ORIGINAL ARTICLE

# Delirium

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**Abstract**

Delirium is an acute organic psychosyndrome resulting from global brain dysfunction after various direct or indirect insults. It is a qualitative consciousness disorder, an confusional state manifesting by many behavioural and psychological symptoms such as psychomotor hyper/hypo-activity, agitation, hallucinations, changeable delusions and many others, fluctuating in time. The most endangered are elderly, polymorbid patients and psychoactive agents, especially alcohol, abusers. Unrecognized and untreated delirium may have lethal consequences or may significantly increase the morbidity and prognosis of the patient. The treatment is based on underlying cause (if any specific present) recognition and management, supportive and symptomatic treatment. In the last one usually the antipsychotics in somatic and benzodiazepines in withdrawal delirium are used.

## Introduction

**Delirium** (earlier the acute organic psychosyndrome, the acute brain syndrome or the acute confusional state) **is defined** as an etiologically nonspecific acute organic brain syndrome, generated on the global brain dysfunction, manifesting by numerous psychological and behavioural symptoms (Smolík 1996; Praško *et al* 2004; Seifertová & Praško 2007; Jirák *et al* 2002; Topinková 2004; Bednařík *et al* 2004).

The acute confusion with coincidental consciousness and attention, perception, thought process, memory, psychomotor activity, affectivity and wake-sleep cycle disorder are characteristic. Delirium is an transitory condition and its' intensity is variable and subsides in 4 weeks or earlier in most of the patients, but sometimes it may last until 6 months (Smolík 1996). It is a frequent, life threatening condition with a high risk of multiple complications. Still delirium remains often undiagnosed and unrecognised even in the intensive care patients (Hovorka & Herman 2010).

In the ICD-10 the delirium is described according to the underlying condition of the patient in section F0 and F1 (Smolík 1996). The symptomatology and diagnostic criteria are almost identical in both sections. F05 category presents delirium, not induced by alcohol and other psychoactive substances as F05.0 – delirium not superimposed on dementia, so described and F05.1 – delirium superimposed on dementia. F1x.x category presents the withdrawal state with delirium (intoxication or withdrawal syndrome with delirium, the 3rd code "x" specifies the type of the psychoactive agent) as F1x.03 – acute intoxication with delirium and F1x.4 – withdrawal state with delirium (e.g. F10.4 delirium tremens, the alcohol withdrawal delirium).

## Clinical appearance

**The onset** of the delirium is acute or rather subacute, for example in the withdrawal states, developing mostly in 24–72 hours (Praško *et al* 2004; Seifertová & Praško 2007; Topinková 2004; Hovorka & Herman 2010; Pompei *et al* 1994; Caplan 2008; Caraceni & Grassi 2003). The prodromal symptoms are non-specific and in about 1–2 days precede the complete delirium development. Those most frequently are anxiety, mild restlessness, vivid dreams, insomnia, and overall hypersensitivity and sometimes clear thinking difficulties. The attention, thought process, memory and clear thinking (the marginal becomes important and vice versa) disturbances and disorders ensue. The **characteristic confusion** develops – disorientation, at first in time, later in situation and personality as well. Also the circadian fluctuation of the symptomatology with intervals of lucidity in daytime and deterioration in the evening and at night is characteristic (**sundown syndrome**). On the other hand recent studies have described the early morning worsening of the symptoms especially in elderly patients (probably due to the specific sleep apnea of the elderly) (Sandberg *et al* 2001; Topinková 2003). The sleep is also disturbed by the vivid and horrifying dreams. In the **fully developed delirium** the illusions, hallucinations (usually visual) and thought process disturbances with unsystematic, changeable delusions (paranoid, persecutory) with full anosognosia and confabulations are present. The psychomotor activity and behaviour is disturbed. The agitation, restlessness, aggression predominate and may unpredictably alternate with hypoactivity and apathy. Delirium may present as a **hyperactive state** with increased arousal, psychomotor activity and agitation with substantial vegetative and other psychological symptoms (illusions, hallucinations, delusions), which is typical for the withdrawal or intoxication delirium. Those patients probably best correspond with the tenacious image of the delirium, they are diagnosed and treated early and their prognosis is stated to be more favourable. In many patients the delirium manifests as a **hypoactive state** with decreased arousal and psychomotor activity and corresponds with formerly described amentia. There are also worse prognosis, delayed diagnostics, treatment and later complications development stated. This type of the delirium encourages to the active diagnostics, especially in patients hospitalized at the ICU and somatic wards. In the rest of the patients the **mixed type of the delirium with fluctuation** between the two mentioned types is present.

The **somatic symptoms** are the components of the delirium, they present at two levels: The vegetative ones comprising tachycardia, blood pressure fluctuations, body temperature increasing, mydriasis, hyperhydrosis, nausea, vomiting and diarrhoea. The neurological ones comprising tremor, ataxia, dysartria, dysfagia, agnosia, aphasia, myoclonus and epileptic paroxysms (usually generalized tonic-clonic convulsions).

The complete or fragmentary amnesia are also among the delirium symptoms. Typical clinical symptomatology is showed in the Table 1.

**Tab. 1.** Clinical signs of delirium (Praško *et al* 2004).

**Psychopathology:**
- Qualitative consciousness disorder – confused up to chaotic mental activity, reduced ability of attention tenacity and distribution;
- Hypoprosexia: difficulties in keeping the vigilance during the examination
- Thought process: may be accelerated or decelerated, fragmented, inconsistent, in more severe forms even disorganized or incoherent with fleeting paranoid ideas or even delusions, judgement disturbances (the patient cannot recognize the reality from his oneiroid dreamy visions);
- Psychomotor activity: increased, decreased or alternating of both, often serious excitation;
- Disorientation: in time, place, situation and sometimes person;
- Perception disturbances: misidentifications, illusions and hallucinations (usually visual, tactile, less frequently auditory);
- Qualitative thought disorders: transient bizarre delusions, often changing;
- Memory: deteriorated, especially short-term;
- Increased suggestibility;
- Sleep-wake cycle disturbances (most frequently circadian inversion with sleepiness by day and restlessness at night)

**Physical signs:**
- Based on brain dysfunction: tremor (mild first, later rough), ataxia, agnosia, dysarthria, dysgraphia, sometimes aphasia, acute symptomatic seizures;
- Based on autonomic nerve system dysfunction: body temperature rising, mydriasis, facial flush, tachycardia, hyperhydrosis, blood pressure oscillations, nausea, vomiting, diarrhoea

**Behavioural disorders:**
- Restlessness and hyperactivity (e.g. touching and manipulation with the bedlinen, getting up from bed) with aggression, combativeness (attacking unreal subjects or persons) or obstructing the general care (patients get up, wonder or "haunt", escape);
- Contrarily apathetic, withdrawn behaviour with decreased activity, up to stupor;
- Oscillating apathy and restlessness with unpredictable changes

There is a complete or partial amnesia after the delirium subsides

**Duration** of the delirium differs and depends on the underlying cause. If it is reversible the recovery comes within day or weeks, mostly in 1–4 weeks.

## Epidemiology

Delirium is one of **the most frequent psychiatric disorders at somatic and psychiatric wards** (Praško *et al* 2004; Seifertová & Praško 2007; Hovorka & Herman 2010; Caplan 2008; Fann 2000; Brown & Boyle 2002). The general incidence at somatic wards is about 10–15%. **The risk of the delirium is increased by**: older age, somatic comorbidity – especially severe and terminal states, dementia, hospitalization itself, admission to the ICU, major surgery (chest, orthopaedic, neurosurgical, abdominal). In patients over 65 years of age the delirium incidence is about 15–30%, and sometimes is also the first sign of the somatic disorder. At the gerontological wards the delirium incidence is 30–50% after major surgery and at the ICU. On the other hand in patients after small surgery (cataract) the delirium incidence is 5% and in elderly population at home is 3–5% only (Jirák *et al* 2002; Bednařík 2004; Hovorka & Herman 2010; Caplan 2008; Milbrandt *et al* 2004). **The delirium, especially the unrecognized and untreated one has a negative impact on the prognosis**, regardless the primary disease: it delays the recovery, prolongs the hospitalization, increases the mortality and morbidity. According to the literature death occurs in 25% of the identified cases (Praško *et al* 2004; Hovorka *et al* 2006). Delirium increases the treatment costs by the 39% at the ICU and by 31% at the standard wards (Milbrandt *et al* 2004). It is generally stated the 30–60% of the deliria remain undiagnosed. Along with the aging and increasing death point of the population with somatic diseases the incidence of the delirium will rise and have more serious social impact (Praško *et al* 2004; Seifertová & Praško 2007; Topinková 2004; Bednařík 2004; Hovorka *et al* 2006; Caplan 2008; Fann 2000; Brown & Boyle 2002).

## Etiopathogenesis and underlying causes

**Delirium develops as an acute, nonspecific global reaction (dysfunction) of the brain to various noxes and their combinations**. There are numerous pathophysiological mechanisms of the delirium development and they are not sufficiently understood yet. The delirium development is associated with generalized disturbance of the oxidative mechanisms, energetic metabolism, homeostasis (electrolyte imbalance, osmolarity, acidobasic equilibrium), disturbance of the agents, needed for the structural and functional integrity of the brain, synthesis, including neurotransmitter, neuromodulator and neurohumoral imbalance (Praško *et al* 2004; Seifertová & Praško 2007; Jirák 2002; Hovorka *et al* 2006; Hovorka & Herman 2010; Caraceni & Grassi 2003). Some authors state the specific brain structures, especially in the right, non-dominant hemisphere and neurotransmitter systems, present the final pathophysiological track ("final common pathway") leading to the delirium manifestation (Bednařík 2004; Bourgeois *et al* 2003; Trzepacz & Van der Mast 2002).

At the level of neurotransmitters, the most important factors responsible for crucial symptoms are acetylcholine deficit and dopamine hyperactivity. The acetylcholine deficit is associated with vigilance decreasing, attention disturbance, confusional states, others cognitive dysfunctions and with the sleep-wake cycle disturbance in the delirium. The cholinergic hypoactivity in the ARAS-thalamic-cortical system is understood to be a cause of the increased vulnerability of the elderly and demented patients. Similarly there is a well known risk of the anticholinergic medication. According to the dopaminergic hypothesis the hyperdopaminergic activity is associated with the agitation development and the therapeutic effect of the antipsychotics and with the excitatory and neurotoxic agent – glutamate release as well (Caplan 2008).

In the alcohol, sedatives and hypnotics withdrawal delirium the **GABA-A transmission** decrease and ensuing glutamate, NMDA, dopaminergic and noradrenergic transmission increase was described. Those findings together with the increase of the free oxidative radicals and intracellular influx of the calcium are associated with the neurotoxicity, damage and destruction of the neurones, increased arousal and sympathetic activity are parts of the delirium tremens characteristic. The benzodiazepines and clomethiazole use is also in accordance with the GABA-ergic model and may have a positive influence on the withdrawal and epileptic seizures. Others presumptive pathogenetic mechanisms are hypercortisolemia, β-endorphine system hyperfunction and cytokine increase (Praško *et al* 2004; Caplan 2008).

**Delirium results from the 3 broad pathophysiological categories interaction** (Praško *et al* 2004; Hovorka & Herman 2010; Caplan 2008; APA 1999; NICE 2010), as we show in the Scheme 1.

- **Individual vulnerability**, or rather patient sensibility to the delirium development results from the individually accumulated risk factors ("patient-related")
- **The underlying causes** of the delirium ("illness-related") are inversely proportional to the vulnerability. The higher vulnerability is present, the minor noxis is sufficient for delirium to develop. For example the postoperative state in elderly or vulnerable patient and vice versa, the serious underlying cause in otherwise healthy or young patient (e.g. brain infection or trauma). The number of potential underlying causes of the delirium is very high even unlimited (Caplan 2008). The broad version is shown in Table 2. There is also a mnemonic device to shortlist the most frequent causes of delirium: "I WATCH

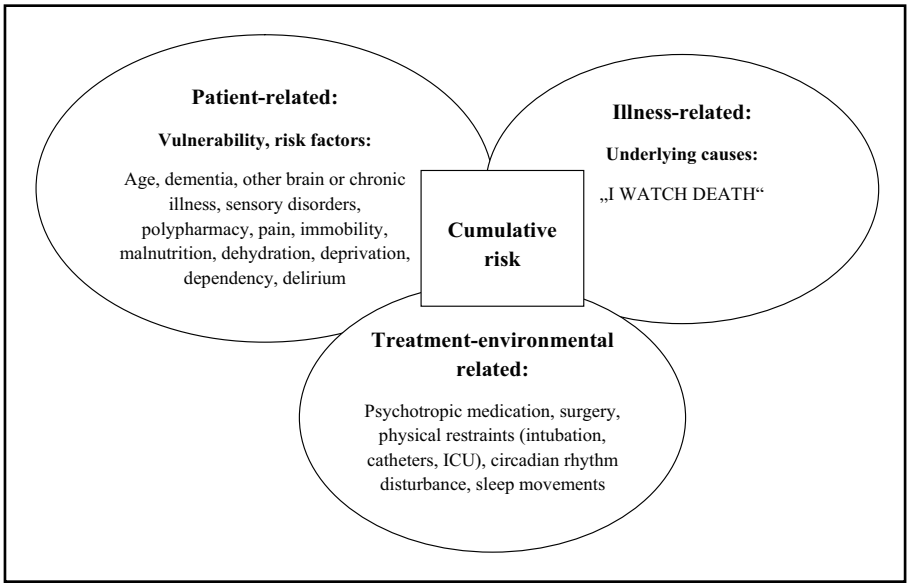
DEATH" (Caplan 2008; Wise & Trzepacz 1996) (Table 3).

- **The treatment related factors**, "treatment-environment-related", also iatrogenic factors (Scheme 1) that are considered to be very important in connection with the intensive care at the ICU (Caplan 2008). It is a risky polypharmacy, anticholinergics included, antihistaminics, corticosteroids, opiates and benzodiazepines (Table 2) and also others restrictions connected with intensive care (Scheme 1) (Caplan 2008; Gaudreau *et al* 2005; Wise *et al* 1999).

## Diagnostics of the delirium

It may sound trivial, but for the diagnostics of the delirium it is crucial event to think about the possibility of its presence. The symptomatic treatment of the delirium must always be preceded by the differential diagnostics of its underlying causes. **The diagnostics of the delirium always covers the two main levels**: the symptomatic and etiologic diagnosis.

- **The symptomatic diagnostics** of the delirium is based on the clinical features earlier described (Table 1). The early diagnosis is considered as an important prognostic factor. Given a frequent incidence of the hypoactive form of the delirium at the somatic wards and in the intensive care, the continuous psychical state monitoring is recommended, especially when the risk of the delirium is high (ICU, postoperative states, Scheme 1). There the use of basic screening scales for non-psychiatric professionals is recommended. The nurses and other treating personnel may be beneficial, because they are in more frequent contact with the patient. There are numerous of those scales for example Confusion assessment Method (CAM), Intensive Care Delirium Screening Checklist (ICDSCH), Delirium Observation Screening Scale (DOSS), Delirium Rating Scale (DRS) and many others accessible on the internet and in the literature (Praško *et al* 2004; Seifertová & Praško 2007; Bednařík 2004; Andrefsky& Frank 2002; Inouye *et al* 1990). As an example we give the Confusion Assessment Method in the Table 4 in a version published in Czech (Topinková 2004). In suspicion of the delirium the medical, preferably psychiatric examination and etiologic diagnostics ensues.
- **Etiologic diagnostics** is crucial when considering the causal treatment and prognosis. It refers to numerous intracranial and extracranial causes, as we show in the Tables 2 and 3. We cannot go along with the symptomatic diagnostics and treatment of the delirium only in case of the causally treatable patient, for example with stroke, SDA, SDH, hydrocephalus, brain abscess, herpetic or other encephalitis, metabolic encephalopathy, bacterial endocarditis, urinary tract infections etc.
- The **diagnostic process follows those steps** (Praško *et al* 2004; Seifertová & Praško 2007; Bednařík 2004; Hovorka *et al* 2006; Hovorka & Herman 2010; APA 1999; NICE 2010; Andrefsky & Frank 2002):
  a. **Complex clinical, physical examination** – especially internal (the chest auscultation, body temperature, blood pressure, ECG included) and neurologic (focal deficit, meningism etc.), the external signs of the head trauma, needle marks after illicit drugs or medication application exclusion,




**Scheme 1.** Elemental pathophysiological factors in delirium development. Usually there are more factors acting at the same time (Caplan 2008).

the eye fundus examination. So the attention must be paid to the associated signs, that may guide us to the somatic cause of the delirium.

**b. Objective history** given by the accompanying person, relatives, general practitioner or documentation. When, where, under what circumstances the delirium had developed, what preceded, how was the course, serious comorbid somatic and psychiatric disorders, the head trauma, epilepsy, suicidal tendencies, drug dependence, pharmacotherapy and its recent changes included. Is it the first episode of such a state?

**c. Subjective history in delirious patients** in its validity is quite limited by the clinical condition and is more likely part of the objective psychiatric examination and the clinical symptoms of the delirium investigation (Table 1). The target signs are: vigilance, orientation, attention, short-term and immediate memory, the familiar objects recognition, perceptual and thought process disturbances, psychomotor activity.

**The general principles of the examination are** – calming tone of voice, sympathy, let the patient to speak spontaneously, asking complementary factual questions – personal

**Tab. 2.** Extracranial and intracranial causes of the delirium (Hovorka *et al* 2006)**.**

**Intracranial organic causes (diffuse, multifocal and focal encephalopathies of different etiology)**

- **Dementia – "delirium superimposed on dementia" of different eitology,** in Alzheimer disease, vascular dementia, dementia in other diseases e.g. Parkinson's, Pick's, Huntington disease, AIDS, hydrocephalus, the normotension hydrocephalus included, Wilson's disease, Wernicke's encephalopathy and dementia in others brain and extracranial causes. Dementia is one of the most important risk factors for delirium development, especially in combination with other noxes.
- **Vascular brain diseases – strokes** acutely, during the stroke, most frequently in first 24–72 hours, in transitory ischemic attacks (reversible as well as irreversible, ischemic and haemorrhagic the subarachnoid haemorrhage included), resulting from stroke in combination with other risk factors, chronic vascular brain diseases (hypertensive encephalopathy, hypoxic-ischemic encephalopathy in atherosclerosis, vasculitis, etc.)
- **Head trauma –** epidural and subdural hematoma, brain contusion, diffuse axonal damage.
- **Brain tumours –** primary and metastatic, the meningeal carcinomatosis included, paraneoplastic encephalopathy and **intracranial hypertension syndrome**.
- **Epilepsy – ictal** (esp. NCSE-nonconvulsive status epielpticus), **postictal** (esp. after cumulated generalized tonic-clonic or complex partial- "psychomotoric" epileptic seizures), less frequently **interictal** (e.g. due to the medication and other risk factors)
- **Neuroinfection –** encephalitis (e.g. viral, herpetic), meningoencephalitis, meningitis, brain abscess, septic embolization, neurolues, etc.

**Extracranial causes**

- **Withdrawal syndromes –** in alcohol, barbiturates, benzodiazepines, opiates dependency, abrupt SSRI discontinuation.
- **Intoxication – psychotropic agents: Illicit drugs and agents –** hallucinogens, psychostimulants, alcohol. **Medicaments** – with anticholinergic effect, tricyclic antidepressantns, atropine, 1st generation antipsychotics (malignant neuroleptic syndrome), serotonin syndrome (esp. in rapid SSRI dose escalation or in combination with other drugs e.g. IMAO, selegilin, with some opioids – tramadol), antihistaminics, anticholinergicly acting antiparkinsonics, L-dopa and dopaminergic agonists, lithium, hypnotics, benzodiazepines, barbiturates and some types of antiepileptics, H2-blockers, betablockers, antihypertensive drugs, antiarrhythmics, digoxine, indomethacine, antiviral agents, antimalarics, antibiotics, corticosteroids etc. **Industrial toxins** – pesticides, carbon monoxide, volatile agents, solvents etc. **Natural toxins** – phytotoxines, mushrooms (atropine), snake venoms.
- **Metabolic and endocrine diseases** causing diffuse encephalopathy e.g. in "end-stage" organ failures (hepatic encephalopathy, uremia, porphyria), hypo/hyperglycaemia, endocrinopathy (thyreopathy, pituitary disorders), dehydration, electrolyte imbalances, vitamin deficiency (B1-Wernicke's encephalopathy, B12, folic acid), malnutrition, etc.
- **Infections –** pneumonia, sepsis, bacterial endocarditis, urinary tract infection, hepatitis, typhoid, malaria etc.
- **Cardiovascular and respiratory diseases –** especially with sings of cardiopulmonary failure, arrhythmias, myocardial infarction, aortal and brain vessels stenosis.
- **Postoperative states –** develop usually in first 3 days, duration is up to 1 week after major chest surgery (cardio-surgery), orthopaedic (fr. colli femoris), neurosurgery, urology (prostate), less frequently ophthalmic surgery (cathracta); this is typical delirium based on multifactorial causes, which is very frequent so called "postoperative delirium"
- **Other diseases –** burn injuries, heat stroke, hyper/hypothermia, anaemia, shock, paraneoplastic states.
- **Other risk factors:**
  **Somatic –** high age without dementia, other risks in elderly patients – urinary and stools retention, pain, vision and hearing disorders, sleep disorders, other organic brain disorders, polypharmacy (esp. risky medication), alcohol dependency, delirium in personal history.
  **Psychosocial stressors** – situational, environmental or staff changes, immobilization, sensory deprivation, the ICU stay with circadian regime disturbance, psychical stress, life difficulties, etc.
  **Combinations of all mentioned risk factors** – extracranial and intracranial

**Mental disorders with delirium**

- Delirious forms of mania.
- Melancholic type of depression.
- Delirious states in schizophrenia, schizoaffective disorder.
- Pharmacologic treatment of the mental disorders complications

**Tab. 3.** The most frequent causes of delirium, mnemonic device "I WATCH DEATH" (Caplany 2008; Wise *et al* 1996). In alphabetical order.

| | |
|---|---|
| **I**nfection | Encephalitis, meningitis, pneumonia, typhoid, sepsis, syphilis, urinary tract infection |
| **W**ithdrawal | Alcohol, sedatives (barbiturates, anxiolytics), hypnotics |
| **A**cute metabolic | Acidosis, alcalosis, electrolyte disturbances, liver failure, renal failure |
| **T**rauma | Postoperative states, heat shock, burn injury |
| **C**NS pathology | Abscess, epilepsy, stroke-ischemic/ haemorrhagic, meningitis, tumour, normotensive hydrocephalus, trauma, vasculitis |
| **H**ypoxia | Anemia, hypotension, CO intoxication, pulmonary embolism, cardial or respiratory failure |
| **D**eficiencies | Vitamin B12, niacin, thiamine (Wernicke's encephalopathy) |
| **E**ndocrinopathy | Hyper/hypo: -adrenalism, -glycaemia, -cortisolaemia, -thyreosis, -parathyreosis |
| **A**cute vascular | Hypertensive encephalopathy, shock |
| **T**oxins or drugs | Drugs, mushrooms, medication, pesticides, solvents |
| **H**eavy metals | Manganese, lead, mercury |

**Tab. 4.** Easy assessment scale for delirium diagnostics, for non-psychiatrists and treating staff, CAM (Confusion Assessment Method).

| | |
|---|---|
| **1.** | **Acute onset, psychical condition and behaviour changes, their fluctuation**<br>Those targeted questions are the source of information in objective history taking, from the family or treating staff. |
| **2.** | **Inattention and lack of concentration**<br>Does patient have any difficulties with concentration? Is he distracted? Is patient loosing attention and context easily, for example during the conversation? |
| **3.** | **Disorganized thought process**<br>Does the patient have disorganized, illogical thoughts flow? Does not keep coherent, factual conversation? Is he switching from one subject to another unexpectedly? |
| **4.** | **Consciousness alteration**<br>Is patient's consciousness lucid (is he vigilant and orientated)? Any other condition is considered a positive answer. Is the patient agitated, hypervigilant, somnolent, soporous or comatous? |
| | **Assessment**<br>Diagnosis of the delirium according to the CAM requires positive both items 1 and 2 and then 3 or 4. |

data, actual complaints and their history, personal history ("biography", relationships, personal characteristics, interests, life problems and troubles, psychiatric and serious somatic illnesses and their treatment etc.).

**d. The laboratory and other supplementary examinations** – when (after the proper clinical examination) the underlying cause of the condition is not clear, or to the completion of the data in already known etiology. Beside the common labs the **toxicological examination** is important.

**The CT** is essential and cannot be put off in patient in risk of the intracranial process – the craniocerebral trauma (brain contusion, subdural and epidural haemorrhage), stroke (intracerebral haemorrhage, subarachnoid haemorrhage, ischemia), brain abscess, hydrocephalus, tumour, advanced to the spinal tap.

**The spinal tap** after contraindications exclusion (CT, fundus oculi examination) should not be put off in patients with possible meningitis, meningoencephalitis or subarachnoid haemorrhage.

**EEG** is crucial in diagnostics of the nonconvulsive status epilepticus (NCSE), that may be distinguished from the other types of the delirium with difficulties and are almost undiagnosable. Although those are rapidly and easily treatable by the antiepileptics (i.v. first) – the clinical condition and EEG is improving. The antipsychotics on the other hand may make the condition worse (Kaplan 1996; Pollock & Mitchell 2000; Hovorka & Janicadisová 2002; Hovorka *et al* 2003, 2007; Jacobson& Jerrier 2000). EEG may also help in diagnostics of the postictal confusional states in epilepsy, where the diffused or regional deceleration is found. Also in other cases the EEG may have a supportive diagnostic relevance: the diffused decelerated background and slow abnormity is found in diffuse encephalopathy (dementia for example), the periodic patterns and triphasic waves may be significant in diagnostics of the acute and subacute inflammatory encephalopathy (encephalitis, abscess) and noninflammatory (metabolic, hepatic). The atypical background of the beta low amplitude is found in the withdrawal states, in the delirium tremens, hyperactive and agitated patients. The regional abnormity is typical for focal brain lesions (Caplan 2008; Jacobson & Jerrier 2000; Hovorka *et al* 2003). But EEG should not replace the morphological, CT examination, especially in head traumas in history and in ambiguous acute states generally.

## Delirium complications

During the course of the delirium many complications may occur. Those, when insufficiently diagnosed and treated, prolong the hospitalization, increase the mortality and other morbidity, the switch of the delirium into the comatose state and other organic psychical disorders included (dementia, personality disorders, affective and cognitive disorders and others).

The most frequent complications are: falls form the bed resulting in injuries (fractures, intracranial haemorrhage), the ICU medical care disturbance by the agitation (extubation, laryngeal injuries, pulling out the catheters and monitoring sensors), internal complications (vomiting, aspiration, aspiration pneumonia, respiratory arrest, arrhythmias, bed sores, sepsis, death), escape from the ward resulting in injury or self-killing (Praško *et al* 2004; Seifertová & Praško 2007; Topinková 2003, 2004; Hovorka *et al* 2006; Caplan 2008). Despite the complete or partial amnesia the experience of delirium is traumatizing for the patient and may lead to the long-term psychical disorders interfering with the full recovery.

## The course and prognosis of the delirium

The duration of the delirium is variable and depends on the underlying cause and general condition of the patient and can be summarized into 3 points (see below) (Praško *et al* 2004; Seifertová & Praško 2007; Jirák 2002; Bednařík 2004; Hovorka *et al* 2006; Pompei *et al* 1994; Caplan 2008). If the cause is reversible, the delirium resolves in days or weeks, usually 1–4 weeks. Rarely it may last longer, till 6 months, the course is usually fluctuating, e.g. in hepatic, renal disorders, malignity, subacute bacterial endocarditis and in elderly patients. The prognosis is less favourable, the full recovery chance is smaller.

**Full recovery** – in the majority of patients with low vulnerability (young, healthy patients) and less severe or reversible underlying cause, the recovery is in 4 weeks. In elderly patients it is longer.

**The fatal ending** – the delirium results in coma and death in about 20–30%. It is connected with severe, irreversible cause (terminal organ failure, terminal stage of the malignity, irreversible brain damage) and with prolonged course of the delirium. The overall mortality in following months after experienced delirium is higher.

**The incomplete recovery** – is connected with irreversible brain damage, persisting neurologic deficit, epilepsy, organic psychical disorders (dementia, personality disorder, affective and cognitive disorders) and in small number of the patients also with functional psychical disorders (affective and psychotic).

## Management of the delirium

The delirium is an etiologically extremely multifactorial syndrome and the various causes often combine with each other. That's why the delirium management needs a complex approach with participation of many specialists (intensive and internal medicine and professionals, neurologists, psychiatrists etc.), the treating personnel and also the family of the patient. The treatment can be divided into six levels.

*Preventive arrangements*

The preventive arrangements are based on the detection and correction of the risk factors, especially in vulnerable patients (Scheme 1). The important and to the treatment susceptible area is the long-term pharmacotherapy optimization in vulnerable patients. There are many types of medicaments, which may participate to the development of the delirium (Table 2). The compensation of the chronic somatic or psychiatric disorders is crucial. In elective major surgery the psychological support is also extremely important (education, anxiety reduction). There is a need to explain all the future procedures to the patient and arrange appropriate environment afterwards (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008, Inouye *et al* 1999). Individually it is worth to explain the risk of the delirium to the patient himself and his family (relatively high incidence, but time-limited condition, underlying causes etc.). The delirium is not a sign of the onset of the permanent madness or psychiatric illness. Numerous studies have proved the positive importance of the multifactorial preventive arrangements. It covers arrangement we present as modification of the environmental conditions (Inouye *et al* 1999). The prophylactic effect of antipsychotics in somatic deliria has not been proved and is not used usually, in elderly patients it does not decrease the incidence of the postoperative deliria, but their severity and duration is reduced (Caplan 2008). In case of high risk of alcohol, sedatives and hypnotics withdrawal delirium it is reasonable to consider the prophylactic administration of benzodiazepines. Although unconventional, some authors see a benefit in continuing with small doses of alcohol in postoperative patients with chronic alcohol intake, but only in cases of good actual condition. (e.g. after orthopaedic surgery in healthy patients – one beer in the bed table).

*The underlying cause elimination and correction*

This is a priority in delirium management, and consists of the treatment of the cause, when possible. It is based on the etiologic diagnostics of the delirium, which should not be predominated by the symptomatic diagnostics and treatment only. More information can be found in etiologic diagnostics (Table 2).

*Care for the overall physical condition*

There are many factors that may significantly affect development and course of the delirium. Those are: patient monitoring and his safety ensuring, care about the homeostasis (hydration, nutrition), vital function support, prevention of the urine and stools retention, pain, anxiety and depression management, early mobilisation, chronic illnesses stabilization, optimization of the medication.

*The environmental conditions adjustment*

The environment **should be safe for the patient and should contribute to his calming down. The general rules are**: quiet and caring environment, the single room preferably or adequate bed distance, no superfluous subjects, frequent controls four per hour with attempts to reorient the patient, the outside noise minimization, soft nigh light for facilitation of the orientation at night, enough time information (wall clock, calendar, the day schedule charts), place and situation information (simple charts for WC, bathroom etc.), frequent visits from relatives, well known objects and photographs, the sensory handicaps correction (glasses, hearing aid), our speech is clear and simple, we try to calm them down, provide a feeling of safety, we do not disprove the delusions or hallucinations (the aggression and anxiety prevention). Just in extreme cases the **mechanical restraints** may be used to ensure patients and others safety but as short as possible (till the required effect is achieved) and with permanent monitoring of the patient (Praško *et al* 2004; Seifertová & Praško 2007; Doubek *et al* 2006). Above mentioned recommendations are necessary to keep also **at the ICU**. The patient with consciousness disorder should be treated the same as the fully conscious one. The watchful and sensitive approach of the treating personnel is absolutely important. Considering their frequent contact with the patient at the ICU, they may significantly contribute to the early diagnostics and monitoring of the delirium (see the scales) and may have a therapeutic effect as well. We minimize the potentially stressful events by the medication (pain, anxiety, hopelessness), keep the quiet environment (extra light and noises). Even at the ICU of the day stereotypes and normal circadian rhythm keeping, for example by the light changes simulation, night TV turning of, possibility of position changes, is important and sometimes underestimated. Patients who do not sleep well at night (e.g. fear of hallucinations) and ask for night conditions evocation during the day should not be complied because this could disturb the circadian rhythms and lead to prolonged recovery (Caplan 2008).

*The symptomatic and supportive treatment*

The symptomatic treatment of the delirium generally **belongs to the treatment of the agitation and psychomotor hyperactivity**, which may result in **aggression and the patients may be dangerous to themselves and others** (Doubek *et al* 2006; Doubek 2004). The agitation and psychomotor hyperactivity and restless-

**Tab. 5.** Recommended dosages of psychopharmacks in symptomatic treatment of agitated form of delirium (Praško *et al* 2004; Seifertová *et al* 2007).

| Drug | Single dose | Maximum daily dose | Single dose in elderly patients | Maximum daily dose in elderly patients |
|---|---|---|---|---|
| **Haloperidol** | Mild agitation: 0.5–2 mg<br>Moderate agitation: 2–5 mg<br>Severe agitation: 5–10 mg | 3–20 mg | Mild agitation: 0.5 mg<br>Moderate agitation: 1 mg<br>Severe agitation: 2 mg | 5 mg |
| **Tiapride** | 100 mg (100–200 mg ) | 800 mg (1800 mg ) | 100 mg | 400 mg |
| **Melperon** | 75 mg | 200 mg | 25 mg | 100 mg |
| **Risperidone** | 0.5–1 mg (2–6 mg ) | 2 mg (16 mg ) | 0.5 mg Not recommended | 2 mg Not recommended |
| **Olanzapine** | 2–5 mg (5–20 mg ) | 30 mg | Not recommended | No recommended |
| **Quetiapine** | 25–750 mg | 900 mg | Not recommended | Not recommended |
| **Sulpiride** | 100 mg | 600 mg | 100 mg | 300 mg |
| **Clomethiazole** | 300 mg | 4.8g (4–12 mg ) | Do not administer | Do not administer |
| **Diazepam** | 10 mg | 90 mg | Do not administer | Do not administer |
| **Lorazepam** | After 3 doses of haloperidol add 0.5–2 mg every 4 hours | Do not administer | Do not administer | Do not administer |

ness can be characterized as unspecified scheme of behaviour, the state when poorly organized and purposeless psychomotor activity, resulting from physical and mental discomfort, predominates. It can be found in several psychical disorders (schizophrenia, anxiety disorders, affective disorders etc.) (Inouye *et al* 1999; Meagher 2001). The symptomatic therapy **is indicated** in agitated and restless psychotic or uncooperative patient (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008; APA 1999; NICE 2010; Doubek *et al* 2006; Doubek 2004). It should not interfere with or postpone the etiologic diagnostics. The goal is to induce adequate sedation to ensure the safety of the patient and the others, to prevent exhaustion, improve the cooperation on treatment. The symptomatic treatment is based on open studies and clinical experience only. There are no given algorithms nor drug dosages and available guidelines represent just a suggestion of possible methods. The drugs are administrated in intermittent boluses, in as low dosages as possible for proper effectiveness, the rapid onset of the treatment and its adjustment to the general condition is essential. The treatment takes several days usually and its premature cessation, just after the improvement of the condition, may result in delirium relapse in next 24 hours.

In the symptomatic therapy the **antipsychotics, short-acting benzodiazepines** and **clomethiazole** are the standards. The dosages are presented in Table 5 (Praško *et al* 2004; Seifertová & Praško 2007). In alcohol withdrawal delirium the supportive therapy is essential.

**The antipsychotics** are considered to be drugs of choice **in patients with somatic diseases**, the dementia included, in accordance with the **"hypocholinergic/ hyperdopaminergic" model of the delirium**. Some of the psychiatric disorders are specific. For example in Lewy body dementia the extreme sensitivity to the antipsychotics side effects is described and is used as a implemental diagnostic criterion, the best tolerated one seems to be quetiapine (Caplan 2008). In patients with Parkinson disease the potentially risk medication (anticholinergic, dopaminergic hyperstimulation) should be corrected first and then the atypical antipsychotics can be used (tiapride, olanzapine, quetiapine), the first generation antipsychotics are contraindicated. In epilepsy the ictal or postictal delirium (treatable by antiepileptics) exclusion comes first. In case of interictal symptoms the primary medication should be modified and after that the low doses of atypical antipsychotics with smaller proconvulsive potential can be used. The drug of choice in patients with agitated form of the delirium the **haloperidol** is worldwide suggested (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008; APA 1999; NICE 2010; Wise *et al* 1999; Doubek *et al* 2006; Doubek 2004; Riker *et al* 1994). It is a typical butyrophenone antipsychotic, which has not anticholinergic nor considerable hypotensive effect, the extrapyramidal side effect (parkinsonian syndrome, tardive diskinesia, malignant neuroleptic syndrome, mostly akathisia) is rare in the somatic patients (may appear after intravenous administration). Nevertheless it is important to think of those side effects similarly as of the potentially proconvulsive acting (provoked epileptic seizures). Contrary to the benzodiazepines haloperidol is more effective in extreme agitation and also affects the delusions and hallucinations. It is an ideal drug in the intensive medicine, there is a flexible intravenous (preferable), intramuscular or oral administration (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008; Doubek *et al* 2006; Doubek 2004). The serum level peak after p.o. administration is in 4–6 hours, 5–20 minutes in iv. administration. The initial bolus is 0.5–10 mg depending on age and severity of symptoms. The recommended dosage is 1–2 mg every 2–4 hours until the patient is pacified well. The dosis maxima pro die is 3–20 mg (Praško *et al* 2004; Seifertová & Praško 2007). The more detailed information about the dosages can be found in Table 5. The intravenous or intramuscular dose may be repeated every 30 minutes until the sufficient pacification is achieved. In severe delirium not reacting to the boluses, according to some authors the continuous iv. infusion of 3–25 mg per hour can be safely used, although 10 mg per hour is the maximal dosage given by the guidelines (Praško *et al* 2004; Seifertová & Praško 2007). When administrated intravenously the ECG monitoring is recommended considering the QTc prolongation possibility carrying the risk of the torsades de pointes and sudden death, attention must be paid also to the hypocalemia, hypomagnesemia, bradycardia, pervious cardiac disorder and drug interactions. QTc interval longer than 450msec or its prolongation over 25% requires an urgent cardiologic intervention, the dose reduction or the discontinuation of the antipsychotic (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008; Hunt & Stern 1995; Sharma *et al* 1998). The visual monitoring of the ECG is preferred to the automatic one (Caplan 2008). After stabilization the administration of the drug should be oral, 2–3 times a day or in one dose in the evening. The dose should be reduced slowly in following 3–5 days and finished with evening administration to prevent the "sundowning" syndrome and to normalize the sleep-wake cycle (Wise & Trzepacz 1996).

Recently the 2nd generation antipsychotics with lower risk of extrapyramidal side effects – risperidone, quetiapine and olanzapine are preferred (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008). The dosages are shown in Table 5. Some of those drugs are not recommended in elderly patients because of the risk of cerebrovascular complications. Risperidone is usually administered in a single dose 0.5–1mg, alternatively divided in more doses. In patients with organic etiology the dose of 2 mg a day is usually maximal. It is a suitable drug in delirium superimposed on dementia (Praško *et al* 2004; Seifertová & Praško 2007). In delirium management in Europe, France and Czech the substituted benzamide tiapride is frequently used. In night deliria

it is administered in one dose of 100–200 mg in the evening. In daytime deliria even in elderly patients it is possible to administer up to 400 mg in 3–4 doses a day (in delirium tremens the doses are twice as high). Tiapride is considered to be appropriate for elderly patients (Praško *et al* 2004; Seifertová & Praško 2007; Topinková 2003, 2004; Brtko 2002). The **melperon** is used similarly, the doses are 75–150 mg a day or 25–100 mg in the evening, the dose is seldom higher than 200 mg a day.

The **typical antipsychotics** like chlorpromazine, thioridazine or perfenazine are not recommended anymore considering their strong anticholinergic and sedative effect and the risk of orthostatic hypotension (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008).

Other group of medicaments used in delirium management are **benzodiazepines**. The short-acting ones are preferred (e.g. midazolam, lorazepam), nevertheless in clinical practice the diazepam, clonazepam and oxazepam are often used. The benzodiazepines are the drugs of choice in alcohol, sedatives and hypnotics **withdrawal deliria**, and are also beneficial for **sleep induction**. The benzodiazepines are used in **acute symptomatic epileptic seizures management** (especially clonazepam, diazepam), that are frequently connected with withdrawal syndromes (up to 30%) and acute phase of the brain lesions (stroke, trauma, inflammatory process) with or without delirium. Such a symptomatic treatment is always time-limited to few days or weeks (in organic brain lesions), when we also temporarily use other types of antiepileptics. Except from the withdrawal syndromes the benzodiazepines in monotherapy are not recommended in delirium management. It does not affect the extreme agitation, hallucinations and delusions sufficiently and may, in some patients, cause the paradoxical excitation and excessive sedation, ataxia or confusion in elderly patients (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008; Wise *et al* 1999; Meagher 2001; Doubek *et al* 2006; Doubek 2004). Other indication for benzodiazepines administration is **the antipsychotics intolerance** (extrapyramidal symptoms) and **combined therapy** (e.g. augmentation of the haloperidol by 1–2 mg of lorazepam). This is beneficial in insufficient effect of the antipsychotics themselves, to rapid sedation induction, the doses and the extrapyramidal symptoms incidence is not as much high then (Praško *et al* 2004; Seifertová & Praško 2007; Caplan 2008; Doubek *et al* 2006; Doubek 2004).

In **alcohol withdrawal delirium** (delirium tremens) the vitamins (B1), electrolytes (magnesium, potassium), glucose and fluids supplementation is crucial (Praško *et al* 2004; Seifertová & Praško 2007; Doubek *et al* 2006; Doubek 2004; Havlůj *et al* 1991). In severe alcohol dependency the pure glucose administration may deplete the last reserves of the B1 vitamin and result in severe Wernicke's encephalopathy or acute cardiomyopathy due to the vitamin B1 deficiency. That's why the infusions should be replenished by thiamine if its oral administration is not possible.

In symptomatic management the **clomethiazole** and **benzodiazepines** are used in accordance with the GABA-ergic model of the delirium. The dosages are given in Table 5 (Praško *et al* 2004; Seifertová & Praško 2007). For pacification and calming down the **clomethiazol**e is used, 1–2 capsules á 300 mg and the dose can be repeated according to the actual condition. In alcohol withdrawal delirium the initial dose is about 4–6 capsules and later 2 capsules every 2 hours until the calming down effect is achieved or until the maximal dose of 24 capsules a day. Clomethiazole used to be available in intravenous infusions, but because of many fatalities due to respiratory failure after inappropriate administration in high doses and insufficient monitoring it was withdrawn from the market. At the ICU under close monitoring the clomethiazole doses may rise up to 7.2 g (12 g) (Praško *et al* 2004; Seifertová & Praško 2007). Clomethiazole may potentially cause respiratory centre depression, bronchial secret accumulation and may cause dependency, that's why it should not be administered longer than 10 day (Doubek *et al* 2006; Doubek 2004). In some cases the clomethiazole therapy was more effective and shorter and better tolerated than benzodiazepines (Havlůj *et al* 1991).

Clomethiazole may, but as a drug of second choice, also be used in organic deliria (Praško *et al* 2004). Alternatively to the clomethiazole, if its administration is not possible, haloperidol may be used in withdrawal delirium (the visual hallucinations reduction, but less effective in psychomotor agitation). Haloperidol may, except from the extrapyramidal effect, also have a potential proconvulsive effect, that increase the risk of acute provoked epileptic seizures in withdrawal delirium. In delirium tremens resistant to benzodiazepines the barbiturates effectiveness is described (Caplan 2008). Recently there were found no significant difference concerning the length of delirium tremens, length of hospitalization or complications between phenobarbital and diazepam and escalating bolus doses of diazepam and barbiturates if necessary reduce the need for mechanical ventilation and ICU length of stay and nosocomial infections appearance (Michaelsen *et al* 2010; Gold *et al* 2007). The parenteral ethanol administration is considered to be obsolent and carries many other organ complications. Nevertheless some authors consider ethanol to be the most natural way to "individual life homeostasis" achievement (Caplan 2008; Hodges & Mazur 2004).

Many wards, especially the psychiatric ones, prefer clomethiazole and **benzodiazepines**, if clomethiazole is not available or there is a contraindication of its use. Benzodiazepines in infusion are administered in high doses (60–90 mg of diazepam equivalent a day) exceeding usual therapeutic doses (Praško *et al* 2004). Because of the risk of respiratory depression in clomethiazole and benzodiazepines intravenous administration, the ICU stay is optimal (Havlůj *et al* 1991).

The clomethiazole and benzodiazepines therapy is short-term and after withdrawal state subsiding

their doses are reduced gradually, in benzodiazepines 15–20% approximately a day (Caplan 2008).

Less frequently there are also **other drugs** used in delirium therapy, e.g. antipsychotics – amisulpiride, ziprasidone, benzodiazepines – alprazolam, bromazepam, flunitrazepam, antihistaminics – promethazine having a good sedative effect and tolerability. In somatic patients and in intensive care are also other drugs used for other stress factors elimination, such as pain. Those are NSAIDs, metamizole, opioids (fentanyl, sufentanyl, alfentanyl). In case of nonconvulsive status epilepticus (NCSE) the therapy is started under EEG controle by intravenous antiepielptics (e.g. benzodiazepines, valproic acid, phenytoin, levetiracetame) and this treatment is long-term. Physostigmine has been effective in many types of deliria according to the "hypocholinergic" model. In practice it is used in anticholinergic delirium therapy only, and the effect is short-term, the therapeutic window is narrow, should be administered slowly, fractionally (1–2 mg repeatedly every 15min) with regard to possible cholinergic hyperstimulation and other known contraindications (Caplan 2008; Doubek *et al* 2006; Doubek 2004). Other cholinesterasis inhibitors (e.g. donepezil) did favourably affect the delirium incidence, but are not used in acute treatment(Caplan 2008).

In **opioid withdrawal delirium** the rotation opioid change is recommended to achieve better analgesic-side effect ratio. The best evidence is in morphine to methadone, fentanyl or oxycodon switch (Doubek *et al* 2006; Doubek 2004; Cherny *et al* 2001). Other rules except from the rotation are the way of application change, antipsychotics, the general condition care (Doubek *et al* 2006; Doubek 2004).

In many cases of delirium management the **rapid tranquilization**, agitation reduction are needed. This is important in acute diagnostic and therapeutic procedures realization (e.g. CT, intensive care). Here different wards use different drugs and methods. For example the iv. benzodiazepines (midazolam – the well controllable administration in bolus or continuously, short-term effect advantage, diazepam – diazepam – long-term effect, accumulation, choice when long-term sedation needed) sometimes in combination with tiapride or opioide (sufentanil – analgesic and sedative effect, morphine) are used. Other possibility is propofol (short-acting anesthetic drug with sedative, amnestic effect, the continuous or bolus administration, noncumulative, beneficial in elective awaking e.g. neurologic examination) (Caplan 2008), possibly in combination with tiapride. Midazolam is considered to be suitable in intensive care, it is administrable temporarily continuously. The unexpected awaking with extubation is here also described (Caplan 2008). For future, because of the high costs, there is a possibility of α2 agonist dexmedetomidin with short-term sedative-analgesic effect and reversible sedation inducement with minimal amnestic effect (Caplan 2008). In extreme cases the intensivist may use the neuromuscular blockage, the curarization with mechanic ventilation for as short time as possible.

*The subsequent care*

The subsequent care consists of psychotherapy, education of the patient himself and his family. We try to explain the causes, symptomatology and bizarre experiences gently. The goal is to understand those features, prevent the feeling of depreciation, guilt and improve the patient integration in his original environment. We invite the family for visits and try to involve them into the care for the patient already in the course of the delirium. Those are people the patient knows for long time, they may represent some peaceful islands of orientation (Praško *et al* 2004).

## Conclusion

The delirium incidence is high in the intensive care, there are many vulnerable patients and other risk factors. The hypoactive, less noticeable forms, that are worse diagnosable and have less favourable prognosis. The early diagnostics and adequate treatment are prognostically extremely important even in the intensive care patients, that's why there is a need to pay appropriate attention to them.

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