Delirium in Older Adults

Subjects: Neurosciences
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Delirium remains a challenging clinical problem in hospitalized older adults, especially for postoperative patients. This syndrome consists of a disturbance in attention and awareness that develops acutely and tends to fluctuate; it is one of the most well-known diseases and cognitive changes, with manifestation during hospitalization or soon after anesthesia and surgery. This complication frequently occurs in older adult patients, has a high risk of in-hospital death, and increases the length of stay.

Keywords: delirium ; postoperative complications ; delirium perspectives

1. Delirium Definition

Postoperative delirium comprises acute onset of disturbances in arousal, attention, and other domains of cognition, hallucinations, and delusions; it can be a hypoactive or hyperactive state or mixed [1]. It is an acute disease that requires the following features:

(A) Disturbance in attention (for example, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment);
(B) Disturbance that develops over a short period (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during a day;
(C) An additional disturbance in cognition (for example, deficit of memory, disorientation, language, visuospatial ability, or perception);
(D) The disturbances in Criteria A and C are not better explained by a pre-existing, established, or evolving neurocognitive disorder, and do not occur in the context of a severely reduced level of arousal, such as a coma (Criterion D must not occur in the context of a severely reduced level of arousal, such as a coma);
(E) There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies [2][3].

Delirium occurs in the hospital up to 1 week post-procedure or until discharge and meets DSM-5 diagnostic criteria. It is also often undetected and underdiagnosed. The screening tools most used for delirium are the four ‘A’s test (Arousal, Attention, Abbreviated Mental Test 4, Acute change) and the Confusion Assessment Method (CAM4) [4]. Cognitive decline is accelerated in people with delirium, and the appearance of delirium after a surgical procedure acts as an alarm for postoperative cognitive dysfunction [5][6].

2. Delirium Pathophysiology

Neuroinflammation, neurotransmitter dysregulation, and brain network disconnection are the common causes of delirium. However, in recent years, it is common to think of delirium as a consequence of multiple simultaneous molecular dysfunctions, which, due to multiple reasons, can lead to this disease [7].

- Systemic inflammation, as a septic shock syndrome, can lead to neuroinflammation with microglial cells activation, neuronal dysfunction, synaptic dysfunction, cellular apoptosis, and neuronal ischemia by the passage through a damaged blood–brain barrier (BBB) of proinflammatory cytokines (such as interleukin (IL) IL6, IL1, IL8, tumor necrosis factor alpha (TNFα), and C reactive protein CRP [8]).

- Stress conditions cause neuroinflammation with the unbalance of the limbic–hypothalamic–pituitary–adrenal axis (LHPA) by increasing cortisol blood levels. Several factors can influence cortisol levels, one of them being an alteration in melatonin pathways caused by sleep deprivation [9].

- Studies have demonstrated that prolonged exposure of neurons to high levels of cortisol, insulin, and glucose leads to neuronal malfunction and damage because of continuous metabolic stress. Therefore, people develop cognitive failure, and the devastating effect is more evident in older adults in which the LHPA axis is often already dysregulated. Inflammatory conditions can lead to hyperactivation of microglia and the consequent release of inflammatory cytokines and direct neuronal damage [10].

- Abnormal gamma-aminobutyric acid (GABA)-related transmission in the nervous system actively contributes to the development of delirium. It has been largely demonstrated that the use of drugs that increase GABAergic synaptic transmission, such as benzodiazepines, increases the risk of delirium manifestation [11].

All these hormonal and neurotransmitter alterations cause oxidative stress to cells which are exacerbated in hypoxic conditions that lead to chaotic neuronal signaling.

3. Delirium Assessment

Firstly, it is fundamental to assess the cognitive function and presurgical mental condition to detect any underdiagnosed pre-existing cognitive function decline [12].

There are several cognitive tests:

- The mini-mental test is one of the most accurate and known cognitive tests, but is often not simple to perform.

- However, the Rapid Cognitive Screen Test (Appendix A) and the Six-Item Cognitive Test are rapid, applicable, and feasible in the surgery ward units [13][14][15][16][17].

People with cognitive deficit have a greater risk of developing *de*lirium, and sometimes this problem is difficult to distinguish from dementia [5].

The delirium diagnosis is a clinical one and must be confirmed by an expert in the field. This acute disease is often underestimated because of its fluctuating nature or the hypoactive delirium type [18].

There are three principal delirium assessment tools.

- The four ‘A’s test (4AT) (Appendix B) is a simple, quick clinical test that requires less than 2 min to perform and is a well-validated bedside test to detect delirium in day-to-day practice and different settings [19]. It does not require special training, and it is easy to implement for delirium diagnosis. A recent article reported this test’s sensitivity and specificity as over 81.5% and 87.5%, respectively [20][21][22][23].

In the end, the 4AT test investigates acute changes or fluctuations [24].

- The Confusion Assessment Method (CAM4) (Appendix C) was developed in 1990. It has high sensitivity (94–100%) and high specificity (90–95%), and is easy to perform [25]. Nurses and physici*ans can perform it, but d*elirium diagnosis can only be confirmed by physician experts in the field. It can be used in clinical and research settings, with expert judgment, and is helpful to avoid hypoactive delirium.

- In recent years, the CAM4 score was also adapted for intensive care units and critically ill patients. The CAM-ICU score for intensive care unit (ICU) patients (Appendix D) has a pooled sensitivity of 80.0% and a pooled specificity of 95.9% [26]. This score investigates the presence of acute onset or fluctuating course and inattention with either disorganized thinking or altered level of consciousness; these features indicate a possible delirium diagnosis [27][28]. Like the CAM4, this tool evaluates the same core features of delirium, but in a different way, with clinical tests or observations. Furthermore, this assessment needs to be combined with the Richmond Agitation–Sedation Scale to evaluate the arousal/sedation [29]. This test is helpful in conditions such as coma or arousal, which nurses can easily perform.

- An alternative to CAM-ICU is the Intensive Care Delirium Screening Checklist (ICDSC). However, this tool must be integrated with agitation [27][30][31][32]. By the way, CAM4, CAM-ICU, and 4AT tools required multiple interviews or clinical observations of the patients.

- The severity of delirium and the clinical course of the delirium can be measured with these tools [33][34][35]. The Delirium Rating Scale—Revised-98 and The Memorial Delirium Assessment have both been traduced in many languages, which is helpful for longitudinal studies and assessing and evaluating answers to the treatments.

- Recently, two delirium-prediction models in ICUs have been introduced: the model for delirium (PRE-DELIRIC) and the early prediction model for delirium (E-PRE-DELIRIC). In these models*, the delirium* prediction, as reported above, demonstrated both a moderate-to-good performan*ce to predict d*elirium, especially in ICU; however, more validations are necessary [36][37][38][39]. These tools allow practicing preventive strategies to avoid delirium in critical patients.

Instruments such as EEG have been proposed to exclude conditions, such as non-convulsive status epilepticus, which, in some instances, can present with behavioral cognitive alterations that can mimic 'delirium'. Moreover, intraoperative EEG monitoring has increased its relevance for its potential role in finding a pattern related to postoperative delirium [40][41][42].

Differently, in recent years, several biomarkers have also been studied, but the best tools with the highest specificity and sensitivity are clinical [43].

4. Postoperative Delirium: Epidemiology and Risk Factors

Postoperative delirium infrequently affects young adults who undergo minor elective surgery. Interestingly, the incidence increases to 15–25% after elective surgery in older adults and reaches more than 50% of cases in high-risk elderly patients who undergo major surgery, such as cardiac surgery, requiring cardiopulmonary bypass or orthopedic hip fracture repair [44][45]. Notably, patients who need ICU admission after the surgery have a higher risk of developing delirium, which is worsened by prolonged mechanical ventilation [45]. Risk factors of developing postoperative delirium could be patient-related, could be different depending on the timing of appearance during hospitalization, and could be medical- or surgery-related factors [46][47]**.** More generally, the risk of developing postoperative delirium derives from the presence of some predisposing factors in addition to one or more precipitant factors[45][46][47][48][49].

5. Perioperative Management of Delirium

The management of delirium starts in the preoperative period, with environmental and clinical strategies and daily neurological assessment by clinicians, and is fundamental. First of all, physicians should promote fast-track surgery and short hospitalization [50][51][52]. The right approach to treat delirium disturbances begins with administrating drugs and medications correctly, avoiding benzodiazepines, and promoting dexmedetomidine and clonidine as sedative and analgesic drugs [53]. During the entire period, physicians should exclude acute neurological damage or metabolic or infective CNS involvement, ensuring correct oxygen delivery (DO_2) by maintaining normal hemoglobin levels, avoiding blood loss, and avoiding uncontrolled pain because it is a possible delirium trigger. Avoiding metabolic alterations, as well as ensuring normal blood glucose, physiologic endocrine function, normal renal function, and hydro electrolytic balance, can reduce delirium risk [10][54]. Furthermore, nurses and physicians should take care of the environmental factors in the hospital unit, and clocks, radio or television, and books could be helpful to maintain attention and orientation. It is crucial to assess CAM fluctuations during the day, and the presence of relatives or next of kin of the patients could also be a resource in delirium prevention [55]. To summarize, actions to avoid or reduce delirium incidence can be divided into three categories: preoperative, intraoperative, and postoperative strategies [56][57][58][59][60][61][62][63][64][65].

6. Therapies for Postoperative Delirium

As primary measures, once postoperative delirium starts, it is possible to use non-pharmacological and pharmacological interventions.

Due to the paucity of evidence, the actual guidelines suggest avoiding pharmacological approaches as first-line therapy both in non-intensive and intensive care settings [66][67][68].

6.1. Non-Pharmacological Interventions: Behavioral and Multimodal Approach

This method seems to be the most effective in delirium treatment. It includes non-pharmacological approaches described as preventive actions above, which can also be treatment solutions.

- It is necessary to understand why the patient is delirious and to treat precipitating factors (such as treating hypotension, giving oxygen therapy when needed, treating overdose of drugs, and controlling pain).

- It is fundamental to free the patient from medical devices as soon as possible. This allows starting early rehabilitation and promoting a reorientation program with the patient's family collaboration.

- In addition, some advantages could come from educational programs for staff to illustrate how to deal with this pathology [69].

However, even if effective, in several circumstances of hospital restrictions or logistic limitations, this therapeutic approach could have a difficult realization. When the behavioral and multimodal approach is not enough to treat delirium, the use of antipsychotic drugs is suggested.

6.2. Pharmacological Interventions

Several drugs have been historically used to treat postoperative delirium, but only a few of them have strong evidence of efficacy.

- Haloperidol (a dopaminergic agonist) is the antipsychotic drug traditionally used in emergency intravenously in both non-intensive and intensive care settings. It seems to reduce the length of delirium and agitation. However, there are some safety issues because it can prolong QTc on ECG. In addition, there are little evidence and guidelines that support its use, with a paucity of data regarding its use in non-intensive care settings [70][71].

- Second-generation antipsychotic drugs, such as risperidone, olanzapine, and quetiapine, have been used in place of haloperidol. However, there is a lack of evidence of their superiority in solving delirium [53][72][73].

- An α_2 agonist, dexmedetomidine, has been used in the ICU setting to treat delirium in mechanically ventilated patients. Recent guidelines suggest it helps to wean patients from ventilators by reducing ventilation days and the length of stay in the ICU. Evidence suggests that it reduces delirium in postoperative cardiovascular patients and. When haloperidol fails, it can be used in non-ventilated patients. As well as dexmedetomidine, the use of clonidine (α_2 agonist) seems to be promising, but further studies are necessary to better define its role in delirium treatment [29][74][75].

- In the end, acetylcholinesterase inhibitors, such as rivastigmine and donepezil or melatonin, seem to help in some clinical settings, but more data are needed [76][77].

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