**DELIRIUM IN ELDERLY**

**Key Concepts**
- Definition of delirium
- Pathophysiology of delirium
- Manifestations of delirium
- Treatment of delirium

**Abstract**
Delirium is a syndrome of several different etiologies characterized by a disturbance of consciousness with accompanying changes in cognition. There are three subtypes such as hyperactive, hypoactive and mixed. Different mechanisms have been proposed to explain the pathophysiology of delirium abnormalities in neurotransmitters such as acetylcholine, dopamine are held responsible for delirium. The management is recognition of condition and treatment of cause of delirium.

**Key words:** Delirium, Serotonin, Tryptophan, Sedative, Alcohol with bloat syndrome.

Delirium is a syndrome of several different etiologies characterized by a disturbance of consciousness with accompanying change in cognition. Characteristic features of the syndrome include impaired short-term memory, impaired attention, disorientation, development over a short period of time, and a fluctuating course. Not all described features need to be present for the diagnosis of delirium, and the intensity of the symptoms ranges widely among patients. One of several approaches to classify delirium is to divide it into motoric subtypes. Three subtypes of delirium are recognized based on the pattern of symptoms:

- Hyperactive, hypoactive, and mixed. Physiologically, delirium is characterized by a derangement of cerebral metabolism with cerebral dysfunction and is usually caused by a general medical illness, intoxication, or substance withdrawal. The syndrome of delirium encompasses a few distinct entities with unique pathophysiology and clinical manifestations. These include sepsis-associated encephalopathy, alcohol withdrawal syndrome, and hepatic encephalopathy.
Pathophysiology

Different mechanisms have been proposed to explain the pathophysiology of delirium. However, these mechanisms are not mutually exclusive and it is likely that they often act in concert. One hypothesis postulates that decreased cholinergic activity may lead to delirium. This hypothesis is supported by the observation that anticholinergic medication use is associated with increased delirium symptoms and that patients with delirium have higher serum anticholinergic activity compared with those without delirium.

Acetylcholine down regulates inflammation. Thus, it is not surprising that there is an imbalance between inflammatory and anti-inflammatory mediators in delirium, with increased levels of inflammatory mediators and a blunted anti-inflammatory response.

In this light, the role of inflammation and its consequent deranged coagulation has been explored in a recent cohort study of mechanically ventilated ICU patients. In this study, five markers of inflammation and four markers of coagulation were measured in the plasma of patients. After adjustment for potential confounders, including severity of illness, higher plasma concentrations of the inflammatory marker soluble tumor necrosis factor receptor-1, and lower plasma concentrations of the coagulation marker protein C were associated with increased risk of delirium. However, an unexpected finding was that lower plasma concentrations of matrix metallo-proteinase-9, another inflammatory marker, were associated with higher risk of delirium.

Another mechanism implicated in the pathophysiology of delirium is overactivity of the dopaminergic system. Clinically, evidence for this comes from case reports associating bupropion, an antidepressant with dopamine and norepinephrine activity, with development of delirium.

Furthermore, a genetic basis for increased dopaminergic system-induced delirium has been substantiated by the demonstration that mutant genes leading to lower cerebral dopamine activity are protective against delirium.

Both increased serotonergic activity and a relative serotonin deficiency also have been associated with delirium.

A high serotonergic state in association with delirium has been classically described in patients with the serotonin syndrome, a condition often emerging from the interaction of medications leading to increased serotonergic effects and that in its most severe form presents with hyperthermia, muscle rigidity, and multiple organ failure.

On the other hand, low levels of tryptophan—an amino acid that crosses the blood brain barrier and is a precursor to neurotransmitters serotonin and melatonin—have been associated with delirium after surgery in patients older 50 years.

Another study found that either high or very low levels of tryptophan are independently
associated with an increased risk of delirium in ICU mechanically ventilated patients.\textsuperscript{14}

Whereas decreased serotonin activity may be implicated in the development of delirium, it also is possible that the production of other metabolites of tryptophan, such as kynurenine, leads to pathway activity that results in neurotoxins predisposing to delirium.\textsuperscript{15}

Patients who are more prone to delirium, such as the elderly or those with underlying central nervous system disease, also may have heightened central nervous system response to inflammatory mediators. It appears that these patients may have an increased number of microglial cells, which are primed and can be readily activated in response to a mild stressor.\textsuperscript{16}

The amino-acid neurotransmitter system has a prominent role in the pathophysiology of alcohol withdrawal syndrome. In particular, chronic alcohol exposure may lead to a decrease in the number of and function of gamma aminobutyric acid receptors and an increase in the N-methyl-D-aspartate receptors. Both mechanisms could predispose patients to alcohol withdrawal syndrome.\textsuperscript{17,18}

**Clinical manifestations**

Delirium typically manifests as a constellation of symptoms with an acute onset and a fluctuating course. These symptoms have been organized into cognitive and behavioral groups. Common cognitive symptoms include disorientation, inability to sustain attention, impaired short-term memory, impaired visuospatial ability, reduced level of consciousness, and perseveration. Common behavioral symptoms include sleep-wake cycle disturbance, irritability, hallucinations, and delusions.\textsuperscript{19}

The manifestations of delirium can vary widely among patients. Whereas some patients may manifest somnolence and even coma, others appear anxious, disruptive, or combative.\textsuperscript{20}

Recognition of this symptom variability has led to the classification of delirium into motoric subtypes. One such subtype is hyperactive delirium, of which the manifestations include agitation, hypervigilance, irritability, lack of concentration, and perseveration. Hypoactive delirium manifests as diminished alertness, absence of or slowed speech, hypokinesia, and lethargy. Mixed delirium, as the name implies, includes manifestations of both hyperactive and hypoactive delirium.\textsuperscript{2}

The clinical manifestations also vary according to the precipitating factors. For instance, patients with bacteremia often present with encephalopathy and declined mental status.\textsuperscript{21}

Conversely, patients with alcohol withdrawal syndrome present with symptoms of an overactive sympathetic central nervous system.\textsuperscript{22}

As a consequence, patients with alcohol withdrawal syndrome commonly have agitation, insomnia, tremor, tachycardia, and hypertension.\textsuperscript{23}
Sedatives
Sedatives have the potential to promote delirium. In an observational study, lorazepam was an independent and statistically significant risk factor for development of delirium whereas other sedatives, such as propofol and opiates, had no statistically significant association with delirium. In a randomized, double-blind trial, 30 hospitalized AIDS patients with delirium were assigned to treatment with haloperidol, chlorpromazine, or lorazepam. Treatment with haloperidol or chlorpromazine resulted in significant improvement in the symptoms of delirium and low prevalence of extrapyramidal side effects. Patients treated with lorazepam had no improvement in delirium and developed treatment-limiting adverse events.

Thus, benzodiazepines are generally avoided for the treatment of delirium in hospitalized patients. In fact, because benzodiazepines are an important risk factor for delirium in critically ill patients, limiting their use may decrease the overall incidence of delirium in the ICU. It should be noted, however, that in patients with alcohol withdrawal syndrome, benzodiazepines are the recommended therapy.

References


