for by a preexisting dementia [70]. Delirious patients are classified into two behavioral subtypes: "hyperactive delirium," in which patients are agitated, loud, combative, and likely to inflict significant harm on themselves or others, and "hypoactive delirium," in which they are withdrawn and have minimal interaction with health providers or family. The relative preponderance, risk factors, and outcomes of these subtypes are not well understood [75].

Much effort has been devoted to creating objective scoring systems for detecting and monitoring delirium clinically in a reliable fashion. Nearly all of these scores are derived from the criteria set forth in the *DSM* [70]. To be clinically useful, bedside scoring systems need to make allowances for characteristics of critically ill patients that increase the challenge of cognitive assessment (eg, endotracheal intubation, mechanical ventilation). Delirium scoring systems that were developed specifically for the ICU include the Confusion Assessment Method for the ICU [76], the ICU Delirium Screening Checklist [77], and the Delirium Detection Score [78].

Epidemiology and outcome

Delirium occurs in up to 30% of patients who are admitted to general medical wards [73,79] and in 10% to 60% of surgical populations [80,81], with particularly high rates observed in patients who sustained hip fracture

or underwent cardiac surgery [82,83]. The highest rates of delirium are reported in patients who are admitted to the ICU, with prevalences of 50% to 90%, depending on the type of delirium scoring instrument used and the population studied [17,76,77]. Delirium in the ICU has been associated with an increased risk for death, prolonged mechanical ventilation, and longer duration of ICU and hospital stay [17,84–87].

Risk factors and pathogenesis

Delirium generally develops in a susceptible patient who is exposed to one or several precipitating factors [88]. Important predisposing factors for delirium include age, male gender, cognitive impairment or dementia, poor functional status, malnutrition, substance or ethanol use, and coexisting medical conditions [17,20,81,89,90]. Precipitating factors include primary neurologic diseases, infection, shock, hypoxia, electrolyte abnormalities, surgery, exposure to a variety of pharmacologic agents, in particular opioids and benzodiazepines, substance withdrawal, mechanical ventilation, bladder and central venous catheterization, restraints, and sleep deprivation [17,20,84,85,90].

The neural mechanisms of delirium are not well explained [91]. Research indicates that delirium is associated with a broad range of pathologic events, including neurotransmitter imbalances, inflammation, specific neuroanatomic lesion patterns, and electrophysiologic changes [1,4,92]. Taken together, these data are consistent with a view of delirium as a syndrome of global cerebral insufficiency analogous to organ system failures observed in sites remote from the brain [68,91,93,94].

The term "septic encephalopathy" has been used to characterize patients who have sepsis and an alteration in mental status that is associated with diffuse slowing on EEG and normal cerebrospinal fluid and neuroimaging [21,95–97]. This form of encephalopathy develops in 23% to 71% of patients who have sepsis, and it is associated with a significantly increased risk for death [97]. Brain histopathology from patients who died with sepsis demonstrates an array of injury mechanisms, including disruption of the blood–brain barrier, cerebral edema, tissue infarction, hemorrhage, vascular thrombosis, microabscesses, and neuronal cell death [98–100]. Recently developed MRI techniques, in particular diffusion-weighted imaging and MR spectroscopy, may allow the in vivo identification of cerebral injury that is not detectable with CT [64,101].

Management of delirium

The management of delirium includes prevention strategies, a thorough review of risk factors, and pharmacologic therapy. Prevention strategies have been proposed as "multi-component" care bundles promoting patient reorientation; sleep; noise reduction; physical therapy and mobilization; avoidance of, or early removal of, catheters and physical restraints; and provision of eyeglasses and hearing aids. Prevention bundles have been associated

with a significantly reduced incidence of delirium [102]; however, the feasibility and efficacy of such measures in the ICU have not been determined.

The cornerstone of delirium management is the identification of predisposing and precipitating factors. Physiologic, metabolic, and pharmacologic precipitants should be investigated aggressively, and, whenever possible, treated or corrected. Common precipitants of delirium in the ICU include primary brain injury, exposure to sedative and analgesic medications, drugs with anticholinergic properties, substance withdrawal, sepsis, respiratory failure, shock, mechanical ventilation, intravascular catheters, and sleep deprivation.

Pharmacologic therapy of delirium is indicated when there is a concern for patient safety (eg, hyperactive delirium), in patients who remain delirious after elimination of precipitants, and in cases where precipitating factors are unknown or cannot be removed promptly (eg, mechanical ventilation). The antipsychotic agent haloperidol demonstrated efficacy in the treatment of delirium in patients who were not in the ICU [103], and it has been advocated as the agent of choice for the pharmacologic management of delirium in the ICU [104]. No placebo-controlled randomized trial has evaluated the efficacy and safety of antipsychotic agents in the ICU. In a retrospective study of 989 mechanically ventilated patients, haloperidol was associated with decreased hospital mortality (no information was given on the incidence of delirium in this population and the reasons why haloperidol was administered) [105]. In a randomized head-to-head comparison that was undertaken in 73 patients, haloperidol and olanzapine were safe and were associated with comparable declines in the ICU Delirium Screening Checklist [106]. A phase II randomized, placebo-controlled trial is evaluating haloperidol and ziprasidone to prevent delirium in mechanically ventilated patients in the surgical or medical ICU [107]. Benzodiazepines may be helpful for treating or preventing delirium that is associated with alcohol and sedative withdrawal; however, in other types of delirium, these agents have been associated with exacerbation and prolongation of symptoms [103].

Cognitive dysfunction after critical illness

In recent years, considerable evidence has accrued to indicate an association between critical illness and long-term cognitive impairment [108]. These data have emerged as increasing attention is directed to characterizing the relationship between critical illness and chronic morbidity [109,110]. The importance of understanding long-term outcomes is underscored in longitudinal studies that showed a decline in hospital mortality of critical illnesses [111,112], as well as randomized trials that demonstrated increased survival with targeted therapeutic interventions for patients who have sepsis and acute lung injury [113–115]. Observational prospective and retrospective cohorts have documented decreased survival, functional outcome, and quality of life in subjects who were evaluated months and years following critical illness [116–118]. Collectively, these results imply that there is a growing

population of ICU survivors, many of whom have chronic and invalidating sequelae that remain poorly characterized, in particular from a mechanistic viewpoint [109,110,119].

Diagnosis

Cognitive function can be evaluated with the help of simple screening tools, such as the Mini Mental State Examination [120], or with more sophisticated neuropsychologic batteries that were designed to assess specific cognitive domains separately, including visual memory, verbal memory, verbal fluency, attention, executive function, visuospatial performance, and fine motor skills [121]. Although the rational interpretation and comparison of neuropsychologic test data are a matter of considerable debate, a widely accepted methodology is to compare test scores before and after a specific event, or to compare them with a population norm.

It has been suggested that cognitive dysfunction is overlooked, underrecognized, and misdiagnosed in the ICU and subsequently [108]. Many providers in the ICU and in rehabilitation medicine are not familiar with cognitive assessment, and many of the abnormalities that are identified using neuropsychologic testing may be subtle and undetectable by standard medical history and physical examination techniques. Lastly, cognitive impairments may be erroneously attributed to other processes, such as concurrent psychoactive medication use, substance use, or psychiatric disorders, in particular, depression [122].

Epidemiology and outcome

Cognitive outcomes following critical illness have been reported in a small number of prospective and retrospective cohort studies [122–128]. These studies focused on survivors of acute respiratory distress syndrome (ARDS) [123–125,128], patients in the medical ICU [122], and patients in the general ICU [126,127]. Twenty-five to 78% of patients who were enrolled in these studies had evidence of cognitive impairment when evaluated with neuropsychologic tests 6 to 24 months following ICU or hospital discharge. Variability in reported prevalences may reflect differences in study design (prospective versus retrospective), neuropsychologic tests administered, time to follow-up, and populations studied.

In a landmark report, Hopkins and colleagues [124] reported a reduction in performance in one or more cognitive domains in 43 of 55 (78%) ARDS patients who were assessed at 1 year. In a separate cohort of 74 ARDS survivors, the prevalence of cognitive impairment was 46% at 1 year and 47% at 2 years [123]. In a retrospective analysis of ARDS survivors who were assessed a median of 6 years after ICU discharge, Rothenhausler and colleagues [125] found cognitive impairment in 11 of 46 subjects (24%).

Similar observations have been made in other subsets of patients who spent time in the ICU. Jackson and colleagues [122] found cognitive

impairment in 11 of 34 (32%) survivors of the medical ICU who were interviewed at 6 months; they also noted a higher incidence of depression and lower premorbid educational status among cognitively impaired patients compared with nonimpaired patients. In a cohort of 51 patients who were discharged from a medical/surgical ICU, Sukantarat and colleagues [126] noted cognitive impairment in 35% at 3 months, with substantially improved test scores when the patients were re-evaluated 6 months later. Finally, a recent report on 30 patients in the ICU who did not have delirium and who were assessed at 2 months indicated impairments in memory tests in 25% and in problem-solving tests in 50% [127].

It is helpful to consider post-ICU cognitive impairment within a framework of indicators of long-term physical, mental, social, and financial functioning [129]. Psychiatric symptoms are reported in 15% to 50% of patients following critical illness. In a seminal report on a cohort of ARDS patients, 51% were not working when they were evaluated at 1 year, and quality of life—as assessed by the 36-item Short-Form General Health Survey—was significantly less than that in an age- and gender-matched normative population [117]. A systematic review found that decreased quality of life was reported consistently across studies of survivors of ARDS [118]. Although it is believed that relationships exists between post-ICU cognitive impairment and psychiatric morbidity, decreased social interaction, and quality of life, data to support these relationships are scarce [125,126].

Etiology and pathogenesis

The pathogenesis of cognitive sequelae following critical illness is largely unexplained. According to one view, impaired cognition might represent a neurodegenerative process that occurs in vulnerable hosts (eg, preexisting neurologic or cognitive dysfunction) who are exposed to one or several factors that are likely to cause brain damage during critical illness. Such factors might reasonably include hypoxemia, hypotension, anemia, fever, hyperglycemia, systemic inflammation, sepsis, various pharmacologic agents, renal failure, and liver failure; however, data to support this hypothesis are scarce [4,108]. One cohort study that compared characteristics of patients who did and did not have post-ICU cognitive impairment found no difference between groups regarding severity of illness, organ dysfunction, admission diagnosis, and delirium [122].

Two interrelated lines of evidence provide important clues to understanding the mechanisms that underlie the long-term cognitive sequelae of critical illness. First, there is a relationship between delirium and cognitive dysfunction, although the precise nature of this relationship is far from well understood [88]. Dementia or poor premorbid cognitive status is identified consistently as a leading risk factor for delirium [17,81]. Delirium, in turn, may substantially increase the risk for long-term cognitive deterioration. In cohorts of elderly medical inpatients who were not in the ICU, subjects

who were diagnosed with delirium during their hospitalization were significantly more likely to develop subsequent dementia and had higher mortality [130,131]. Although such an association has not been demonstrated in ICU patients, it remains an appealing and testable hypothesis [132]. Second, it has been suggested that cognitive dysfunction may result from occult brain injury. Histopathologic and neuroimaging studies suggest specific patterns of brain injury in association with events such as severe hypoxemia [133–135], sepsis [64,98,99,136], or acute lung injury [137]. A brain CT study of ARDS survivors indicated significant brain atrophy and hydrocephalus ex vacuo when compared with matched control subjects [138]. Taken together, these data suggest a theoretical framework in which delirium or encephalopathy are clinical markers of a brain injury process that is manifested subsequently as cognitive impairment, and therapies that are aimed at preventing or treating delirium might have an impact on cognitive dysfunction.

Summary

Recent research highlights a spectrum of cerebral dysfunction acquired in critical illness, which may take the form of coma, other states of impaired consciousness, delirium, or cognitive impairment. These disorders are common and may be associated with a deterioration in the physical and mental well-being of survivors of the ICU. Although advances have been made in recognizing brain dysfunction in critical illness and in delineating its impact, fundamental questions persist regarding its etiology, pathogenesis, and natural history. These questions need to be addressed with a combination of basic science, translational and clinical approaches.

Large-scale cohort studies are necessary to provide insight into the complex relationships between post-ICU cognitive impairment, events occurring in the ICU, and premorbid function. The neural substrates of delirium should be explored using available functional and metabolic brain imaging protocols. There is a need to elucidate brain injury mechanisms that are related to systemic insults, such as hypoxemia, shock, inflammation, and sepsis. The postulated toxic effects of commonly administered drugs (eg, sedatives and analgesics) should be investigated using experimental and epidemiologic paradigms. Results from these studies will provide a mechanistic framework for designing effective prevention and treatment strategies to decrease the long-term burden of critical illness.

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