

# Delirium (Clinical Presentation, Diagnosis and Treatment): Updates for Neurologists and Psychiatrists

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## ABSTRACT

Delirium is a sudden change in the way a person thinks and acts. People with delirium cannot concentrate on what is happening around them, and their thinking becomes disorganized. This can cause fear in the person with delirium, their family, caregivers and friends. The dominant symptom of delirium is impaired consciousness, which is manifested by a false orientation in the environment, as well as attention disorders. Delirium can be developed within hours or days. Symptoms may come and go. The most common causes include hypoglycemia, metabolic disorders, hypoxia, infections (meningitis, pneumonia, sepsis, etc.), cardiovascular diseases, cerebrovascular accidents, epilepsy, uremia, liver failure (hepatic encephalopathy), head injuries, hormonal disorders and burns. Certain circumstances may increase the risk of developing delirium. The best way to treat delirium is to find and treat its cause. Sometimes it takes a lot of tests to determine the cause of the disease. This review article discusses current trends in classification, clinical presentation, diagnosis and treatment of delirium. Provided information should be helpful for practicing psychiatrists, neurologists, ICU specialists and general physicians.

**Keywords:** Delirium, cognitive impairment, clouding of consciousness, neuropsychiatry, neurology, psychiatric disorders, stroke, cerebrovascular accident.

## INTRODUCTION AND CLINICAL PRESENTATION

Delirium as a medical condition was first described by Hippocrates; it is characterized by disorders of consciousness, orientation, memory, thinking, perception and behavior. The onset of delirium is acute and the symptoms can fluctuate. It occurs in hyperactive, hypoactive, or mixed form in half of admitted patients who have previously had dementia and is associated with a poor prognosis. Despite its clinical significance, delirium is often not diagnosed, misdiagnosed and confused with dementia or depression.<sup>[1]</sup>

Recognizing depression is the main, but not the only task of the doctor. It must be borne in mind that depressive manifestations can appear in the framework

of heterogeneous (complex) mental disorders.<sup>[2-3]</sup> In this regard, there is a need to distinguish between different forms and causes of depression within the framework of non-manifest mood disorders (cyclothymia, dysthymia), psychogenic disorders (reactive depression and depression within the framework of anxiety and post-traumatic stress disorder), mental disorders due to medical conditions and organic disorders of elderly age.<sup>[4-7]</sup>

Symptoms of delirium usually develop over a period of hours or days, but can occur suddenly. With a gradual onset, patients may experience transient fatigue, decreased concentration, irritability, anxiety or depression. There may be cognitive disorders and hypersensitivity to light and sound. As usual, there are sleep disorders

and daytime sleepiness. Sleep disturbance characterizes by waking up after vivid dreams and nightmares in a state of disorientation and excitement. In a state of daytime drowsiness, patients have difficulty distinguishing between dreams and real feelings.

Although confusion is a cardinal characteristic of delirium, it is difficult to determine this symptom. Traditionally, clinicians assess consciousness by responding to stimuli: the patient is overly agitated (hyperalert) to stimuli; brisk (normal); lethargic (patient is dormant, but easily awakened) or comatose (not awakened).<sup>[7]</sup> The Glasgow Coma Scale allows physicians to quantify the state of consciousness in delirium patients.<sup>[8]</sup>

Difficulty in selective focusing on certain external stimuli disrupts cognitive processes; if attention is switched quickly and involuntarily, the registration of new information is disrupted what leads to disorientation and memory deficits. Thought becomes illogical or bizarre; patients are unable to make adequate and simple decisions. Insight and judgment to understand the situation are declined. The content of thoughts can be poor and stereotypical, but rich in images and fantasies. Often reduced abstract thinking, persecutory delusions and impaired ability to count. The differential diagnosis with delusional disorder and bipolar disorder is required as the described clinical picture shares similar signs, symptoms and presentation with these disorders.<sup>[9-12]</sup>

Speech is often impaired; is slow, poorly organized, incoherent and inappropriate, the patient has difficulty in selection of words. Patients experience difficulties in writing and write with mistakes.

Both short-term and long-term memory is impaired, confabulations occur in 8–15% of patients and relate to actions that the patient has never done, often patients tend to perceive strangers as relatives. In severe cases patients are disoriented, they are unable to realize

whether they are at home or not, whether they are dressed or not, and even whether they are lying or standing.<sup>[8,11]</sup>

In addition to hypersensitivity, perceptual disturbances can progress to illusions and hallucinations. Macropsia and micropsia may be presented, stationary objects seem to be moving with feeling of deformation of the own body. Illusions include, for example, the perception of stains on the floor as crawling insects (pareidolia or pareidolic illusion). Visual hallucinations often occur only at night, they are diverse – from simple flashes to seeing different animals and people. Auditory hallucinations include simple sounds, music, voices, and less frequent – tactile hallucinations. Patients with delirium perceive hallucinations as a reality, and the response to them can even be life-threatening.<sup>[1,7,8]</sup>

Patients with delirium experience three variants of psychomotor disorders: hyperactive, hypoactive and mixed.<sup>[13]</sup> Hyperactive delirium occurs in 15-21% of patients and is characterized by agitation, autonomic hyperactivity (sweating, tachycardia, dilated pupils, dry mouth and tremor). Hypoactive delirium is more difficult to diagnose due to polymorphism or lack of clinic presentation, occurs in 19-70% of patients. Mixed forms occur in 43-56% of patients, only a small proportion of patients (4-14%) do not have psychomotor disorders. In some patients, urinary and fecal incontinence is noted.<sup>[11,13]</sup>

Behavioral problems are a threat. When patient is aroused there is a risk of hip fracture or cardiovascular collapse. Suicidal behavior can be the result of hallucinations or mania.<sup>[13,14]</sup> Hypoactive patients are at risk of dehydration, nutritional depletion and bedsores.

Fear, anxiety and depression are very common symptoms of delirium.<sup>[7,8,13]</sup> They have different causes, often depending on the nature of the underlying medical and surgical diseases, the patient's personality, premorbid mental disorders, the patient's relationship with family and recent events in

the patient's life. The course of delirium can have unpredictable fluctuations; symptoms can be intermittent and fluctuate during the day with deterioration at night.

### PREVALENCE OF DELIRIUM

Delirium is a common pathological condition among elderly patients. During the admission (for any reason) 15-20% of elderly patients meet the criteria for the risk group of delirium. Among them, delirium develops in the hospital, according to various authors, with a frequency of 5 to 30%. In general, surgical patients at risk with the frequency of delirium is 10-15%, after open heart surgery, its frequency reaches 30%, and in hip fractures 50%. Among people in advance care homes, the incidence of delirium is 1-2%. [15-16] In total, more than 2.3 million elderly people suffer from delirium in the United States. [17]

### AETIOLOGY AND PATHOLOGY OF DELIRIUM

The aetiology of delirium is unknown. It is a complex disorder, with the influence of provoking factors on vulnerable patients with conditions conducive to delirium. Similarly, the pathogenesis has not yet been studied. No structural changes in the brain have been identified, and neuroimaging studies have yielded controversial results. [7,8,16-19] The electroencephalogram (EEG) shows a slowing of cortical background activity, the appearance of delta and theta activity, which correlates with the degree of cognitive impairment, but is not specific. The effectiveness of oxygen therapy suggests that one of the mechanisms may be a violation of oxidative metabolism of the brain. [20] Neurophysiological studies have revealed dysfunction of the prefrontal and parieto-temporal cortex, subcortical structures, thalamus, and basal ganglia, especially in the non-dominant hemisphere. The leading hypothesis of pathogenesis is neurotransmission disorders, inflammation and chronic stress. [8,16,17,20]

Evidence has been obtained that delirium may be mediated by disruption of cholinergic systems [16-18,20] Anticholinergic intoxication, which leads to behavioral and EEG manifestations of delirium, may be reversible under the influence of cholinesterase inhibitors. Hypoxia and hypoglycemia lead to decreased synthesis of acetylcholine. [21,22] Serum anticholinergic activity is associated with delirium in patients with internal and surgical diseases and in those receiving electroconvulsive therapy. [20] It is also associated with cognitive impairment in the elderly (who are in nursing homes).

Dopaminergic hyperactivity may also contribute to delirium due to exposure to acetylcholine. Levodopa can promote delirium, and dopamine receptor antagonists (antipsychotics) effectively treat its symptoms. [21-23] There is less evidence for participation in the pathogenesis of compounds such as norepinephrine, gamma-aminobutyric acid, glutamate, serotonin and the like.

Delirium may be associated with central nervous system effects of cytokines such as interleukins-1, 2, 6, tumor necrosis factor  $\alpha$ , and interferon. They increase the permeability of the blood-brain barrier and disrupt neurotransmission. [23,24] Clinical and EEG manifestations of delirium have been described in patients receiving  $\alpha$ -interferon. Delirium occurs in half of patients with chronic cancer treated with interleukin-2 and lymphokine-activated T-killers. [25] Hypercorticism in chronic stress has a detrimental effect on the 5-HT<sub>1A</sub> receptors of the hippocampus, which contributes to delirium. In general, the clinical heterogeneity and multifactorial nature of delirium suggest multiple pathogenetic mechanisms. [26]

### RISK FACTORS OF DELIRIUM

The most powerful risk factor for delirium is dementia - it has 25-75% of patients, the presence of dementia increases the risk of delirium by 5 times. [7,13,16,20] The study of brain metabolism showed that

dementia and delirium are two points of a single continuum of cognitive disorders, rather than separate diseases. [23,25,26]

The risk of delirium is also higher in patients with severe somatic pathology, concomitant mental illness, impaired mobility (immobilization). Hyponatremia, visual and hearing impairment are also risk factors. Changes in the room where the patient lives, changes in the patient's room temperature, etc., can contribute to delirium occurrence.

In bipolar disorder, a person alternates between periods of agitation (mania/hypomania) and depression. [27,28]

There are asymptomatic (euthymic) periods between them. The illness lasts during whole life. The risk of developing bipolar disorder over a lifetime is one to two percent and is equally prevalent worldwide. Alcoholism and drug addiction often accompany bipolar disorder. Moreover, the abuse of alcohol and psychoactive substances can be observed in both manic and depressive phases. In some cases, during periods of remission, alcoholics may consume alcohol in moderate doses, maintaining self-control, or even give it up altogether, but the gradual increase in dependence leads to the fact that all symptoms of addiction and alcoholism persist in the absence of phases. [29]

Alcoholic delirium is a condition caused by abstinence from alcohol. Physically, it is manifested by tremors, irregular heartbeats and sweating. People can also see or hear what others do not. Sometimes a person has a fever or convulsions that can lead to death. [30] These symptoms usually appear as early as 48 hours after abrupt cessation of alcohol use and can last up to five days. Without proper treatment, mortality is up to 37%, so it is very important to identify early signs of abstinence. [30]

Almost all classes of medications can potentially cause delirium. The most important of these are anticholinergic drugs, sedatives and hypnotics. Vulnerability depends on the presence of dementia, the type and severity of background disease,

although studies of the association between anticholinergic drugs and the severity of delirium have not shown additional effects of dementia. The risk increases with the simultaneous appointment of more than three drugs.

Attention deficit hyperactivity disorder (ADHD) and autism are common among children and adolescents, but also occur in adults. [31-34] Often, cases of childhood autism are accompanied by symptoms of ADHD. Approximately 30% of young children with autism have symptoms of ADHD. Most ADHD medications tend to increase the amount of the neurotransmitters - dopamine (DA) and/or norepinephrine. It is recommended that Bupropion never be combined with monoamine oxidase inhibitors (MAOIs) or taken within 14 days of an MAOI because the result can be serious and even fatal reactions such as high body temperature, muscle rigidity, twitching, and agitation, resulting in delirium, and coma. [35]

Among surgical patients, the risk of delirium is associated with dementia, low cardiac output, hypotension and anemia in the perioperative period, postoperative hypoxia, use of anticholinergic drugs, catheterization of the bladder. [7,11,13-16]

In the treatment of mental illness, various groups of psychotropic drugs are used: neuroleptics, antidepressants, tranquilizers, mood stabilizers and stimulants. They have different effects on the condition of the dental system, causing hyper- or hyposalivation, reducing pain sensitivity, which contributes to the transition from acute to chronic dental diseases. [36] Dentists who work with the elderly and people with mental illness should be aware of the risks associated with delirium during dental treatment, especially when using sedatives and anesthesia.

Pathological gambling can become a serious problem for humans, in particular, causes depression and suicidal thoughts. [37]

This problem is not only related to young people and also has a relationship with delirium, especially patients with

Parkinson's disease. [38] An important side effect of Parkinson's disease (or its treatment) is pathological gambling. [39] Easy access to internet gambling has brought temptation into the homes of vulnerable patients. They may run up substantial debts before the problem is recognized. People with Parkinson's disease comorbid pathological gambling may be more exposed to delirium compared to people without pathological gambling.

## DIAGNOSTIC PROCEDURE AND PROGNOSIS OF DELIRIUM

In clinical practice, the diagnosis of delirium is often incorrectly made. The main reasons are the "skipping" of delirium in the absence of arousal, aggression and hallucinations, as well as its fluctuating course of symptoms. It requires careful and detailed documentation of the course of symptoms by attending physician and the nurses on duty, who see the patient throughout the day.

Diagnostic criteria for delirium well-presented in Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). [40] It includes:

- 1) impaired attention (decreased ability to concentrate, maintain and switch attention);
- 2) the disorder, developing over a short period of time (usually several hours or days), characterizes by a change in the state of attention and consciousness in relation to the affected person, has a tendency to daily fluctuations in the severity of symptoms;
- 3) Additional cognitive disorders (memory deficits, disorientation, speech disorders, visual-spatial abilities or perception);
- 4) the disorders described in paragraphs 1 and 3 may not be due to other pre-existing chronic or developing neurocognitive disorders (including dementia) and do not occur during disturbances of consciousness, such as coma;
- 5) information from the patient's history, objective examination or additional investigations prove that the disorders are a direct physiological consequence of somatic

(body) disease, poisoning or withdrawal symptoms.

Delirium may also be diagnosed with help of the Tenth Revision of the International Classification of Diseases and Related Health Problems (ICD-10). [41] It includes:

- A. Disorders of consciousness and attention;
- B. Global cognitive impairment;
- C. Psychomotor disorders;
- D. Sleep / wake cycle disorders;
- E. Emotional disorders.

The clinical diagnosis is based on a careful history taking by questioning the relatives of the patient or the medical staff under whose supervision the patient was. Detailed history and physical examination are performed to identify conditions that contribute to the onset, progression, and persistence of delirium. The main groups of such conditions are drug intoxication, cardiovascular and neurological disorders, as well as infections. It is important to remember that delirium may be the only manifestation of a severe illness.

Drug treatment contributes to up to 40% of all cases of delirium. In addition to cholinolytics, anticholinergic properties have numerous drugs of other groups (digoxin, furosemide, cimetidine, prednisone). The possibility of withdrawal of alcohol or sedatives should also be considered.

Laboratory tests (blood sugar, electrolytes, kidney and liver tests) and a hidden infection (such as a chest x-ray) can help identify the trigger. However, it cannot be detected in 15–25% of patients. [8,16,17]

Examination of cerebrospinal fluid is indicated for patients with fever and suspected meningitis. Studying the EEG can be useful. The frequency of false-positive results of this test is 17%, and false-negative is 22%. The role of neuroimaging has not yet been determined, its feasibility is questionable, except for patients with focal neurological symptoms and difficulties with neurological examination.

Differential diagnosis includes:

- 1) delirium due to intoxication;



- 2) delirium due to withdrawal of alcohol and/or psychoactive substance;
- 3) disorders of consciousness that do not meet the criteria of delirium, but occur in other mental disorders, most often in dissociative (conversion) disorders, acute stress reactions, catatonia, schizophrenia and epilepsy;
- 4) dementia;
- 5) depression.

Differential diagnosis should mainly be made with dementia and functional mental illness. For the clinician, one of the most difficult situations is a sudden change in the cognitive functioning and behavior of a patient with dementia, many of whom will be diagnosed with delirium. However, such changes can also be caused by depression or a stress response to pain and environmental changes. Differentiation is hampered by the lack of cooperation of the patient. Depression is characterized by similar episodes in the anamnesis, the absence of fluctuations during the day and the dominance of depressive feelings. Manic states are also characterized by a history of euphoria / irritability. In both of these conditions, the EEG will be normal. In schizophrenia, the cognition is clear, hallucinations, unlike delirium, are systematized, bizarre, and unrelated to the environment.

The prognosis for delirium in elderly patients is poor. It is an independent predictor of prolongation of functional incapacity, duration of admission and death. In many patients, the symptoms of delirium persist for 6 months or longer, and background dementia progresses rapidly. Better premorbid status has a positive effect on the consequences of delirium.

## TREATMENT OF DELIRIUM

The basis of treatment of delirium is the diagnosis and treatment of conditions that contribute to the occurrence of delirium. If possible, cancel or reduce the dose of psychotropic, narcotic or anticholinergic drugs. It is important do not rush to correct arousal or aggression with

antipsychotics – assessing the patient's condition and finding the causes of delirium is the main role at this stage of treatment. Rapid and adequate treatment of somatic diseases, ensuring sufficient oxygenation of the brain, water-electrolyte balance and analgesia are necessary. Supportive care includes feeding, support of motor and psychosocial needs, prevention of aspiration, falls and bedsores.

Sometimes the symptoms of delirium are so pronounced that rapid pharmacological control is vital. Antipsychotics should be administered in minimal doses for as short a time. It is advisable to use haloperidol, which has a relatively small sedative, anticholinergic and antihypertensive effect. An initial dose of 0.5 mg is adequate. The action begins in 10-30 minutes, and the peak of action in 40 minutes (for oral administration – 4-6 hours). Therefore, the injection should not be repeated earlier than 20-30 minutes. Sometimes rapid drug loading with repetition of a successful dose every 30 minutes is necessary for control of restlessness and aggression. CNS depressants (benzodiazepines, barbiturates) should be avoided as they may worsen delirium. The exception is delirium associated with the withdrawal of alcohol or sedatives and hypnotics, when prescribed chlordiazepoxide 25-50 mg every 6 hours or diazepam 2-5 mg every 12 hours (with or without haloperidol).

There is currently little evidence that non-pharmacological measures such as face-to-face contact reduce symptoms, but measures such as general care and support are helpful. It is important that maintaining visual, verbal and tactile contact with relatives reduces behavioral disorders. During agitation, it is necessary to have a constant control over the patient.

Systematic detection and treatment of delirium in a hospital (geriatric facilities) improves the prognosis. Interestingly, these measures are more effective in a surgical hospital than in general medical wards.

In many cases, delirium occurs and persists after hospitalization of patients under the influence of factors such as drug intoxication, infections or unusual environment. Non-drug measures (supportive care, anxiety reduction, etc.) can reduce the risk of delirium in elderly surgical patients. Patient-controlled analgesia significantly reduces the risk of delirium. Patients should be provided with comfortable environment for night sleep and day activity.

Elderly patients often do not have a complete set of symptoms of delirium. One or more symptoms that may precede brief presentation of delirium or may not progress to it.

There are three main ways to improve the treatment of delirium that are still under research and have not been approved yet. First of all, it is the creation of medication that affects neurochemical disorders. Increased serum cholinergic activity in these patients suggests that cholinergic drugs (rivastigmine and donepezil) may be appropriate in the treatment of delirium. Temporary remission, which can be achieved after injections of flumazenil, a short-acting benzodiazepine receptor antagonist, suggests that similar longer-acting drugs may be useful. The effect of mianserin indicates the possible effect of 5HT-receptor antagonists. The use of selective dopamine antagonists that affect certain receptors (separately on D1, D2, D3 and D4) is also considered.

The second possible way is to reduce serum anticholinergic activity.

The third field of research is the actual nature of delirium and a possible change in perceptions of it. In many patients, the symptoms persist even after 12 months both in the presence of dementia and without it. These findings suggest that in many elderly patients, delirium is a chronic disease with periods of exacerbation, which are identified as episodes of delirium. Therefore, it can be concluded that such patients need careful monitoring and, if necessary, the

prescription of drugs that improve cognitive function (e.g., donepezil).

## CONCLUSIONS

Delirium is an acute reversible organic mental disorder characterized by impairment in attention and cognitive function, increased or decreased psychomotor activity, and impaired sleep and wakefulness. About 10-15% of patients in general wards have signs of delirium, but most often delirium occurs among patients in ICU. Delirium increases the mortality of patients in the ICU, increases the duration of admission and the cost of treatment. In addition, it is associated with an increased risk of developing cognitive impairment. The development of delirium in adult patients is associated with four main factors: impaired consciousness, the presence of a history of hypertension, alcoholism, as well as the severity of the patient's condition on admission. There are two main methods of treatment: non-pharmacological and pharmacological. Delirium is a serious and complex problem that is associated with adverse outcomes, including increased mortality in hospitals. Prevention of delirium is possible and necessary. It is important to help patient as early as possible in order to reduce the severity and duration of delirium and its outcome.

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