Neurocognetive Dysfunction in Critically Ill Patients after Long-Term Illness in ICU

Essay
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Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABG	Arterial blood gases
APA	American psychiatric association
APOE	ApolipoprotienE
BUN	blood urea nitrogen
CAM-ICU	Confusion Assessment Method in intensive care unit
CBC	Complete blood count
CNS	Central nervous system
DDS	Delirium detection score
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiography
EEG	Electroencephalography
EPS	Extra pyramidal symptoms
GABA	Gamma amino butyric acid
ICD ١٠:	International Classification of Diseases
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
LAT١	Large neutral amino acid transporter type١
LOS	Length of stay
NREM:	None rapid eye movement
Nu-DESC	Nursing Delirium Screening Scale
POD	Post operative delirium
RASS	Richmond Agitation-Sedation Scale

REM:	Rapid eye movement
SATs	Spontaneous awakening trials
SBTs	Spontaneous breathing trials
SCCM	Society of Critical Care Medicine
SSD	Subsyndromal delirium
UTIs	Urinary tract infections

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Introduction

Until relatively recently, critical care practitioners have focused on the survival of their patients and not on long-term outcomes. The incidence of chronic neurocognitive dysfunction has been underestimated and underreported, and only recently has it been studied in critically ill patients. However, neurocognitive outcomes have been the subject of extensive investigation in other medical populations (e.g., patients undergoing coronary artery bypass grafting) for many years ***(Hopkins and Jackson, ٢٠٠٦)***.

Critical illness can lead to significant neurocognitive impairment. The neurocognitive impairment persist for months and years, and may have important consequences for quality of life, the ability to return to work, overall functional ability, and substantial economic costs. The mechanisms of the neurocognitive impairment are not fully understood but likely include hypoxia, glucose dysregulation, metabolic derangements, inflammation, and the effects of sedatives and narcotics among other factors. The contribution of these factors may be particularly significant in patients with preexisting vulnerabilities for the development of cognitive impairments ***(Hopkins and Jackson, ٢٠٠٦)***.

Critical illness often results in multiple system organ dysfunctions, including neurologic dysfunction, and is associated with poor neurologic outcomes. Investigation of the effects of critical illness on neurologic dysfunction has been relatively neglected compared to the effects on other organ systems ***(Raja et al.,)***.

Delirium is a frequent phenomenon in critically ill patient populations there is some evidence that those who have delirium in the intensive care unit (ICU) are at greater risk for cognitive dysfunction in the years to come ***(Jackson et al.,***).

Many different terms have been used to describe this syndrome of cognitive impairment in critically ill patients, including ICU psychosis, ICU syndrome, acute confusional state, encephalopathy, and acute brain failure so the critical care literature has recently conformed to the recommendations of The American Psychiatric Association (APA) and other experts that the term 'delirium' be used uniformly to describe this syndrome of brain dysfunction ***(Ely et al.,*** **).**

Multiple risk factors can affect markedly the patient in the ICU leading to disturbance of the level of consciousness and deterioration of the general state. (e.g., hypoxemia Depression and anxiety) are known to exacerbate the manifestations of cognitive impairment ***(Ely et al.*** ***b)***.

Hopkins and Jackson (٢٠٠٦) also have reported that the cumulative dose of some sedatives may contribute to neurocognitive impairments and affect sequelae in critically ill patients. The etiology of neurocognitive impairment is undoubtedly multifactorial and is the subject of ongoing discussion and research.

Treatment of delirium in the ICU is a largely unstudied territory. Once delirium is identified in ICU patients, management should focus upon identifying potential precipitating factors, providing supportive care, and preventing further complications ***(Inouye,*** ٢٠٠٦***a)***. Once life-

threatening complications such as hypoxemia, hypoperfusion, metabolic derangements, severe pain, and infection have been excluded, attention should turn to the patient's medications and environment in an attempt to minimize any factor that might exacerbate delirium. Attention should be also directed at reorientation, mobilization, provision of family support and of hearing or visual aids, patient's comfort, including proper positioning and removal of unnecessary catheters, and encouragement of a normal sleep-wake cycle.

Small studies report the improvement of sleep among critically ill patients who were randomized to receive a ٦-minute back massage or to receive therapeutic touch by a specially trained nurse or receiving music therapy in their recovery room ***(Cox and Hayes,*** ***)***.

Pharmacologic therapies to treat the symptoms of delirium should be reserved for patients demonstrating agitation with risk for self-harm, including pulling at catheters or endotracheal tubes, and should occur only after nonpharmacologic treatment has been initiated.

If medication is to be used, choices include antipsychotics such as haloperidol or resperidone, benzodiazepines, or antidepressants with hypnotic effects ***(Milbrandt et al.,*** ***)***.

Aim of the Work

The aim of this work is to review current literature related to neurocognitive dysfunction in critically ill patients after long-term admission in the ICU including pathophysiology, risk factors, clinical presentation, prevention and management.

Pathophysiological Considerations for Neurocognitive Dysfunction after Long-Term ICU Admission(Delirium)

For many aging people in good physical condition who yield to an acute illness, cognitive decline is the main threat to their ability to recover and enjoy their favorite activities; for those whose physical activities were already limited, cognitive decline is a major additional threat to quality of life ***(Stern and Carstensen,*** ***).***

Mounting evidence shows that many survivors of care in the ICU experience months and maybe years of cognitive impairment equating to mild and in some cases severe dementia. In the past few years, research has shown that the development of delirium during the initial ICU admission is one of the strongest predictors of prolonged cognitive impairment and mortality ***(Jackson et al.,*** ***).***

Hence, diagnosis, management, and interventions aimed at reducing the acute neurocognitive effects of critical illness are of great importance. Unfortunately, more than ٢٥ terms are used in the literature to refer to delirium, such as subacute befuddlement, ICU psychosis, acute brain dysfunction, encephalopathy of critical illness, and toxic confusional state. Others simply refer to delirium as confusion or neurologic impairment. ***(Hopkins et al.,*** ***).***

Additionally, the development of delirium often goes unnoticed in the ICU because we think of it as 'part of the scenery' or an expected and inconsequential outcome of mechanical ventilation and other therapies necessary to save lives in the ICU ***(Ely et al.,*** ***b).***

What is Delirium?

Delirium is defined in the APA, Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV as a disturbance of consciousness and cognition that develops over a short period of time (hours to days) and fluctuates over time ***(Justic,*** ***).***

Many different terms have been used to describe this syndrome of cognitive impairment in critically ill patients, including ICU psychosis, ICU syndrome, acute confusional state, encephalopathy, and acute brain failure so the critical care literature has recently conformed to the recommendations of The American Psychiatric Association (APA) and other experts that the term 'delirium' be used uniformly to describe this syndrome of brain dysfunction ***(Ely et al.,*** ***).***

Cost of Problem

Among medical ICU patients, delirium is associated with multiple complications and adverse outcomes, including self-extubation and removal of catheters, failed extubation, prolonged hospital stay, increased health care costs, and increased mortality ***(Milbrandt et al.,*** ***).***

Ely and coworkers (***a)*** studied ٢٧٥ mechanically ventilated medical ICU patients and determined that delirium was associated with a threefold increase in risk for ٦-month mortality after adjusting for age, severity of illness, co-morbidities, coma, and exposure to psychoactive medications. The association between ICU delirium and increased mortality was subsequently confirmed in two other cohort studies.

Delirium may be a predictor of long-term cognitive impairment in survivors of critical illness. ***Jackson et al. (٢٠٠٧)*** reviewed nine prospective studies that included nearly ١،٩٠٠ non-ICU patients who were hospitalized

for medical and surgical treatments and reported that delirium was associated with cognitive decline over ١ to ٣ years after hospital discharge. The relationship between ICU delirium and long-term cognitive impairment is the subject of ongoing investigations, but preliminary data suggest that the association is significant. Recently, this association was examined in patients who were mechanically ventilated for acute respiratory failure in medical ICUs. Prolonged periods of ICU delirium were associated with an increased risk for long-term cognitive impairment at ٣ months post-discharge ***(Jackson et al., ٢٠٠٧).***

To understand delirium and its long-term consequences, it is necessary to explain acute brain dysfunction at the neurologic level. Delirium may be caused by widespread brain dysfunction rather than localized disruption in many neurological diseases ***(Yokota et al., ~ ~ ~).***

Further evidence suggests that this widespread brain dysfunction may lead to cell death in the central nervous system (CNS) and some functional neuroimaging studies reported that neuronal atrophy could be related to delirium ***(Kitabayashi et al., ٢٠٠٧).***

The definite pathophysiology of delirium is poorly understood but multiple promising hypotheses are the subject of ongoing research. Unfortunately, the majority of studies supporting these hypotheses were conducted in non-ICU patients. Thus, significant research is needed to elucidate the complex interplay between the mechanisms of critical illness and delirium ***(Kitabayashi et al., ٢٠٠٧).***

Most investigators agree that delirium seems to be a functional rather than a structural lesion. Electroencephalographic (EEG) studies show global

functional derangements in patients with delirium, characterized by generalized slowing of cortical background activity with the appearance of delta and theta activity. Neuroimaging studies coupled with cognitive testing demonstrate a generalized disruption in higher cortical function, with dysfunction in the prefrontal cortex, frontal and temproparietal cortex, fusiform cortex, lingual gyri, subcortical structures, thalamus, and basal ganglia. The leading hypotheses for the pathogenesis of delirium focus on the roles of neurotransmission and inflammation ***(Kishi et al.,*** ***).***

In some circumstances, such as infection or cancer, delirium may be mediated through cytokines, such as interleukin-٢ and tumor necrosis factor. Although delirium has long been considered a transient syndrome, several of these basic mechanisms may not be completely reversible, particularly those resulting in hypoxic damage. Acute stress with high levels of cortisol may also contribute to delirium. The dose and duration of the noxious insult, along with the degree of vulnerability of the patient, also may exert great influence on the ultimate reversibility of delirium ***(Kitabayashi et al., ٢٠٠٧).***

The following are the most suspected mechanisms that can explain pathophysiology of delirium.

Neurotransmitter Imbalance

Delirium is theorized to be a neurobehavioral manifestation of imbalances in the synthesis, release, and inactivation of neurotransmitters that normally control cognitive function, behavior, and mood ***(Trzepacz,*** ***).***

Derangements of multiple neurotransmitter systems have been implicated in the pathophysiology of delirium, with the greatest focus being given to dopamine and acetylcholine. These neurotransmitters work in opposition, with dopamine increasing and acetylcholine decreasing neuronal excitability. An imbalance in one or both of these neurotransmitters results in

neuronal instability and unpredictable neurotransmission. Specifically, an excess of dopamine or depletion of acetylcholine have been associated with delirium ***(Flacker et al.,*** ***)***.

The most widely postulated mechanism for delirium is the failure of cholinergic transmission. Evidence supporting this hypothesis includes the frequent association of anticholinergic drugs with delirium, the reversal of delirium with procholinergic drugs such as physostigmine, the increased levels of serum anticholinergic activity in some delirious patients, and the benefit of cholinesterase inhibitors in some cases of delirium. Other neurotransmitter systems, such as dopamine, serotonin, norepinephrine, and γ-aminobutyric acid, may also play a role in delirium, but the evidence is less well developed ***(Trzepacz,*** ***).***

The next figure ١ explains this relationship between different neurotransmitters imbalance and the occurrence of multiple neurocognitive dysfunctions.

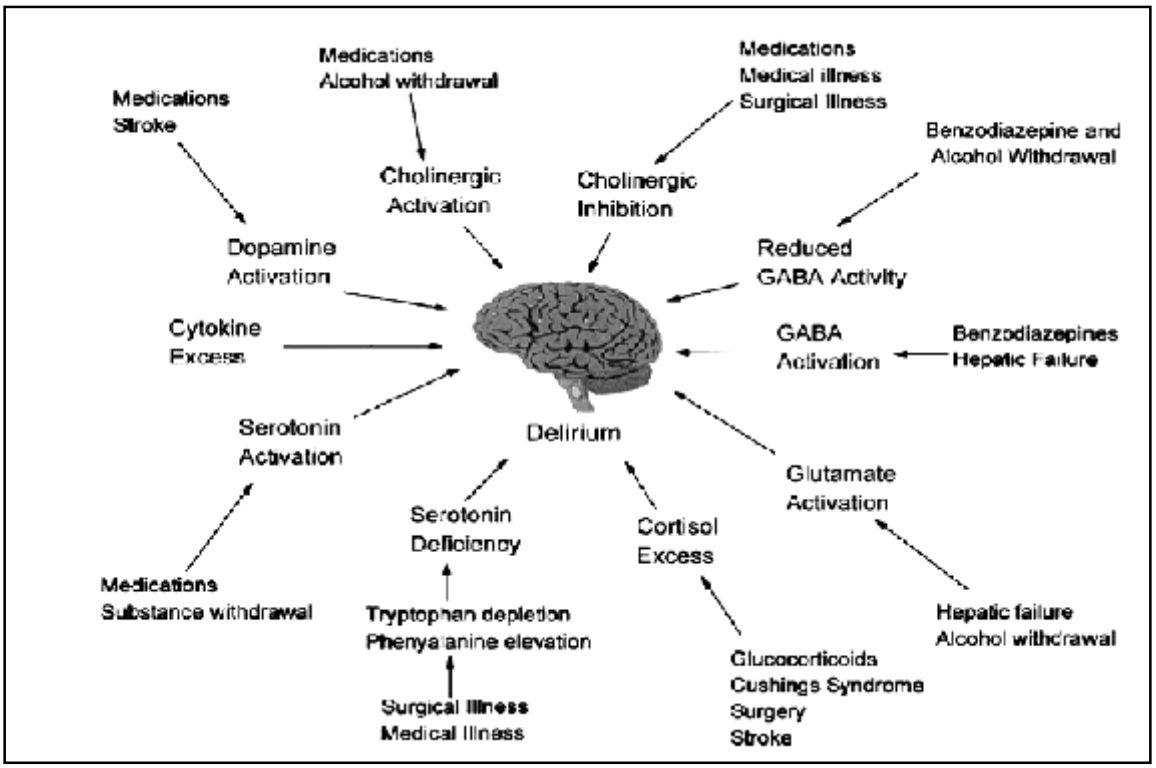

Figure ١. Neurotransmitters and biomarkers of delirium. Adapted from ***Flacker et al.*** ***( ).***

Inflammation

Inflammation plays a significant role in the dysfunction of multiple organs caused by critical illness and inflammatory abnormalities induced by endotoxins and cytokines probably contribute to the development of ICU delirium ***(Marshall,).***

Inflammatory mediators produced during critical illness (for example, tumor necrosis factor-α, interleukin-١, and other cytokines and chemokines) initiate a cascade of endothelial damage, thrombin formation, and microvascular compromise ***(Wheeler and Bernard).***