Delirium in the Critically Ill Patients

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13.1 Delirium Terminology

The term delirium derives from the Latin verb "delirare," which literally means "to go out of the groove." In fact, "de" means to be away and "lira" means furrow, giving the idea of a maniac plowing a field with no rationale plan. The first report of a disease similar to delirium is the one given by the ancient Greek physician and philosopher Hippocrates (460 B.C–371 B.C), who introduced the word "phrenitis" to describe a disease characterized by fluctuating disorientation and agitation. Nevertheless, it is with Celsus and other Roman writers that the term delirium was used interchangeably with the word "phrenitis," to indicate a disease-associated temporary change in mental status characterized by agitation, and the word "lethargus" in case of confusion associated with drowsiness. Nowadays, the term delirium is still underused in clinical settings. Instead, terms such as ICU psychosis, ICU syndrome, acute confusional state, septic encephalopathy, acute brain failure, depression, dementia, etc., have often been used in ICU as synonyms, frequently meaning very different entities [1]. This confusion in terminology could partially be responsible for the low detection rate of delirium among ICU physicians, who recognize less than half of the cases of this condition [2].

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13.2 Defining and Identifying Delirium

Early diagnosis of delirium is of paramount importance [3–7]. Unfortunately, there are no instrumental diagnostic means to detect delirium, which therefore remains a clinical diagnosis. Delirium is not a disease but a syndrome with a wide spectrum of possible aetiologies [8]. Its presentation may also be variable. In fact, it may present itself in hyperactive, hypoactive, or mixed forms. Although it is a common belief that the hyperactive—characterized by agitation, restlessness, and emotional liability—is the most frequent presentation of delirium, this is not true since it accounts for just 1.6% of the cases. Instead, hypoactive delirium—characterized by decreased responsiveness, withdrawal, and apathy—and mixed forms are far more frequent, accounting for 43.5% and 54.1%, respectively [9]. The prognosis seems to be worse with hypoactive delirium, possibly due to relative underdiagnosis and consequently delayed treatment [10]. In addition, there is a particular type, the so-called subsyndromal delirium, which presents one or more symptoms of delirium that never progresses to a full diagnosis. It is associated anyway with a worse outcome [11].

Delirium presents an acute or subacute onset of altered cognition or a disturbance in perception that is not better attributable to a preexisting dementia. It typically involves a reduced capability of focusing and maintaining attention and may or may not include delusions [12]. Reference standards for the diagnosis of delirium are the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) [13] and the tenth revision of the *International Statistical Classification of Diseases and Related Health Problems* [14]. However, these diagnostic criteria need extensive training to be applied in clinical practice [15]. In fact, ICU staff typically do not recognize delirium in almost three quarters of patients who have this condition. Instead, proper screening by trained nurses were able to identify delirium in up to 64% of patients, previously judged to be delirious by a psychiatrist, a geriatrician, or a neurologist [16].

In order to facilitate the diagnosis of delirium by non-psychiatrists, some different tools have been developed. In particular, two scales are useful and commonly utilized in the intensive care unit setting: the Intensive Care Delirium Screening Checklist (ICDSC) [17] and the Confusion Assessment Method for the ICU (CAM-ICU) [18] (Table 13.1). Although such scales are fundamental in objectively diagnosing delirium for research purposes, their sensitivity is a matter of debate. Some studies have shown a high sensitivity when such assessments were performed by bedside nurses [19], whereas other studies have shown conflicting results [20]. Used without a sedation scale, both the scales do not differentiate hyperactive from hypoactive delirium and do not quantify the relative importance of individual elements. Moreover, these tools identify delirium the presence or the absence of delirium, although it is clear the severity of delirium can differ. Despite these limitations, the CAM-ICU and ICDSC are currently the two accepted methods for identifying delirium in ICU [21].

Table 13.1 Scoring systems for the diagnosis of delirium in critically ill patients

System, Scoring Method, and Criteria Confusion Assessment Method for the ICU (CAM-ICU)

1. An acute change from mental status at base line or fluctuating mental status during the past 24 hr

and

2. Inattention

Evaluated by an Attention Screening Examination (ASE):

1: AUDITORY (pt. must squeeze the operator hand when a random letter A is pronounced ex. SAVEHAART)

2: VISUAL (5 pictures among 10 are the same: pt. must recognize it)

Test is positive if more than two errors

and

4. Disorganized thinking

Asking 4 yes or no questions having the patient follow a simple command. Positive if more than 1 error

or

3. Altered level of consciousness

Positive if RASS ≠ 0

= DELIRIUM

13.3 Relevance of the Problem

As showed by the American Association of Retired Persons, delirium is one of six leading causes of injuries associated with hospitalization in patients over 65 years of age [22]. The incidence of delirium is difficult to determine. In ICU, 20–50% of lower severity patients or those not receiving mechanical ventilation experience at least one episode of delirium during their stay. In those receiving mechanical ventilation, the incidence increases, reaching 80% [18]. Populations with variable severity of illness and under-recognition of the syndrome can in part explain this broad range in incidence figures [23, 24].

Delirium is often seen as a temporary attenuation of brain function, usually followed by a full remission. However, strong evidence exists that delirium augments risk of intubation by three times and predicts additional ten days in the hospital, each day of delirium increasing the risk of a prolonged hospital stay by 20% [25]. Similarly, Salluh et al. [26], found that, even after correcting for variables such as age, sex and Apache II, critically ill patients with delirium had an increased mean length of stay and increased mean duration of mechanical ventilation (almost 2 days longer than patients without delirium). In addition, delirium is associated with a higher ICU and in-hospital mortality in both the short term and the long term. As demonstrated by Ely et al. [27] in mechanical ventilated patients, the probability of survival at 6 months shows a threefold decrease in those patients who developed

delirium. In addition, researchers found an increased risk of death after delirium in different postoperative populations, in elective and emergency surgery [28].

As regards cognitive sequelae, patients who manifest delirium during hospitalization are at higher risk of developing short-term (months) and long-term (>12 months) cognitive impairment, with memory, attention, and executive function problems [29–31]. Moreover, the duration of delirium is directly related to the development of cognitive impairment [29, 32]. Some investigators found an increased incidence of dementia up to 5 years after postoperative delirium (POD) [33]. In addition, delirium has been associated with post-traumatic stress disorder 3 months after surgery [34]. In addition, these patients have an increased level of care dependency or limitations in basic activities of daily living up to 12 months, which in turn increases their risk of institutionalization and decreases their quality of life [4, 6, 35–40]. Unsurprisingly, this condition is responsible for an increase in hospital and ICU costs [41]. From what we discussed above, it is evident that delirium in the critically ill imposes a large burden on individuals and society. Therefore, monitoring for delirium in ICU prevention and treatment of this condition become fundamental issues.

13.4 Risk Factors

The risk of developing delirium can be seen as the product of predisposing and precipitating factors, the first ones being those related to the patient (i.e., intrinsic vulnerability) and the second those which can act as triggers [42]. Although predisposing factors are present before ICU admission and are difficult to modify, precipitating factors occur during the course of critical illness. They may involve factors of the acute illness itself or be iatrogenic; these latter are potentially modifiable by preventive or therapeutic intervention.

With regard to predisposing factors, in many trials advanced age resulted in an increased risk of delirium [43–49]. However, although chronological age plays a role in predisposing to delirium, it probably acts as a surrogate variable for the accumulation of age-related risk factors that are differentially expressed among individuals. It is almost certainly the sum of these risk factors that is most important in determining the probability of delirium [50]. Another factor that strongly predisposes to delirium in hospitalized patients is alcohol abuse regardless of other existing conditions [51]. Comorbidities, such as respiratory, cerebrovascular including stroke, cardiovascular, and peripheral vascular diseases, diabetes, anemia, Parkinson's disease, depression, chronic pain and anxiety disorders [37, 52, 53], vision or hearing impairment, severity of illness on admission, smoking history, and drug use may also predispose patients to delirium [28, 35]. In particular, in the case of "multimorbidity," i.e., a situation in which clinical patterns, evolution, and treatment become more complicated than the simple sum of the different illnesses, the capability to cope with stress is reduced and global vulnerability, including the risk for delirium [50], is increased.

Functional status, often regarded as the sixth vital sign, is defined as the sum of capabilities required (including social and cognitive functions) to perform daily activities such as dressing, cooking, washing, taking care of oneself, etc. [54]. Recently, many studies have shown an association of poor functional status with a series of postoperative complications such as wound infection and increased mortality, including delirium [40, 55]. The term "frailty" indicates a condition in which a critically reduced functional reserve due to multiple organ dysfunction limits the patient's ability to cope with stressors and therefore predisposes to loss of physiological homeostasis [56]. Frailty has been demonstrated to be a predisposing factor for the development of delirium in the elderly who have undergone surgery [57–59].

Regarding precipitating factors, many illness-related conditions such as acidosis, anemia, fever, infection, sepsis, hypotension, metabolic imbalances such as hyper-/hyponatremia, acidosis, hyperbilirubinemia, and hyperazotemia can trigger delirium [37, 53, 60]. Patients often wake up in the unfamiliar surroundings of the ICU with no recollection of the previous days or even weeks, and this can be extremely confusing for them. In the perioperative period, preoperative fluid fasting and dehydration [61] can also increase the risk of developing delirium. Moreover, iatrogenic factors such as immobilization (i.e., catheters and restraints), medications (i.e., opioids, benzodiazepines), and sleep disturbances may also increase the risk. In particular, the latter two are extremely frequent in most of the critically ill patients and are potentially susceptible to modification. They are examined in detail below.

13.5 Sedative and Analgesic Medications

Patients in Intensive Care Unit routinely receive sedative and analgesic medications to reduce anxiety and pain. These medications, however, are not without harmful effects. For example, continuous intravenous sedation is associated with prolonged mechanical ventilation as compared with sedation via intermittent boluses [62].

The existence of an association between delirium and exposure to sedative and analgesic medications is well known. In a combined surgical/medical ICU study, researchers demonstrated morphine as the strongest predictor of delirium [63]. Ouimet and colleagues [64] determined that coma-inducing sedatives and analgesics were associated with delirium with an odds ratio (OR) of 3.2 (95% confidence interval [CI] = 1.5–6.8). Marcantonio and coworkers [65] reported that benzodiazepines increased the risk of postoperative delirium in the study population in comparison to patients who were not receiving benzodiazepines (OR = 2.7, 95% CI = 1.3–5.5). In a study by Pandharipande and colleagues [66], lorazepam was an independent risk factor for daily transition to delirium (OR = 1.2, 95% CI = 1.2–1.4) in a dose-related way. Although studies have consistently identified lorazepam and midazolam as risk factors for delirium, the data regarding opioids is contradictory, since untreated pain does represent itself a risk factor for delirium. For example, Ouimet and coworkers [64] found that in ICU patients mean daily opioid doses

were lower among patients with delirium than among those without delirium. Similarly, in 541 hip fracture patients, Morrison and colleagues [67] determined that those treated liberally with opioid analgesics (>10 mg/day parenteral morphine sulfate equivalent) were less likely to develop delirium than patients who received less analgesia. Treatment with meperidine was an exception since this drug increased the risk for delirium as compared with other opioids [66]. More recently, apart from pain, studies have found an association between these drugs and delirium in at risk population [68–70]. Therefore, it is advisable to use these drugs judiciously and to provide adequate analgesia especially in the critically ill.

13.6 Sleep Disturbances

Critically ill patients uniformly suffer from sleep disruption. Typically, the sleep of a critically ill patient is characterized by a predominance of waking state and light sleep (sleep stages II and I). Instead, there is a relative lack of rapid eye movement (REM) and deep sleep (delta sleep, formerly referred to as non-REM sleep stages III/IV) [71–74]. Multiple reasons are responsible for sleep disturbances in ICU: underlying disease, mechanical ventilation, pain, drugs, and a hard environment (noise, lights, lab draws, vital sign, invasive procedures, etc.) [75]. There is no doubt that a relationship between delirium and sleep disturbances do exists. Central components of delirium—that is, inattention, fluctuating mental status, and cognitive dysfunction—are also characteristic of patients with sleep deprivation. Nevertheless, even if sleep deprivation is plausible as a contributing factor in the onset of delirium, data definitively establishing it as an independent risk factor is still lacking [76]. Sleep interventions—i.e., promoting natural sleep, use of ear plug, limit lights and noise at night, etc.—may be a promising approach for improving delirium-related outcomes, although bias issues, varying methodologies, and multiple confounders make it difficult to draw any conclusion on this strategy. Further systematic studies are needed in order verifying the link between sleep interventions and delirium-related outcomes [77]. For further information, the reader is referred to the dedicated Chap. 11.

13.7 Pathophysiology

Given the individual and social impact of delirium in terms of short- and long-term complications, a treatment based on solid pathophysiological bases would be largely desirable. Unfortunately, despite important advancements in neuroimaging, pathophysiology of delirium remains poorly understood. Several theories have been proposed to explain pathophysiology of delirium. Difficulty in outlining a definitive theory is partially due to the complex interplay between delirium and the baseline illness. The detailed analysis of all these theories is beyond the purpose of this chapter. Here, we report synthesis of the main mechanisms

involved in the genesis of delirium: inflammation, decreased cerebral blood flow, and neurotransmitter imbalance.

13.7.1 Inflammation

Inflammation has a strong association with the development of delirium in sepsis. A recent multicenter trial [78] estimated encephalopathy associated with sepsis with a prevalence of 32.3%. It is often believed that delirium in sepsis is mediated by inflammatory cytokines and endotoxin [79]. Studies demonstrated an increased incidence of delirium in septic patients with higher systemic inflammatory markers such as C-reactive protein, cortisol, and interleukin 8 (IL-8) [80, 81]. Researchers demonstrated that inflammatory mediators are able to activate microglia, which has a role in maintaining neuronal population's homeostasis by the phagocytic clearance of dysfunctional neurons. However, activation of microglia can lead to increased tissue levels of nitric oxide and reactive oxygen species, determining the onset of a self-maintaining loop between tissue damage and inflammation. As a result, damage of the blood-brain barrier (BBB), alterations in cerebral blood flow (CBF), endothelial dysfunction as well as changes in neurotransmitter levels can occur, leading to a clinically evident syndrome [82, 83].

13.7.2 Decreased CBF

As we have seen, microvascular compromise can result from inflammation. Studies [84, 85] with neuroimaging techniques have shown a decrease in CBF in delirious patients not only in sepsis but also in other clinical states. In particular, in a study with computed tomography (CT), researchers found a reduction in CBF of 43% in patients during delirium and even more in the frontal lobes [84]. Therefore, a reduction in CBF may be a common pathway of delirium in sepsis and other conditions. Too few studies have been published up to now to draw definitive conclusions. Further studies are needed to explore the role of reduced CBF in the development of delirium.

13.7.3 Neurotransmitter Imbalance

Clinical findings of the deliriogenic properties of some anti-cholinergic medications suggest that alterations in acetylcholine and the monoamines (dopamine, norepinephrine, and serotonin) levels within the central nervous system may predispose the development of delirium [74]. Many of the risk factors, such as anesthetics and opiates, can affect the release of acetylcholine and the availability of postsynaptic receptors. Moreover, some drugs routinely used during anesthesia as opiates or volatile anesthetics may affect acetylcholine release at neuronal synapsis [86].

As we have already pointed out, inflammation itself may be responsible for an imbalance in production of neurotransmitters. In particular, acetylcholine deficit can be induced by ischemia or through a direct inhibitory effect of inflammatory mediators [87]. Nevertheless, trials conducted with cholinesterase inhibitors showed no effects in terms of prevention and treatment of delirium [88, 89]. These findings are consistent with a multifactorial hypothesis in the genesis of delirium.

13.8 Approaches to Prevention and Treatment

In ICU, before initiating any treatment, physicians must address and rule out all the life-threatening complications of critical illness that may lead to delirium such as hypoxia, hypercapnia, hypoglycemia, shock, etc., identify possible discontinuation of patient's psychiatric medications, and check for exposure to deliriogenic drugs. Only at that point, both non-pharmacological and pharmacological treatments should be considered. Non-pharmacological multicomponent approaches are widely renowned as the most effective strategies for reducing frequency and duration of delirium [90]. In the non-ICU setting, risk factor modification has resulted in a 40% relative reduction in the development of delirium [91]. In particular, early mobilization, sensory reorientation, favoring natural sleep, earplugs, eye masks, noise control strategies, pharmacy medication review (i.e., reducing the exposure to "deliriogenic" drugs), music therapy, physical therapy, cognitively stimulating activities, family presence, bright light therapy, and education and orientation programs are proven to be effective strategies (some in the non-ICU and others in the ICU patients as well) [37, 50, 62, 91–93]. On the contrary, no convincing and reproducible evidence of effectiveness exists regarding the use of antipsychotics to prevent and treat delirium in ICU. In fact, some trials demonstrated no significant differences in rates of delirium between groups [94–96]. In some others, there was a reduction in the incidence of delirium but no effects in terms of clinical outcomes (complications, mortality, and hospital length of stay) or either they were not measured [97, 98]. A trial conducted with rivastigmine was halted because of an increase in mortality in the treated group [88]. Besides, the heterogeneity of the populations studied in the different trials makes it difficult to draw any conclusion. By the way, there is no evidence at the moment that treatment with haloperidol reduces the duration of delirium in adult ICU patients, whereas atypical antipsychotics (risperidone, olanzapine, quetiapine) may do. Moreover, antipsychotics are not recommended in patients at significant risk of torsade de pointes (i.e., patients with baseline or medication induced prolongation of QTc interval) [99]. Some encouraging results came from one recent double-blind randomized controlled trial in which post-cardiac surgery patients receiving dexmedetomidine (an alpha 2 agonist) for prevention purposes had a reduced incidence of delirium [100]. Regarding the treatment of established delirium, a study comparing dexmedetomidine with haloperidol in patients with hyperactive delirium, dexmedetomidine was associated with a shorter time to extubation and shorter ICU length of stay [101]. Therefore, currently

available guidelines suggest administering continuous IV infusions of dexmedetomidine for sedation to reduce the duration of delirium in adult ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal [99].

Conclusions

Delirium in the critically ill is a frequent and often under-recognized condition, burdened by an increased risk of prolonged mechanical ventilation, longer hospitalization, medium- and long-term cognitive impairment, and death. This is because delirium is far from being a temporary attenuation of brain function, usually followed by a full remission, but it is associated with the activation of complex neuronal pathophysiological pathways that may have not only acute but also long-term effects. Therefore, early recognition and treatment, as well as preventive measures, are of paramount importance. Clinical guidelines strongly support and recommend the use of specific diagnostic scales, which have to be applied routinely at the bedside. Guidelines also recommend non-pharmacological prevention and treatment strategies, whereas no sufficient level of evidence recommends the use of antipsychotics to prevent and treat delirium in the ICU.

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