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Current Concepts in the Diagnosis, Pathophysiology, and Treatment of Delirium: A European Perspective

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Abstract Delirium is a complex syndrome defined as an acute, fluctuating syndrome of altered attention, awareness, and cognition. Delirium is common in the elderly, but unfortunately underdiagnosed. The consequences could be significant such as an increase in mortality, hospitalization, loss of autonomy, and increased risk to be institutionalized. The predisposing and precipitating factors are well known, but the pathogenesis is not yet identified clearly. However, evidence that delirium is a neurotoxic factor which develops due primarily to neurotransmitter (cholinergic insufficiency) and inflammatory (increase in stress response/neuroinflammation) mechanisms is increasing each passing day. Delirium is associated with serious complications, but can also be treatable if diagnosed early and managed properly. It is important to develop primary and secondary prevention and therefore close contact with the patient, ensuring adequate vision, hearing, nutrition, hydration, and sleep; informing the caregivers about delirium for recognizing early symptoms of delirium, mobilizing the patient as early as possible, and managing the pain are strongly recommended. Besides, clinicians must identify the real underlying medical conditions. If non-pharmacologic interventions are insufficient, pharmacologic therapy should be implemented.

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Introduction

Delirium is an acute alteration of cognition hallmarked by disorganized thinking and inattention and a major healthcare concern in countries with aging populations [1]. Delirium is a potent and well-recognized indicator of health-care quality across many settings [2••], and is an independent risk factor for length of hospitalization, increased functional impairment, medical complications (e.g., urinary incontinence, falls, decubitus ulcers), and admission to a nursing home [1]. Although delirium is associated with poor outcomes and is expensive, it remains disproportionately ignored relative to its impact [3]. It is defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-V) [4]. Key diagnostic features include an acute onset and fluctuating course of symptoms, inattention, impaired consciousness, and disturbance of cognition (e.g., disorientation, memory impairment, language changes) [5, 6]. Supportive features include disturbance in sleep–wake cycle, perceptual disturbances (hallucinations or illusions), delusions, psychomotor disturbance (hypoactivity or hyperactivity), inappropriate behavior, and emotional lability [3].

Epidemiology

The prevalence of delirium in the community is 1–2 % but increases in the setting of general hospital admissions to 6–56 % [7], with the higher prevalence associated with increased age and increased severity of medical illness [8]. Increased

prevalence is noted in general intensive care units (ICUs) and in cardiac ICUs with 32 % [9] and 42 % [7, 10] rates, respectively. Postoperative prevalence of delirium in elderly patients ranges from 9 to 87 %, and elderly patients with dementia and those undergoing cardiothoracic, emergency orthopedic procedures, vascular surgery, or cataract removal are at higher risk for developing delirium [7, 11].

Pathogenesis

Considering physiopathological processes of delirium, it is possible to see that numerous precipitating and predisposing factors, each of which would facilitate development of delirium, are interacting with each other in the majority of cases. As conventional electrophysiological tests, brain imaging and neurotransmitter analyses are not always possible in the cases with this disease picture and the results of animal studies do not overlap one-to-one; physiopathological mechanisms of delirium have not been fully elucidated as of yet [12]. Diversity of defined risk factors and neurochemical abnormalities suggests that brain dysfunction in delirium results from the interaction among numerous systems. Therefore, it seems impossible to explain the picture by a single etiological theorem. However, evidence that delirium is a neurotoxic syndrome which develops due primarily to neurotransmitter (cholinergic insufficiency) and inflammatory (increase in stress response/neuroinflammation) mechanisms is increasing [12].

According to the neurotransmitter hypothesis, etiological factors cause neurotransmitter abnormalities by impairing cerebral oxidative metabolism, and consequently, cerebral dysfunction occurs. Decrease in cholinergic activity, increase or decrease in serotonergic and γ-aminobutirynergic (GABAergic) activity due to oversecretion of dopamine, norepinephrine, and glutamate may result in delirium's presenting itself with different symptoms [13]. Many biological factors may interfere directly with neurotransmission and/or cellular metabolism, including drugs, hypercortisolism, electrolyte disturbances, hypoxia, or impaired glucose oxidation. The list of potential neurotransmitters involved in delirium is long, but a relative cholinergic deficiency and/or dopamine excess are the most commonly inferred, correlating with the adverse effects of anticholinergic or dopaminergic drugs [2••].

Inflammatory response is the other causal mechanism. Delirium can accompany many medical and surgical conditions with increased inflammatory response. Therefore, delirium may manifest itself as a picture that accompanies sepsis-related multi-organ failure [14], sometimes as a clinical manifestation of underlying simple urinary system infection or pneumonia (particularly in demented elderly), and sometimes as a postoperative complication [15]. It is thought that cognitive changes occur in acute systemic inflammation due to impaired cellular and molecular synergistic relationships in different regions of the brain, primarily the hippocampus [16]. It is known for a long time that proinflammatory IL-1 has an important role in neurophysiological processes in memory consolidation probably in the way to regulate synaptic plasticity [17]. IL-6, as well, is effective in hippocampal dysfunction [18]. Contrarily, IL-10 balances the effects of IL-1 and IL-6, and this appears to prevent behavioral and cognitive harmful effects of cytokines [19]. In delirium, the decrease in the expression of hippocampal brain-derived growth factor and increase in mitochondrial dysfunction and oxidative stress are involved in neuroinflammation that causes learning and memory defects [20]. All of this information suggest that local cerebral reactive oxygen species, proinflammatory cytokines, metalloproteinases, nitric oxide, and chemokines can impair learning and memory processes by influencing synaptic plasticity and long-term potentiation processes [21]. In addition, peripheral inflammatory stimuli produce changes resulting in neuronal injury and altered permeability of blood–brain barrier (BBB) [22].

On the other hand, insulin-like growth factor I (IGF-I) is one of the proteins that play a role in human development and in the regulation of various metabolic and brain functions. IGF-I levels decrease with age. IGF-I has an effective role in the development of the BBB, neuronal excitability, synthesis of the myelin sheath, blood vessel maturation, neuronal vitality, proliferation, differentiation, synaptogenesis, and transport and metabolism of cerebral glucose. IGF-I plays a supporting role relative to neuronal plasticity. There are many studies reporting that IGF-I levels are low in delirium, and this low level is associated with the clinical manifestations and duration of delirium [23].

Risk Factors

Risks for delirium can be divided into predisposing and precipitating factors [24]. Predisposing factors such as age, visual impairment, hearing impairment, severe illness, and cognitive impairment are the baseline vulnerabilities of an older person. In addition, geriatric syndromes, such as dementia, depression, malnutrition, pressure ulcers, urinary incontinence, polypharmacy, chronic pain, and falls are associated with delirium. Precipitating factors are the acute and noxious insults experienced by an older person such as infection, metabolic derangement, or surgery [25]. The development of delirium results from a complex interrelationship between predisposing and precipitating factors. These risk factors are shown in Table 1 [12, 26•].

It is of special importance that elderly patients undergoing surgery have a high risk of postoperative delirium which is associated with both short- and long-term adverse events. Postoperative delirium affects up to 73 % of patients with a mean prevalance of 36.8 %, influenced by pre-operative

Table 1 Risk factors for delirium (adapted from [12, 24, 25, 26•])

Predisposing factors	Precipitating factors	Delirium-inducing medications
Age (older than 65 years)	Dehydration	High risk
Male sex	Fracture	Anticholinergics (antipsychotics…)
Chronic pain	Hypoxia	Benzodiazepines
History of baseline lung, liver, kidney, heart, or brain disease	Infections	Dopamine agonists
Terminal illness	Ischemia	Meperidine
Alcoholism	Medications	Lithium
Dementia	Metabolic derangement	Moderate risk
Depression	Poor nutrition	Alpha-blockers
Elder abuse	Severe illness	Antiarrhythmics
Falls	Shock	Digoxin
History of delirium	Surgery	Nonsteroidal anti-inflammatory drugs
Malnutrition	Uncontrolled pain	Antihypertensives (beta blockers, clonidine)
Polypharmacy	Urinary retention	Sedatives/hypnotics
Pressure ulcers	Stool retention	Low risk
Sensory impairment	Sleep deprivation	Metoclopramide
Inactivity	Hypo/hyperglycemia	Narcotics other than meperidine
Traumatic Brain Injury	Corticosteroids	Calcium channel blockers
Poor functional status	Intensive care unit setting	Antivirals
Social isolation		Tricyclic antidepressants
		Antibiotics
		Anticonvulsants
		Low-potency antihistamines

features of the elderly, surgical technique used, and type of anesthesia [12, 16].

The risk is higher in patients who have emergency surgery than those who have elective surgery. It could be seen in all kinds of surgery including cataract. However, it is most commonly seen after cardiovascular and hip fracture surgeries. Major postoperative complications, loss of functional independence, falls, increased length of hospital stay, discharge to long term care, and death were reported as adverse outcome measures. Therefore, preoperative geriatric assessment is essential in older patients, because, it not only informs the risk/benefit ratio for surgery but also identifies high-risk patients for early preoperative interventions and planning of intra- and postoperative care [27].

Clinical Presentations and Diagnosis

Delirium may occur within days or sometimes hours. There are three core symptom domains including a "cognitive" domain, a "higher level thinking" domain (language and thought process), and a "circadian" domain (sleep-wake cycle and motor behavior) [28].

Clinical presentation of delirium can range from frank somnolence to more awake and alert states. Patients may manifest clinical findings of obvious confusion with inappropriate response to questions. Sometimes, patients can focus initially but are distractible, impersistent, or perseverative on bedside evaluation. Restlessness, disheveled appearance, picking, and talking out loud when alone in the clinic may be observed. Generally, motor behavior abnormalities may also be observed in the patients. Delirium may be presented with hypoactive, hyperactive, and mixed subtypes according to these behaviors. The features of hypoactive delirium are psychomotor slowing, decreased in oral intake, limited engagement with the environment, inconvenience, tearfulness, withdrawal, and apathy. On the contrary, agitation, restlessness, anxiety, disinhibition, disordered thinking, and perceptual disturbances of hallucinations and delusions are usually seen in the hyperactive subtype of delirium. Hyperactive delirium may be associated with patient and staff injury, and is more responsive to pharmacologic treatment. Hypoactive delirium is associated with a worse outcome. Cognitive and behavioral changes frequently fluctuate and follow a diurnal pattern. Assessment during periods of more lucid behavior can lead to the conclusion that patients are cognitively intact leading to the diagnosis being delayed or overlooked. In mixed delirium, patients often fluctuate between hypoactive and hyperactive subtypes of the disease [12, 28].

Also, there are some patients who display some of the symptoms without developing the full syndrome and are intermediate in severity between non-delirious controls and full

syndromal delirium, namely having subsyndromal delirium (SSD). Subsyndromal delirium seems to be associated with the same risk factors as delirium [12].

Standardized tools may help to efficiently and accurately diagnose delirium. The Confusion Assessment Method (CAM) is a widely used delirium screening instrument based on the DSM-III-R criteria [5]. The test is quick, easy, and inexpensive. Screening for delirium is positive if symptoms are acute at onset and have a fluctuating course, and the patient exhibits inattentiveness plus disorganized thought or altered consciousness [5].

Prevention and Treatment

Non-Pharmacologic Interventions Primary prevention of delirium is the most effective strategy to reduce delirium and related complications. Non-pharmacologic interventions and treatment of the underlying cause/s are the first step of the management. For initial symptom management, non-pharmacological approaches are the first-line strategy and include discontinuation or dose reduction of anticholinergic and psychoactive drugs, family, or companion involvement for reorientation and comfort [2••]. At this stage, all the risk factors for delirium as shown in Table 1 should be eradicated. All these interventions may decrease the incidence of delirium up to 40 % [12, 26•, 29].

Suicidality, violence potential, fall risk, and wandering risk, inadvertent self-harm risk should all be assessed with appropriate measures taken to ensure safety. Use of restraints should be minimized as they may increase agitation and hence decrease safety [30]. The patient should be stabilized in a quiet room if possible. Initially, finger-stick glucose should be obtained. To prevent Wernicke's encephalopathy, 100 mg of intravenous (i.v.) thiamine should always be administered before giving glucose 50 ml of D50W i.v. Initial screening test for detecting etiology of delirium should include blood work-up, including complete blood count, glucose, electrolytes, renal and hepatic tests, thyroid function, cultures, chest x-ray, and urinalysis. Further investigations based on clues from history, physical examination, and previous results are indicated if initial analyses fail [31].

Pharmacological Interventions Antipsychotics have been the medication of choice in the treatment of delirium. However, there are no The Food and Drug Administration (FDA)-approved medications for delirium and clinicians must be aware that these drugs for the treatment of delirium can have significant side effects. Thus, the drug should be given in the lowest possible dose for the shortest duration. Also, pharmacologic agents should be reserved for patients with severe agitation, which may result in the interruption of essential medical therapies (e.g., intubation, intraaortic balloon pumps, dialysis catheters) or which may endanger the safety of the patient, other patients, or staff [2••, 3, 30].

Haloperidol is considered to be the fist preferred agent for the pharmacological management of delirium, with its high-potency and minimal anticholinergic and cardiovascular side effects. It is recommended to start haloperidol with a dose of 1.0 mg orally or parenterally, and to repeat the dose every 20 to 30 min until the patient is calm enough to participate in the management. Vital signs should be checked before repeating each dose. Subsequently, a maintenance dose of one half of the loading dose should be administered in divided doses over the next 24 h, with tapering doses over the next few days [31–33].

Regarding the newer antipsychotic medications in the treatment of delirium, it was demonstrated that risperidone, olanzapine, and quetiapine were as effective and safe as haloperidol [34, 35]. In addition, it was reported that olanzapine might reduce the incidence but increase the duration and severity of delirium [36]. Beside these reports, it is essential to keep in mind that these atypical antipsychotic drugs were issued a blackbox warning by FDA due to their 1.6–1.7 times higher death rate when compared to placebo in patients with dementia [37].

There are some drugs for the treatment of delirium which are recommended in certain conditions. Benzodiazepines are used in the cases of withdrawal syndromes from alcohol and sedative-hypnotic drugs, agitation with regard to neuroleptic-malignant syndrome, and patients with catatonia or severe extrapyramidal reactions. Lorazepam is the first choice with a starting dose of 0.5 to 1.0 mg in geriatric population. It does not have active metabolites and has advantages such as its parenteral form and relatively less half-life which is approximately 10 to 15 h [32, 38••].

Prevention and treatment of delirium in the ICU is very crucial, and studies are generally based on targeting decreasing the opioid requirements, aiming to lower the incidence of delirium. Recently, a new agent with its sedative, analgesic, and anxiolytic properties has revealed satisfactory outcomes. Dexmedetomidine, a centrally acting alpha-2 agonist is highly selective and has been found to have mild cholinergic activity and to be effective without causing significant respiratory depression unlike other studied medications. However, it is reported to cause bradycardia and hypotension at high infusion rates [39–41].

A few trials have addressed the potential utility of cholinesterase inhibitors for the prevention of postoperative delirium because of the central cholinergic deficiency hypothesis in delirium. But, the results have been disappointing [42]. Melatonin plays a central role in the regulation of the sleep–wake cycle which is frequently disrupted in delirium. In addition, alterations of melatonin metabolism may be effective in development delirium. According to a study, melatonin (5 mg two times before intervention) was reported to be a successful

therapeutic agent against postoperative delirium in elderly patient [43]. It was demonstrated that 0.5 mg/day of melatonin for up to 14 days was associated with lower delirium risk compared with placebo, and it was recommended that nightly melatonin could have potential protective effect for delirium in elderly patient [44]. Ramelteon, a melatonin agonist, was found to be associated with a lower risk of delirium (3 vs 32 %) when administered nightly to elderly patients admitted for acute care [45•].

Prognosis

Delirium has been previously considered to be a transient, reversible condition; however, recent studies [46, 47] have documented that delirium may be more persistent than previously believed. Delirium has deleterious effects on long-term cognitive functioning in elderly patients with dementia. The duration, severity, and underlying cause(s) of delirium may be important in these deleterious effects. It has been documented that at least some patients never recover their baseline level of cognitive functioning. The mortality rate of patients with delirium is high and can be as much as 30 %. Only one third of patients recover from delirium, with the remaining patients suffering a permanent decline in cognitive function [1, 3].

Conclusion

Dementia is a highly varied syndrome ranging from hypoactive to hyperactive states, with a number of recognized precipitating factors and predisposing factors. It is always a medical emergency, as it may reflect an underlying acute medical issue, and it may portend or possibly cause worse cognitive and other health outcomes. Delirium management requires an efficient and accurate diagnostic process, and rapid and effective treatment. Given the fact that delirium can be prevented in at least one third of cases, delirium prevention is of special importance.

Compliance with Ethics Guidelines

Conflict of Interest Pinar Soysal, Derya Kaya, and Ahmet Turan Isik declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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