ORIGINAL ARTICLE

Delirium in surgery intensive care unit

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Abstract

Delirium is a common event in the hospitalized surgical patiens. The pathophysiology of delirium is incompletely understood yet, but numerous risk factors for the development of delirium have been already identified.

A literature review was performed using the National Library of Medicine PubMed database and Web of Science, including all resources within the period 1991–2011, additional references were found through bibliography reviews of relevant articles. The key word "delirium" with the following terms:"intensive care unit","antipsychotics", "benzodiazepine", "opioids", "elderly", "management". Constraints limiting time period of publications or their language were not applied. Reference lists of publications identified by these procedures were hand-searched for additional relevant references.

Delirium in the ICU (intensive care unit) is not only a frightening experience for the patient and his or her family; it is also a challenge for the nurses and physicians taking care of the patient. Furthermore, it is also associated with worse outcome, prolonged hospitalisation, increased costs, long-term cognitive impairment and higher mortality rates. Predisposing factors, such as age, impairment, and nature and severity of comorbidity, increase the risk of experiencing delirium during hospitalization. The management of delirium involves the concurrent search for and treatment of the underlying aetiology while actively controlling the symptoms of delirium. Antipsychotics are demonstrating efficacy in controlling the symptoms of delirium with less extrapyramidal side effects.

Proper diagnosis and treatment is important in the medical setting and significantly decreases the burden on the patient, caregivers, and medical system.

Introduction

Delirium is a neuropsychiatric syndrome characterized by an acute onset of disturbances of consciousness, attention, cognition, and perception that tend to fluctuate in time during the day and usually have an underlying etiological, physiological factor. Delirium is a complex psychic, behavioral and somatic reaction to diverse disturbances in cerebral metabolism (Lipowski 1990). The term delirium is derived from the Latin verb "off the track" and has to specify the condition of reversible madness (Tobias *et al* 1988). Delirium is a common event in the course of hospitalization but still underdiagnosed in many cases. Underrecognition of this syndrome leads to distress for patients and their caregivers, increased morbidity, length of hospitalization, and mortality. The age of the patient and the severity of the comorbid illnesses contribute

to a higher incidence of delirium in the medically ill (Han *et al* 2011).

Delirium is the most common psychiatric disturbance found at a general surgical ward, and its mortality and morbidity may get over all other psychiatric diagnoses. Only dementia has a higher mortality rate. Given the complexity and acuteness of many procedures, surgical postoperative units often have a larger proportion of patients with delirium, increasing the amount of hours required by staff (Ebert *et al* 2001; Walzer & Herrmann 1998). In a study of patients admitted to the ICU, 50% of which were receiving mechanical ventilation, Ely *et al* (2001) found that 81.3% of patients developed delirium. The duration of delirium was associated with the length of stay at the ICU and in the hospital. Delirium was the strongest predictor of duration of stay in the hospital even after adjusting to the severity of illness, age, gender, race, and days of benzodiazepine and narcotic drug administration (Ely *et al* 2001).

Symptomatology of delirium

Delirium can be characterized as a global, etiologically nonspecific, cerebral dysfunction, with concurrent disturbances of consciousness, attention, perception, memory, thinking, psychomotor behavior, emotion, and the sleep-wake cycle. The primary feature of delirium is a diminished lucidity of awareness of the circumstances and the environment. An acute or abrupt onset of the disturbance, relative brief duration, and fluctuation of symptoms are other defining features of delirium. Time, place and situation orientation is often abnormal in delirium. Disorientation typically fluctuates during course of the delirium. Generally, orientation in time is the area most likely impaired, with orientation to person usually preserved. Perceptual abnormalities in the course of delirium typically represent an inability to discriminate various sensory stimuli and to integrate actual perceptions with past experiences (Lipowski 1990). Patients tend to personalize events and circumstances, conversations, misinterpret objects in their environment, and become obsessed with irrelevant environmental or inner stimuli (Tobias *et al* 1988). Misinterpretations generally take the form of visual or auditory illusions and halucinations. Restlessness, paranoia and sleep phobia may result.

Three clinically different forms of delirium, based on arousal disturbance and psychomotor behavior, have been recognized (Liptzin & Lefkoff 1992; Meagher *et al* 1996). These subtypes included the "hyperactive" (agitated) subtype, the"hypoactive" (lethargic) subtype, and a "mixed" subtype with alternating features of hyperactive and hypoactive delirium (Ross *et al* 1991). The most common type is the mixed form (46%), followed by the hyperactive (30%) and the hypoactive (24%). Classic "waxing and waning" pattern is commonly seen in surgical patients who appear agitated and combative, with alternating episodes of somnolence and hypoactivity. The most clear and least controversial is the hyperactive type, characterized by marked restlessness, hypervigilance, rapid speech, irritability, heightened startle, combativeness, hallucinations, delusions, agitation, and disorientation. This pattern is often seen in states of withdrawal from depressive substances like alcohol or intoxication by psychostimulants. Patients with this hyperactive subtype of delirium often have such concomitant autonomic signs as sweating, trembling, tachycardia, pallor, mydriasis, hyperthermia, piloerecton, and gastrointestinal distress. These patients often require sedation. The most difficult type of delirium to recognize is the "hypoactive type", characterized by apathy, and reduced alertness, psychomotor retardation, lethargy, unawareness of the environment, confusion and sedation, episodes of unresponsiveness or staring, but rarely by hallucinations, delusions, or illusions (Millar 1981, Farrell and Ganzini 1995). Hypoactive arousal states are often initially perceived as depressed or demented states. Hypoactive patients tend to be older, to have more severe cognitive disturbances and have poorer prognosis (Andrew *et al* 2005; McCusker *et al* 2001, Peterson *et al* 2006). It is estimated that approximately two-thirds of deliria are either of the hypoactive or mixed subtype (Ross *et al* 1991, Breitbart *et al* 1995).

Epidemiology

The overall prevalence of delirium in the community is generally low; nevertheless delirium is common in hospitalized patients, especially in intensive care units. The prevalence of delirium in the somatically ill patients ranges from 5% to 85%, depending on the age, health of the patient, and type of unit. Eissa *et al* (2003) conducted postoperative confusion assessment in 48 cardiac surgery patients. They found that nonstructured ward interviews conducted by ICU physicians accurately detected confusion in only 2% of the patients. Nevertheless, when the Short Portable Mental Status Questionnaire was used, delirium was found in 31% of the same patient sample. These results are similar to those found by Rolfson *et al* (1999), who followed 71 patients after cardiac surgery to detect the incidence of delirium using the Confusion Assessment Method (Inouye 1990), the Mini-Mental Status Examination (MMSE; Folstein *et al* 1983), the Clock Drawing Technique (CDT; Dal Pan 1989; Sunderland *et al* 1989), and DSM-III-R criteria. They found that delirium was present in 32.4% of subjects.

The intensive care units, emergency department, geriatric psychiatry ward, oncology, and alcohol treatment units have particularly high rates of delirium (McNicoll *et al* 2003). For general surgery patients, the incidence has been documented to be 15% (Millar 1981). The prevalence of delirium in the Intensive Care Unit (ICU) is reported to vary from 20 to 80 % (Burkhart *et al* 2010). Cardiothoracic and orthopedic

surgery patients experience a higher incidence of delirium at 30% and 50%, respectively (Smith 1989, Williams *et al* 1985). USA nationwide statistics suggest that delirium may be found in up to 30% of general postsurgical patients, 25% to 50% of hospitalized older patients, 28% to 63% of orthopedic older patients, 30% to 67% of postcardiotomy patients, and 30% to 80% of ICU patients (Smith & Dimsdale 1989; van der Mast & Roest 1996). Delirium affects 60 to 80% of ventilated patients and is associated with worse clinical outcomes including death (Agarwal *et al* 2010). Maldonado (2003a) studied the incidence of delirium in 251 patients in the postsurgical setting. 14% were confirmed to be delirious. As a group, delirious patients were older, remained hospitalized longer, and had a higher total hospital care costs. The average number of days from symptomatic onset to resolution was 10.8 days for untreated patients and 6.3 days for treated patients.

In general, the mortality and morbidity of any serious disease are doubled if delirium ensues (Cole 2004). The mortality risk is greatest in the first two years after the illness, with a higher risk of death from heart disease and cancer in women and from pneumonia in men (Francis *et al* 1990).

Risk factors

The age of the patient (including high age and very low age), underlying physical condition, malnutrition, low BMI, sensory impairment (mainly vision), pre-existing cognitive impairment, type and severity of the illness, prior episodes of delirium, brain damage, history of stroke, anoxia, sleep deprivation, and certain psychiatric diagnoses, including a history of alcohol and other substance abuse contribute to a higher incidence of delirium (Elie *et al* 1998). Various medications can cause delirium, and the combination of more than three drugs during the course of a hospitalization increases the risk of developing delirium. Precipitating factors such as infection, acute severe illness, metabolic abnormalities, and hypoxia frequently cause delirium. The integrity of the blood–brain barrier may be closely involved as a predisposing factor (Khan 2005). Because of the reduced ability to maintain hemostasis in the brain, metabolites and drugs more easily enter and interfere with cognitive functions. Medical conditions compromising cerebral or leptomeningeal functions; neoplastic disease; systemic illness; hepatic, renal, or respiratory impairment; and infections present higher risks of developing delirium. Certain surgical patients (i.e., those undergoing cardiac surgery or hip replacement) are at increased risk of developing delirium due to the type or complexity of the surgical procedure (use of a cardiopulmonary bypass (CPB), intraoperative anesthetic agents, and postoperative complications) (Bucerius *et al* 2004; Eriksson *et al* 2002; Litaker *et al* 2001; van der Mastet al 1999). Pacients with dementia or patients suffering from other conditions associated with deficient brain function (i.e. traumatic brain injury, drug and alcohol abuse and withdrawal) have a lower threshold for developing delirium and do so with greater frequency. Other risk factors include frequent room changes, physical restraints, and use of Foley catheter. Patients exposed to certain medication seem to have an increased risk of delirium. This is particularly important when this medication is applied in combinations or has a high anticholinergic potential. Pandharipande *et al* (2008) studied the prevalence of and risk factors for delirium at surgical intensive care units (SICU) and trauma intensive care units (TICU) patients. Patients requiring mechanical ventilation for more than 24 hours were prospectively evaluated. 100 patients were enrolled. Prevalence of delirium was 73% in the SICU and 67% in the TICU. Multivariable analyses identified midazolam exposure as the strongest independent risk factor for transitioning to delirium. Opiate exposure showed an inconsistent message, such that fentanyl was a risk factor for delirium in the SICU but not in the TICU, whereas morphine exposure was associated with a lower risk of delirium. Agarwal *et al* (2010) evaluated the prevalence of delirium in ventilated burn patients. Adult ventilated burn patients at two tertiary centres were prospectively evaluated for delirium for 30 days or until intensive care unit discharge. Prevalence of delirium was 77% of cases with a median duration of 3 (1–6) days. Exposure to benzodiazepines was an independent risk factor for development of delirium, whereas intravenous opiates and methadone reduced the risk of developing delirium, possibly through reduction of pain in these patients.

Pathophysiology

Delirium is not a distinct disease but it is a syndrome with many possible causes that results in a similar constellation of symptoms. Delirium should be thought of as having a multifactorial ethiology (e.g., older woman with a history of mild baseline cognitive impairment and steady benzodiazepine use, status post hip surgery, who develops urinary tract infection postoperatively). Etiologically, many factors can cause delirium on a physiological level. As the general site of regulation of arousal and attention, the reticular formation and its neuroanatomical connections play a principal role in the symptomatology of delirium. The clinical importance of oxygen in the pathogenesis of delirium has been reported in several studies. In retrospective analysis of intensive care unit patients, three measures of oxygenation (hemoglobin, hematocrit, pulse oximetry) and the two of metabolic stress (sepsis, pneumonia) were worse in patients prior to developing delirium, despite no difference in illness severity between groups (Seaman *et al* 2006). Brown (2000) noted that the hospitalized patient´s homeostasis is impeded by the increased O_2 demand from acute illness and fever. Anemia is also commonly encountered

among hospitalized patients, which can further limit O_2 delivery to the brain (Burgeois *et al* 2003). Concerning specific changes in neurotransmitters in delirium, the two most accepted hypotheses are one of a reduction in acetylcholine activity and other of an excess of dopamine activity (Trzepacz 2000). Arousal, attention, the sleep-wake cycle, and memory are heavily dependent on acetylcholine via its nicotinic and muscarinic receptors (Picciotto and Zoli 2002). Dopamine has important roles in attention, mood, motor activity, perception, and executive functioning. In specific hypoxic encephalopathy model, dopamine release was shown to increase 500-fold, whereas gamma-aminobutyric acid (GABA) release was increased only 5-fold (Globus *et al* 1988). This massive increase of dopamine results from a breakdown in adenosine triphosphate-dependent transporters (decreased reuptake) during anoxic depolarization. Hyperactivity of dopamine can lead to delirium, as can be seen with drugs such as L-dopa or cocaine (Burgeois *et al* 2003). The therapeutic use of antipsychotics addresses the hypothesis of dopamine excess associated with delirium.

The pathophysiology of delirium is still incompletely understood, but numerous risk factors for the development of delirium have been identified in ICU-patients, among which are potentially modifiable factors such as metabolic disturbances, hypotension, anaemia, fever and infection (Burkhart *et al* 2010). Frequently, a combination of factors contributes to the delirious state. Guillamondegui *et al* (2011) studied patients with delirium among the traumatic brain injury population in which outcomes are affected by hypoxic events in the early injury period. Of the total 173 enrolled population, 57% patients were positive for delirium and 55% demonstrated cognitive impairment at 12-month follow-up. There was no significant association between hypoxia and ICU delirium. Ventilator days, ED pulse, and blood transfusions were significant independent predictors of delirium.

The underlying causes of delirium

Etiologic factors of delirium can differ over the life cycle. Although delirium in younger populations is less frequent than in elderly persons, traumatic injuries, infectious diseases, as well as HIV and illicit drug use, can precipitate delirium also in young people. Lipowski (1990) described the effect of age throughout the life cycle on etiologic causes of delirium. In childhood and young adulthood, risk factors include infection, meningitis, HIV, and cancer. In young adulthood, abuse of illicit drugs is a more likely cause of delirium compared with the older population for whom serious illnesses and prescribed medication precipitates delirium.

The causes of delirium may be the intracranial processes, extracranial ones, or a combination of both. The most common etiologic factors are as follow (Francis *et al* 1990).

Postoperative conditions

Causes of postoperative delirium can include prolonged effect of anestesia, infection, thrombotic and embolic complications, lung atelectasis, side effect of postoperative analgesia etc (Ely *et al* 2001, Eissa *et al* 2003, Maldonado *et al* 2003c) Patients who have undergone open heart surgery are particularly at risk for microembolization and subsequent delirium (Bucerius *et al* 2004, van Dijk *et al* 2004).

Intracranial causes

There are causes like cerebral trauma, especially involving loss of consciousness, postcontussive states, hemorrhage, vascular abnormalities, subarachnoid hemorrhage, brain infection, transitory ischemic attacks, neoplasma (primary or metastatic), dementia, stroke, and hypertensive encephalopathy (Maldonado 2000a, Guillamondegui *et al* 2011).

Low perfusion conditions

Various conditions and disorders that decrease adequate cerebral perfusion can cause delirium. Common causes are hypovolemia, congestive heart failure, and other antecedents of decreased pulse volume such as arrhythmias, and anemia, which decrease oxygen binding (Burgeois *et al* 2003, Seaman *et al* 2006). Maintenance of fluid balance and strict fluid intake and output monitoring are essential in the overall management of delirious states.

Infection induced

Infection is a common cause of delirium in hospitalized patients (Burkhart *et al* 2010). Pneumonia, encephalitis, bacteraemia septicaemia (especially caused by gram-negative bacteria), and meningitis are common offenders. The elderly patients are particularly susceptible to delirium secondary to urinary tract infections.

Metabolic and endocrine disturbances

Metabolic causes of delirium include electrolyte disturbances, vitamin deficiency states, and hypoglycaemia. The most common endocrine causes are hypofunction or hyperfunction of the thyroid, pituitary, adrenal, pancreatic, and parathyroid gland. Metabolic causes may involve consequences of particular organs failure, such as uremic encephalopathy, hepatic encephalopathy, and post-dialysis delirium resulting from kidney dysfunction, hypoxia resulting from lung disease etc.

Medication and substances induced delirium

Numerous drugs have been noted to precipitate delirium. The most common ones include corticosteroids, narcotics (especially opioids), and NSAIDs, antihypertensive drugs as methyldopa and reserpine, bronchodilators, benzodiazepines, histamine (H2) receptor antagonists (cimetidine), digoxin, baclofen, tricyclic antidepressants, antiarrhythmics, colchicine, sedative-hypnotics, and anticholinergics (Karlsson 1999). The

Tab. 1. The most important causes of delirium (Seifertova & Prasko 2007).

INTRACRANIAL:
- tumors (primary, metastasis)
- cerebral trauma (subdural, epidural hematomas, cerebral contusion)
- neuroinfections (meningitis, encephalitis, embolization, neurosyfilis, brain abscess)
- dementia (vascular, Alzheimer disease, AIDS)
- vascular strokes (transitory ischemic attacks, vasculitis, atherosclerosis, subarachnoid bleeding, hypertensive encephalopathy)
- post epileptic periods

EXTRACRANIAL:
- infections (pneumonia, typhoid fever, urinary tract infection, other bacteraemia and septicaemia)
- cardiovascular disorders (cardiac failure, arrhythmia, myocardial infarction, aortal valve stenosis)
- respiratory failure
- carcinomatosis
- metabolic and endocrine diseases (uraemia, dehydration, hypoglycaemia, electrolyte disturbances, liver failure, pancreatitis, diabetes mellitus decompenzations, hypothyreosis, hyperthyreosis)
- nutrition (thiamine depletion, long-time starving)
- anaemia
- toxic (hallucinogens, psychostimulants, barbiturates, anticholinergics, tricyclic antidepressants, L-dopa, indomethacin, digoxine, cimetidine, antiarrhythmics, benzodiazepines, antihypertensive drugs, lithium, malignant neuroleptic syndrome, industrial toxins, carbon monoxide, poisonous plants, atropine, poisonous mushrooms, snake venoms)
- withdrawal syndrome (alcohol, barbiturates, anxiolytics, opiates dependencies)
- large blood loss
- postoperative conditions (cardiac, eye surgery), hip replacement and trauma
- other (burn injuries, hypothermia, sunburn, pain, urinary or stool retention in elderly patients)

PSYCHIC:
- delirious forms of mania
- melancholic depression (pseudodementia)
- schizophrenia, schizoaffective disorder
- acute stress reaction
- adjustment disorders (elderly patients after environment changes)

Tab. 2. Examples of drugs possibly acting as delirogens

Antimicrobial agents
Acyclovir, gancilovir
Aminoglykosides
Amphotericine
Antimalarials
Cephalosporines
Chloramfenicol
Ethambutol
Interferon
Isoniazide
Metronidazole
Rifampicine
Sulphonamides
Vancomycine

Anticholinergics
Antihistaminics, H1
Spasmolytics
Atropine and related dugs
Benztropine
Phenothiazines – thioridazine
Tricyclic antidepressants – amitriptyline
Trihexyfenidyle

Antiparkinsonics
Amantadine
Bromocriptine
Levodopa

Analgetics
Opiates
Salycilates

Cytostatics
Aminoglutethimide
Asparginase
Dacarbazine (DTIC)
5-fluorouracile
Hexamethylenamine
Methotrexate (intrathecal)
Procarbazine
Tamoxiphen
Vinblastine
Vincristine

Anti-inflammatory drugs
Corticosteroids
NSAIDs

Cardiotonics
Beta-blockers
Captoprile
Clonidine
Digoxin
Dysopiramide
Lidocaine
Methyldopa
Mexiletine
Procainamide
Quinidine
Tocainide

Anticonvulsants
Phenobarbital
Phenytoin
Valproic acid and relative drugs

Sedatives and hypnotics
Barbiturates
Benzodiazepines

Stimulants
Amphetamine and related drugs
Cocaine
Ephedrine and related drugs
Theophylline

Others
Antihistaminics H2 (cimetidine)
Baclofen
Bromides
Chlorpropamide
Disulfiram
Ergotamine and related drugs
Lithium
Metrizamide (intrathecal)
Podophylline (absorption)
Propylthiouracile
Quinacrine
Timolol - ophthalmic

commonly used benzodiazepine lorazepam has been shown to independently increase delirium development in ICU patients (Pandharipande *et al* 2006). Medicaments with high anticholinergic activity are known to precipitate delirium (Han *et al* 2001). People with impaired cholinergic transmission, such as those with Alzheimer´s disease, are especially susceptible. The intensity of delirium corresponds with plasma anticholinergic activity (Tune and Egeli 1999, Tune 2000). From the narcotic analgesics, meperidine can produce an agitated delirium with tremors, seizures, and myoclonus. Lithium-induced delirium occurs at blood level greater than 1.5 mEq/L, and is associated with early features of lethargy, stuttering, and muscle fasciculations. Many commonly prescribed drugs, including cimetidine and ranitidine, which are not typically associated with anticholinergic properties, precipitate delirium.

Drug-induced delirium may be the result of drug interactions and polypharmacy and not the result of a single agent. Also can be caused by the combination of drugs of abuse and prescribed drugs (e.g. cocaine and dopaminergic antidepressants).

The list of illicit drugs that can produce delirium is large. These include LSD (lysergic acid diethylamide), psilocybine, heroin, and amphetamines. Other agents include barbiturates, cannabis (laced with phencyclidne /"superweed"/), mescaline.

Substance withdrawal delirium

Alcohol and some sedative drugs (benzodiazepines) can produce a withdrawal delirium when abruptly discontinued or substantially reduced (Maldonado 2000a). Withdrawal delirium is associated with abnormal vital signs, tremor, diaphoresis, nausea and vomiting, diarrhoea, tachycardia, sweating, pupillary changes, etc. Patients generally complain of abdominal and leg cramps, insomnia, nightmares, illusions, chills, hallucinations. Alcohol withdrawal delirium is potentially fatal. Withdrawal delirium is much more common in hospitalized patients than in patients living in the community. For example the incidence of delirium tremens is 1% of all those with alcoholism, but 50% of hospitalized alcohol abusers (Bourgeois *et al* 2009).

Sensory and environmental changes

Especially elderly people are vulnerable to develop environment-change related delirium when admitted to hospital. Patients with pre-existing dementia, who may have learned to cope with cognitive deficits at home, often become delirious once hospitalized (Koponen *et al* 1989, Ely *et al* 2001, Fick *et al* 2005). The nature of intensive care unit itself often leads to periods of high sensory stimulation or low sensory input, for example at night. The parameters of time, like external events, are often absent at night, and can lead to increased rates of delirium during nightime hours.

The course of delirium

The average delirium episodes continuing of 3–13 days are commonly reported, although in patients with "beclouded" dementia 20 days was the mean (Koponen *et al* 1989, Ely *et al* 2001). Once appropriate treatment is introduced, most patients with delirium will recover during 48 to 72 hours. Persistence beyond 30 days has been described to occur in as many as 13–50% of delirious elderly patients (Marcantonio *et al* 2000). Patients with hypoactive subtype of delirium have been shown to have longer duration of delirium than do those with the mixed or hyperactive subtypes (Kelly *et al* 2001). When looking at the mortality and morbidity of patients who develop delirium during their hospital stay compared with those who did not, the incidence of death is as high as 8% versus 1% (Ely *et al* 2001). Delirious patients have also an increased risk of mortality during the next year. Delirious patients have prolonged hospitalization (i.e., 12 vs. 7 days), compared with patients suffering from the same medical problem who do not develop delirium as a complication (Ely *et al* 2001; Francis *et al* 1990). Similarly, patients who develop delirium while in the hospital have a greater need for placement in nursing homes 16% versus 3% – in patients without delirium (Francis *et al* 1990). It has been estimated that about 40% of delirium cases develop some form of chronic brain syndrome (Pompei *et al* 1994). Longer duration of delirium was an independent predictor of worse cognitive performance 3 and 12 months later. Duration of mechanical ventilation, alternatively, was not associated with long-term cognitive impairment (Girard *et al* 2010).

When the underlying cause of delirium is managed successfully, the symptoms gradually move away during 3–7 days. But some symptoms in certain population may take weeks to resolve. The patient age and the duration of delirium affects the symptom resolution time. In general, the patient has patchy memories for events that occurred during delirium. Patients who wake up in restraints are often quite upset wondering what had happened and why they had to be mechanically restricted. They should be calmed down and reassured that they are not responsible for their behavior while being delirious and that no one resents them for the behavior they may have had exhibited.

Differential diagnosis

Delirium needs to be differentiated from dementia primarily, because these two conditions may have different prognosis (Lipowski 1990). Contrary to the changes in dementia, those in delirium have an acute onset. The symptoms of dementia tend to be relatively stable in time, whereas delirium displays wide fluctuation with periods of relative lucidity. Attention and orientation are more commonly disturbed in delirium, although the later can become impaired in advanced dementia as well. A nondelirious patient suffering from demen-

tia has characteristically intact attention and alertness. Perception abnormalities, the sleep-wakefulness cycle alterations, and abnormalities of speech are more common in delirium. Delirium is more likely to be reversible than dementia. Delirium and dementia can occur simultaneously; in fact, the presence of dementia is a risk factor for delirium (Fick *et al* 2005). Often delirium must be differentiated from psychotic states related schizophrenia or mania. The psychotic schizophrenia symptoms are more constant and better organized than symptoms of delirium. Schizophrenic patients seldom have the clouded consciousness usually seen in delirium. Apathetic and lethargic patients with delirium may occasionally resemble depressed individuals, but those are not disorientated.

Management

Once delirium has been recognized, the etiological agents are important to be identified and managed. For the elderly patients, the first step generally involves discontinuing or reducing the dosage of potentially delirifacient drugs. Some types of delirium can be reversed with proper medication, such as physostigmin administration in anticholinergic delirium. However, the most responses to the treatment are not as immediate, and attention must be focused on agitated and psychotic behavior management, protecting the patient from unintentional self-harm, and manipulating the environment to minimize additional impairment. Supportive therapy should include fluid and electrolyte maintenance adequate nutrition. Desorientated patients should be reorientated in time, place, and situation gently and repeatedly. Clinicians must acknowledge that vision and hearing impairments can produce confusional states, and appropriate prosthetic devices may be beneficial.

Prevention of delirium

Strategies to prevent delirium are important as well. Crucial conditions are the prevention and management of common risk factors, including avoiding oversize sedation and analgesia and creating an environment that enhances reintegration (Pandharipande *et al* 2008, Burkhart *et al* 2010). Four risk factors – vision impairment, severe illness, pre-existing cognitive impairment, and dehydratation – were used in one predictive model (Inouye *et al* 1993, Freter *et al* 2005). Nine percent of the low-risk patients (those with none of the four factors) later developed delirium compared with 23% of those with one or two factors and 83% of those with three of four factors. Inouye *et al* (1999) conducted a study of 852 hospitalized patients for manifestations of delirium. In this study, researchers only corrected environmental factors commonly associated with increased risk for delirium, and they observed a 40% reduction in odds for delirium. The intervention consisted of simple techniques applied by the hospital staff, including reorientation, appropriate cognitive stimulation three times a day, the implementation of a nonpharmacologic sleep protocol to help normalize patient's sleep–wake cycle, early mobilization after surgery or extubation, timely removal of catheters and restraints, correction of sensory deficiencies (i.e., eyeglasses and hearing aids), and early correction of dehydration and electrolyte abnormalities.

Maldonado *et al* (2003c) attempted to prevent delirium by avoiding the use of benzodiazepines and related agents (e.g., midazolam, propofol) during the postoperative state. Their study involved 90 patients randomized into three different postcardiac surgery sedative protocols. One group was randomized to the "old" standard of care, midazolam. The second group was randomized to the "new" standard of care, propofol. The third group was randomized to the study drug, dexmedetomidine, a potent alpha-2 agonist, which achieves sedation by suppression of norepinephrine release at the level of the locus ceruleous. Postoperatively, patients were randomized to receive one of three postoperative sedation protocols: dexmedetomidine (loading dose 0.4 μg per kg, followed by 0.2–0.7 μg/kg/hour), propofol (25–50 μg/kg/minute), or fentanyl-midazolam (50–150 μg/hour and 0.5–2 mg per hour, respectively). Patients were then observed for the development of delirium and neurocognitive deficits. The incidence of delirium for the entire study population was 34% (31/90). The incidence of delirium for patients on dexmedetomidine was 3% (1/30), for those on propofol 50% (15/30), and for patients receiving midazolam 50% (15/30). Patients who developed postoperative delirium experienced significantly longer ICU stays (4.1 vs. 1.9 days, $p<0.001$) and longer total hospitalization (10.0 vs. 7.1 days, $p<0.001$) compared with patients without delirium. The findings of this prospective, randomized clinical trial suggest that sedation with dexmedetomidine can significantly reduce the incidence of postoperative delirium in cardiac surgery patients undergoing valve surgery with CPB (cardiopulmonary bypass).

Pharmacological treatment of agitation

The standard approach to delirium management includes identification and elimination of factors contributing to the delirium in addition to pharmacologic

Tab. 3. Management of delirious patient (Burgeois *et al* 2009).

- identify and correct the underlying cause
- protect the patient from unintentional self-harm
- stabilize the level of sensory input
- reorient patient as often as possible
- employ objects from the patient´s home environment
- provide supportive therapy (fever control, hydratation)
- streamline medications
- correct sleep deprivation
- manage behavior with appropriate pharmacotherapy
- address postdelirium guilt and shame for behavior that occurred during confusion

and nonpharmacologic treatment interventions. The adequate treatment of delirium includes the following steps:

- Accurate diagnosis of the condition;
- Identification of the etiologic cause(s) of delirium;
- Treatment of underlying medical problems;
- Management of the behavioral and psychiatric manifestations of symptoms to prevent the patient from harming himself or others.

Thus, all appropriate medical tests should be ordered and reviewed in a timely fashion, and all abnormal findings addressed. Modifiable precipitants may be an undetected urinary tract infection, select medications, pneumonia, sepsis, organ failure, or a host of other variables. Anticholinergics, benzodiazepines, corticosteroids, powerful dopamine agonists, and some opioids are best limited when feasible (Morita *et al* 2005). The fundamental aim of treating delirium is not to control agitation or hallucinations alone; it is to prevent and reverse the delirium and thus mitigate associated morbidity and mortality risks.

Pharmacologic intervention is often needed to decrease the patient's level of agitation and achieving behavioral control. Once agitation is present, treatment consists of the use of typical and atypical antipsychotics. Medical and surgical services managed their delirious patients with varying combinations of drugs, including opiates, benzodiazepines, propofol, and neuroleptic agents, usually on the „as needed" basis. The consultant psychiatrist is the most appropriate person to recommend such medication. Antipsychotics constitute the primary pharmacologic intervention (Breitbart *et al* 2002). Intravenous antipsychotic mediated sedation is recommended for the emergency treatment of the agitated and mixed type of delirium. The drug of choice for the agitated, delirious patients has traditionally been haloperidol, because of its minimal anticholinergic effects, minimal orhostasis, limited sedation, and flexibility in dosing and administration with oral, intramuscular, and intravenous routes (APA 1999). Intravenous administration of haloperidol is superior to oral administration because the intravenous route is more reliably absorbed, even in patients with systemic failure. Haloperidol is still the drug of choice for the treatment of delirium and can be given intravenously in incremental doses of 1 to 2 mg every 2–4 hours as needed, with further titration until desired effects are seen (Bourgeois *et al* 2009, Burkhart *et al* 2010). Furthermore, it does not require the patient's cooperation,

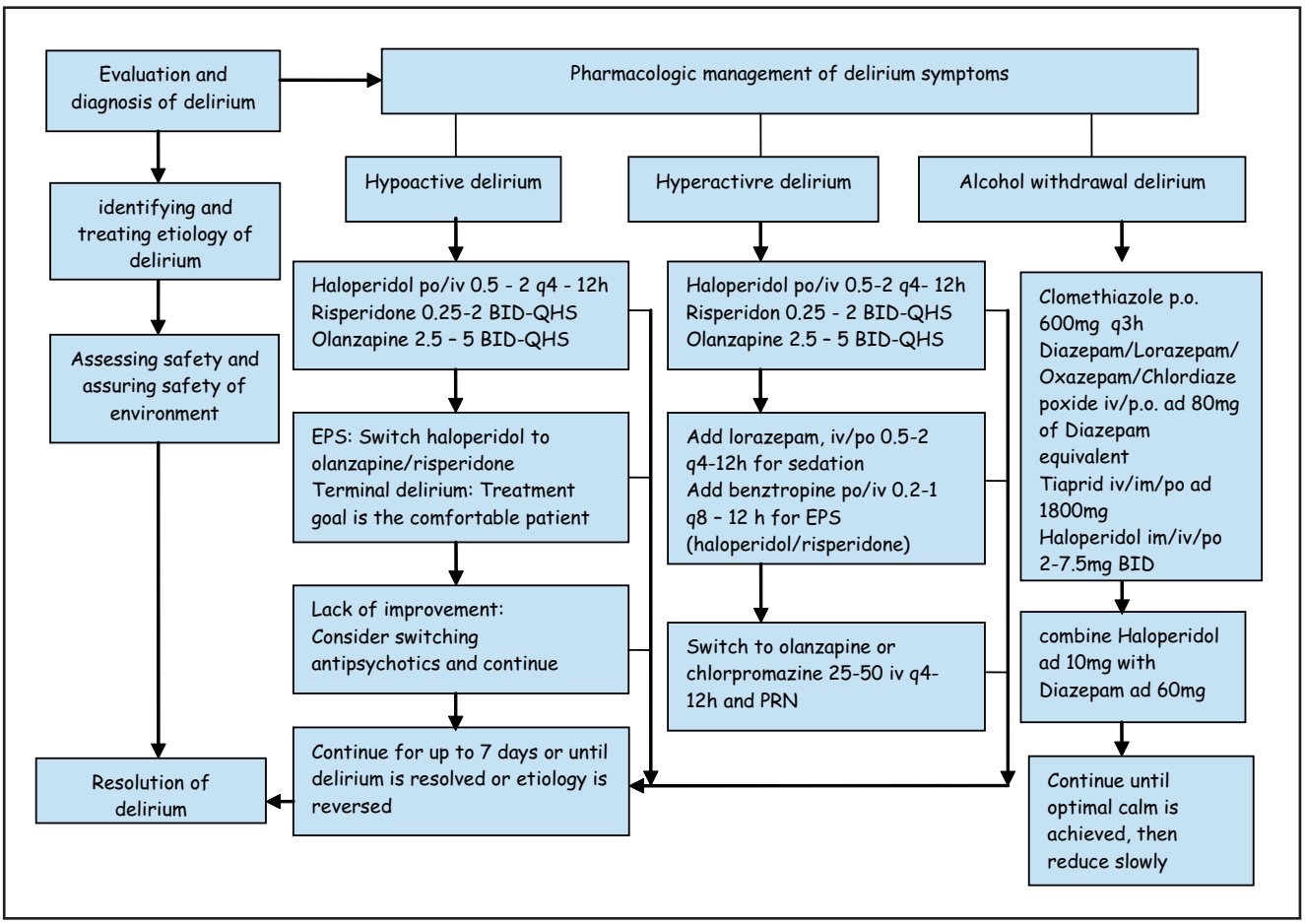

Fig. 1. Delirium management.

thus allowing for its administration even if the patient is agitated or unable to cooperate. Both oral and intravenous forms have been used for more than 40 years and have an extensive track record of safety and efficacy in even the most ill medical and surgical patients (Bourgeois *et al* 2009). Once stabilized, patients are often transitioned to a twice-daily or a daily bedtime oral dose, which is then continued or slowly tapered until the delirium is resolved. In severe delirium refractory to boluses, continuous haloperidol infusions of 3–10 mg/hour have been used safety (Riker *et al* 1994, APA 1999). Several studies suggest that the intravenous use of high-potency antipsychotic drugs is associated with minimal effects on blood pressure, respiration, and heart rate (Inouye *et al* 1999; Riker, Fraser, & Cox 1994; Sanders, Murray, & Cassem 1991; Stern 1994; Ziehm 1991). Extrapyramidal symptoms may be less common with haloperidol administered intravenously as opposed to orally and intramuscularly. An electrocardiogram should be obtained before administration of haloperidol, especially with continuous infusion. If the QTc interval is greater than 450 msec, use of intravenous haloperidol can precipitate an abnormal cardiac rhythm known as Torsades de pointes (Glassman and Bigger 2001). Prolonged QTc intervals beyond 450 msec or 25% above baseline should prompt a cardiologic consultation, a dosage reduction, or discontinuation of the antipsychotic agent (APA 1999).

Benzodiazepines are commonly used as adjunct in the treatment of delirium, there are reasons to believe that their use may aggravate or perpetuate delirium because they all have some anticholinergic load. Benzodiazepines also can cause disinhibition at the lower doses usually given for "sundowning" or older patients. Therefore, there have been attempts to treat delirium without the use of antipsychotics or benzodiazepines (e.g., lorazepam, midazolam).

Recent studies have advocated the use of newer antipsychotics for management of behavior and psychotic symptoms of delirium. Agents as quetiapine, olanzapine, and risperidone have been used successfully. These newer medicaments may have lower incidences of dystonia and dyskinesia, but still carry the risk of QT prolongation, particularly in patients with electrolyte abnormalities (Glassman & Bigger 2001). One study suggested that antipsychotics of 2 generation may have a greater incidence of adverse effects than typical agents, excluding EPS (Bender *et al* 2004). There is also evidence that some atypical antipsychotics may aggravate or cause delirium (e.g., clozapine, olanzapine), probably due to their anticholinergic potential (Bender *et al* 2004).

Data on most atypical agents are limited to small case reports (risperidone: Horikawa *et al* 2003, Mittal *et al* 2004). The largest risperidone study was reported by Parellada *et al* (2004). Authors recruited 64 delirious patients and started them on risperidone at the time of diagnosis. There was no comparison group. They reported improvements on all measures after 7 days of treatment. However, to further confuse the issue, there are at least four reports of risperidone-induced delirium (Chen & Cardasis 1996; Kato *et al* 2005; Morikawa

Tab. 4. Drug dosage in delirium management (Seifertova & Prasko 2007).

Drug	Single dosage	Maximal dosage per day	Single dosage in elderly	Maximal dosage per day in elderly
haloperidol	Mild agitation: 1.5–2 mg Moderate agitation: 2–5 mg Severe agitation: 5–10 mg	3–20 mg/die Severe agitation till 100 mg/ die	Mild agitation: 0.5 mg Moderate agitation: 1 mg Severe agitation: 2 mg	5–10 mg/die
tiapride	100–200 mg	1 800 mg/die	100 mg	400 mg/die
melperon	75 mg	200 mg/die	25 mg	100 mg/die
risperidone	2–6 mg	16 mg/die	0.5 mg	2 mg/die
olanzapine	5–20 mg	40 mg/die	Not recommended	Not recommended
quetiapine	25–750 mg	900 mg/die	Not recommended	Not recommended
sulpiride	100 mg	600 mg/die	100 mg	300mg/die
clomethiazole	300 mg	4–12 g/die	Avoid	Avoid
diazepam	10 mg	90 mg/die	Avoid	Avoid
lorazepam	After the 3rd dose of Haloperidol 0.5–2 mg of lorazepam QQH	8 mg	Avoid	Avoid

et al 2002; Tavcar & Dernovsek 1998). Liu *et al* (2004) conducted single-blind risperidone versus haloperidol study. They treated 41 subjects with a mean daily dose of risperidone of 1.2 mg ± 0.75 mg per day. The authors found no significant difference in the efficacy or frequency of response rate between haloperidol and risperidone on any of the measures (i.e., DRS, MDAS). The only published (Han & Kim 2004) double blind randomized study looked at 28 patients with delirium who were randomly assigned to receive a flexible-dose regimen of haloperidol or risperidone over a 7-day treatment period. The severity of delirium was assessed by using the MDAS (Breitbart *et al* 1997) and the DRS. The study authors found no significant difference in the efficacy, frequency, or rate of response between haloperidol and risperidone on any of the measures (i.e., DRS, MDAS). Similarly, there were no clinically significant side effect differences among study groups.

Regarding the use of quetiapine, there are three little case studies reported to date (Torres *et al* 2001, Sasaki *et al* 2003, Kim *et al* 2003) The largest quetiapine study was conducted by Pae *et al* (2004), who treated 22 subjects with a mean daily dose of quetiapine of 127.1 mg ± 72.2 mg per day. In this group, the mean duration of symptoms was 8.5 ± 4.5 days. These studies found no significant incidence of EPS. Sim *et al* (2004) reported on a case in which quetiapine was suspected of causing delirium. Schwartz and Masand (2000) carried out a single-blind quetiapine versus haloperidol study of 11 delirious subjects. The quetiapine average daily dose was 200 mg per day. The authors reported an effectiveness of >50% in reducing DRS scores. When compared with haloperidol, there was no difference in onset of symptom resolution, duration of treatment, and overall clinical improvement.

There are two studies on olanzapine use for the treatment of delirium. Kim *et al* (2001) showed improvement at relatively low doses (5.9 ± 1.5 mg per day) and no evidence of EPS. Breitbart *et al* (2002) reported that olanzapine was effective in treating 76% of delirium patients, but they recorded problems with excessive sedation in 30% of patients. Sipahimalani and Masand (1998) conducted a single-blind study using olanzepine versus haloperidol. Eleven patients with delirium were treated, using a mean daily dose of olanzepine of 8.2 mg ± 3.4 mg per day with a reported improvement on the DRS of 40%, compared with a 60% improvement on the haloperidol group. There are two single case studies on the use of ziprasidone for the management of delirium (Leso & Schwartz 2002; Young & Lujan 2004).

Addressing the theory that proposes delirium has been caused by a central cholinergic deficiency state, some researchers have attempted to use acetyl cholinesterase inhibitor agents. Most of the reports have consisted of small series of case reports associated with the use of rivastagmine in the treatment of delirium in older persons (Dautzenberg *et al* 2004; Kalisvaart *et al* 2004; van den Bliek & Maas 2004). Moretti *et al* (2004) conducted an open (nonrandomized) study of 246 patients with vascular dementia who exhibited symptoms of delirium. Their data suggest a positive effect, but more stringent and better-designed randomized studies are needed.

The psychiatry service used flexible but routine doses of haloperidol, with lorazepam used in cases of agitated delirium or to help promote sleep. The treatment regime doses were usually adjusted on 24-hour intervals and maintained a haloperidol–lorazepam ratio of at least 2:1 (the H2A protocol). There have been reported cases of sudden death in patients simultaneously taking parenteral lorazepam and parenteral olanzapine so this combination should be avoided. Nevertheless, due to the possibility that benzodiazepines themselves may contribute to delirium, the lowest effective dose was always used. The lower use of central nervous system (CNS) depressant medication (e.g., benzodiazepines, propofol) was also associated with a lower incidence of cognitive dysfunction and respiratory depression (thus resulting in lower intubation rates and faster extubation times). Whenever possible, no benzodiazepines could be used. Whatever antipsychotic is chosen, the patient should be carefully monitored for muscle rigidity, unexplained fever, tremor, and other warning signs of neuroleptic side effects, especially neuroleptic malignant syndrome.

Intravenous haloperidol use was more effective than oral use (Inouye *et al* 1999; Maldonado *et al* 2003a, Sanders, Murray, & Cassem 1991; Stern 1994). Further research suggests a decreased incidence of extrapyramidal symptoms when the intravenous route versus the oral route is used (Maldonado 2003, Maldonado 2000b). Patients receiving intravenous haloperidol experienced much lower extrapyramidal symptoms than patients receiving the oral form (7.2% vs. 22.6%). The most common forms of extrapyramidal symptoms observed were pseudoparkinsonism (50%), akathisia (32%), and acute dystonia (14%).

Delirium tremens management

Chronic alcohol misuse is more comon in surgical patients than in psychiatric or neurological ones (Moore et al., 1989). After admittion to the surgical ward (due to the trauma, acute abdomen e.c.) the intake of alcohol is suddenly discontinued and the withdraval syndrome may arrise very quickly. Its´ most severe complication is delirium tremens (DT), characterized (besides the typical psychological and behavioral symptoms of delirium itself) by massive tremor, sweating and often substantial autonomic hyperactivity, electrolyte dysbalance, fever or epileptic paroxysms. Left untreated DT may lead to death due to sudden cardiovascular or pulmonary complications. The treatment comprises early diagnostics (including searching for sings of chronic alcohol abuse on admittion) and medicamental intervention as well as thorough supportive therapy and requires continuous monitoring at SICU. The usuall symptomatic medi-

cation are benzodiazepines – Diazepam, Lorazepam, Oxazepam, Midazolam, Chlordiazepoxide – in high doses (till 80–90 mg of Diazepam equivalent pro die), Clomethiazole till 4.8 g pro die or Tiapride till 1800mg pro die. Haloperidol 10–15 mg pro die can also be used, but recently is being prefered in combination with BZD, not in monotherapy.

Conclusions

Delirium is an acute, usually reversible, syndrome of impaired higher cortical functions hallmarked by generalized cognitive disturbance with one or multiple underlying causes. It is most common in surgical inpatients, especially at intensive care units. Proper diagnosis and treatment is important in the medical setting and significantly decreases the burden on the patient, caregivers, and medical system.

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