The Prevention and Treatment of Delirium in Elderly Patients Following Hip Fracture Surgery

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Abstract: Osteoporotic hip fracture needs a specific approach and treatment, since elderly patients are at high risk for adverse outcomes after surgery. In particular, delirium often occurs in the peri-operative period, and it is associated with death, hospital-acquired complications, persistent cognitive impairments, poor functional recovery after surgery and increased healthcare costs.

The pre-operative assessment of the risk factors for delirium improves the preventive measures. The delirium diagnostic tools should be included in the standard of orthogeriatric cure for hip fracture. Given the increasing complexity of the clinical pictures, we present a review of the available treatment options for delirium in patients with hip fracture. The metabolic pre-operative disorders and the management of co-morbid diseases are specific targets of treatment in order to optimize the outcomes after surgery. In particular, elderly patients with Alzheimer's disease are highly vulnerable to hip fracture and delirium, and they are severely frail with reduced physiologic reserves.

An integrated approach combining environmental and pharmacological strategies is useful in the delirium treatment, with a close collaboration between the orthopedic and geriatric team.

Keywords: Alzheimer's disease, BDNF, cortisol, hip fracture, metabolism, neurotransmission.

INTRODUCTION

Osteoporotic hip fracture needs a specific clinical approach and treatment, since elderly patients are at high risk for adverse outcomes after surgery [1, 2]. Adverse events (anaemia, water-electrolyte imbalance, uncontrolled diabetes, heart failure, acute infections, delirium, functional and cognitive decline) increased the length of stay in hospital and the risk for institutionalization [1]. Delirium occurs with high frequency (25-65%) and it is associated with death, hospital-acquired complications (such as pressure sores), persistent cognitive impairments and poor functional recovery after surgery [3-6]. The incidence of hip fracture in elderly patients at high risk for delirium, such as Alzheimer's disease (AD), is rising, due to the increasing population aging. In selected cases, patients do not recover from delirium and the persistent delirium is invariably associated with the most adverse outcomes.

The estimated healthcare cost for the care of delirium is significant, more than 150 billion dollars per year in United States [7].

PATHOPHYSIOLOGY OF DELIRIUM

The pre-operative assessment of the risk factors for delirium improves the preventive measures.

The not modifiable predisposing factors are age and residing in a long term care facility [8-10]. The cognitive/sensory and functional impairment, alcohol abuse and depression are conditions at risk.

The delirium risk assessment should be included in the standard of orthogeriatric cure for hip fracture.

The metabolic pre-operative disorders (electrolytes, glucose, oxygen, hemoglobin) and the co-morbid diseases (cardiac, pulmonary, hepatic and renal failure) are specific targets of treatment in order to optimize the outcomes after surgery [8, 9] Fig. (**1**).

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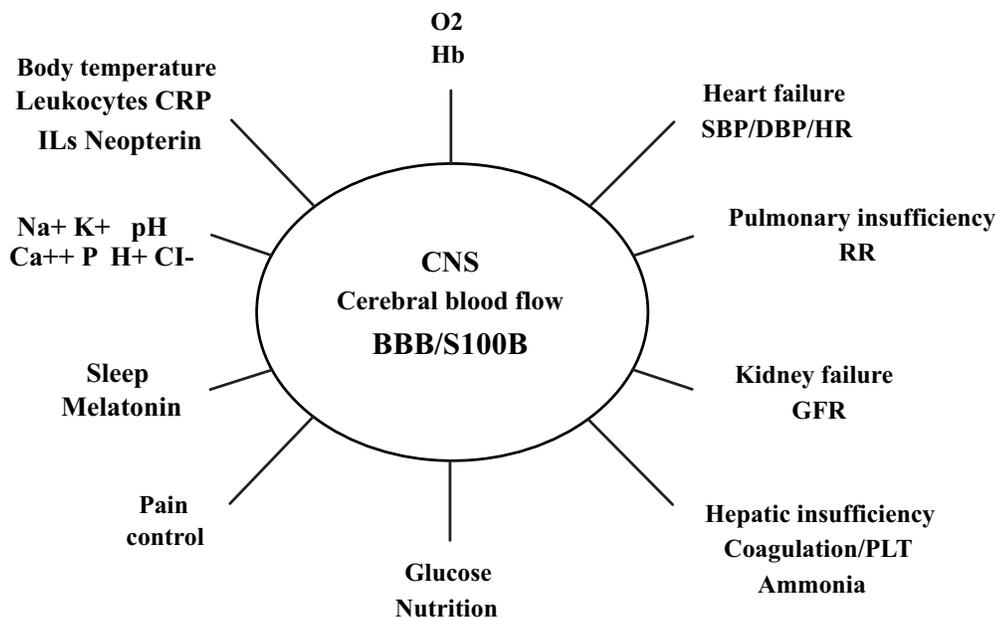
Fig. (1). Main clinical parameters involved in the brain functioning.
BBB = blood-brain barrier, CNS = central nervous system, CRP = C- reactive protein, GFR = glomerular filtration rate, Hb = hemoglobin, HR = heart rate, ILs = interleukins, O2 = oxygen, PLT = platelet count, RR = respiratory rate, SBP and DBP = systolic and diastolic blood pressure.

An increase of circulating S100B-protein (a calcium binding protein) has been found in delirium, suggesting a significant brain damage; the role of this potential biomarker in the pathophysiology of delirium needs further evaluations [11].

Hospital-related precipitating factors for delirium involve the reduced patient mobilization and include: The bed side rails, the urinary catheter, the continuous intravenous therapy by central and peripheral line, the venous pump compression therapy and the preoperative skin traction. A recent Cochrane review update suggested that skin or skeletal tractions routinely used prior to hip fracture surgery are not useful; the persisting use of pre-operation tractions should be included in a specific trial [12]. Animal models mimicking the reduced mobility demonstrated that immobilization may cause widespread reduction in brain acetylcholine (Ach) levels [13].

Disruption to the 24-hour circadian cycle, sleep and melatonin secretion have been linked to the development of delirium [14].

The malnutrition (with deficit of vitamin B1, B6 and B12), the dehydration, the polypathology/ polypharmacology, the inflammation with or without fever increase the risk for delirium [10, 15].

On the contrary, the delirium may be the expression of a post-operative complications, such as infections (urinary tract infections, broncho-pneumonia, sepsis) and, more rarely, cerebrovascular diseases (transient ischemic attack, stroke).

Several drugs are involved in the development of delirium, since they may interfere with neurotransmission pathways [16-20]. Elderly subjects usually present a reduced physiologic reserve in the central nervous system (CNS), with about 30% neuron loss in neocortex, hippocampus, locus coeruleus and substantia nigra. Moreover, Ach, norepinephrine (NE), serotonin (5-HT), dopamine (DA), and gamma-aminobutyric acid (GABA) concentrations decline with increasing age [21].

The concepts of allostatic load, homeostenosis and frailty describe from different points of view the condition of elderly subjects (particularly, AD patients) that are highly vulnerable to stress and illnesses (hip fracture is a typical example), because of the lack of physiologic reserves [22].

The presence of dementia increases the incidence of post-operative delirium from 32% to 100% after orthopedic surgery [23]. Therefore, when AD patients present an osteoporotic hip fracture, the clinical management becomes more complex [24]. Baseline mild cognitive impairment is also predictive of post-operative delirium [25, 26]. Potential mechanisms of altered neurotransmissions associated with delirium are summarized below Fig. (**2**).

Central cholinergic deficiency has been described in delirium, in relation to: - drugs with direct and indirect anticholinergic activity (atropine, digoxin, furosemide, atenolol and beta-blockers, cimetidine and histamine H2 receptor antagonists, sedating H1 receptor antagonists, diazepam and benzodiazepines, haloperidol, olanzapine and atypical antipsychotics, oxcarbazepine, amitriptyline, oxybutynin and most incontinence drugs, dopaminergic agonists, barbiturate, codeine, meperidine, morphine and opiates, anesthetic agents); - fever, with increased serum anticholinergic activity (due to cytokines, immune-derived substances, endogenous opioids); - an impaired central acetylcholine production (dependent on oxygen and glucose citric acid cycle) [27-32].
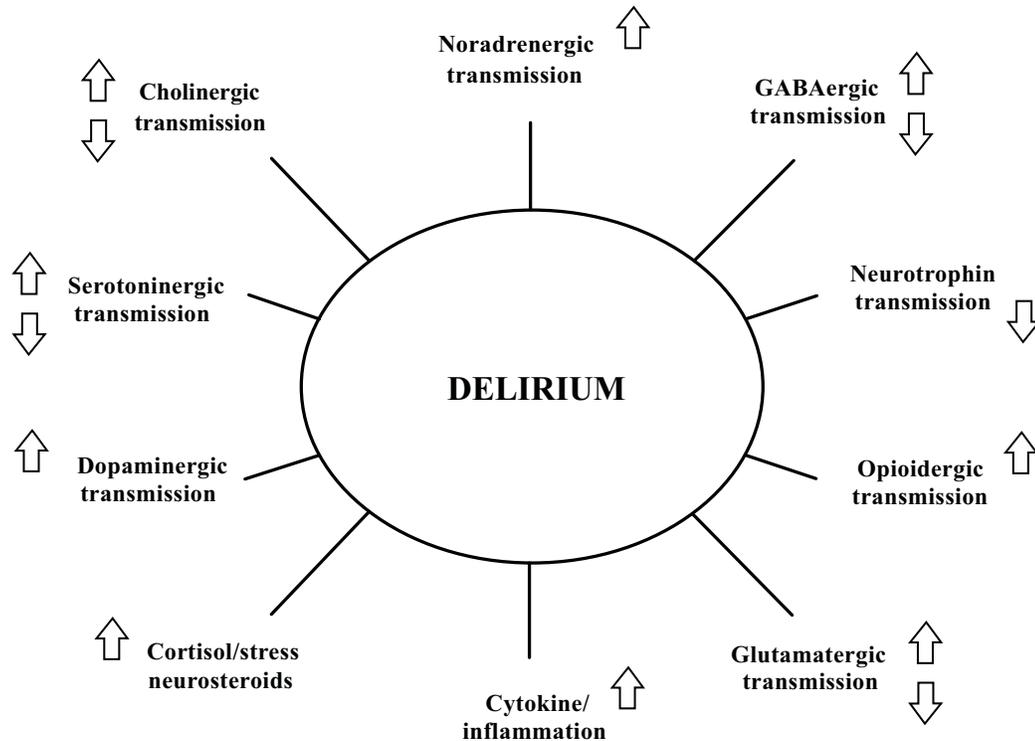
Fig. (2). Neurotransmission disorders in delirium.
GABA = gamma-aminobutyric acid

In sporadic cases, central cholinergic hyperactivity (trigger for delirium) has been reported during tacrine administration in AD patients [33].

Central dopaminergic hyperactivity has been found in delirium, in relation to drugs (buproprion-associated delirium) or to frontal/parietal brain lesions (resulting in increased DA transmission in subcortical areas) [34, 35]. Increased central DA accumulation may be related to reduced conversion of DA to NE (oxygen dependent) and reduced catabolism by the catechol-O-methyltransferase. Variations in the DA transporter (SLC6A3) gene have been associated with delirium following hip fracture [36].

Two main families of DA receptor (D1 and D2) are expressed in the brain. The D1 receptor family activate the adenylate cyclase; it is divided in the D1 receptor itself (post-synaptically localized in the striatum for motor control and in the limbic system) and the D5 receptor (post-synaptically present in the hippocampus). The D2 receptor family inhibits the adenylate cyclase; it is divided in the D2 receptor itself (pre- and post-synaptically localized in the striatum for motor control and in the pituitary for prolactin secretion control), the D3 receptor (present in the olfactory bulb for reward control) and the D4 receptor (localized in the frontal cortex for cognitive function) [37, 38].

Central serotonergic hyperactivity has been found in delirium, associated with drugs with direct and indirect serotonergic activity (monamine oxidase inhibitors, serotonin reuptake inhibitors) [39-43]. On the other side, central serotoninergic deficiency is a possible cause of delirium: it occurs when neutral large amino acids (such as leucine, isoleucine, phenylalanine, methionine and tyrosine) competi-

tively entry into the brain during systemic illnesses and catabolic states and they reduce central tryptophan availability [44-47].

Central GABAergic hyperactivity has been described in delirium, with significant effects since GABA is a strong inhibitory transmitter. GABA hyperactivity may be related to drugs (fluoroquinolone antibiotics activating GABA-A receptor), endogenous benzodiazepine-like substance, withdrawal of pre-existing sedative drugs or neurosteroids that increase GABAergic tone [48-51]. On the contrary, decreased GABAergic activity is common in substance (ethanol) or CNS depressant drug withdrawal. Benzodiazepine exposure (GABA mimetic agents) has consistently been associated with delirium in intensive care unit studies [52, 53].

Central catecholaminergic hyperactivity in delirium is common, in relation to sleep deprivation or to stress reaction (hypoxia, acidosis) [54-57].

Disruption in the circadian rhythms of beta-endorphin is associated with the stress response of trauma and surgery (anesthetic agents). Opioidergic hyperactivity is involved in the appearance of delirium [58, 59].

Central glutamatergic hyperactivity has been described in delirium [n2], in relation to substance withdrawal (in particular, alcohol withdrawal) [60]. On the other side, central glutamatergic hypoactivity is typical of dissociative anesthetics drugs (phencyclidine, ketamine), inducing schizophrenia-like clinical pictures with hallucinations, by blocking N-methyl-D-aspartate (NMDA) receptors [61]. Metabotropic glutamatergic (mGlu) receptor activation involving mGlu2R and mGlu3R have antipsychotic effects in human [62]. Substances with glutamatergic activity, such as the kynurenines

(quinolinic and kynurenic acid, NMDA receptor agonist and ionotropic receptor antagonist, respectively), derive from 5-HT metabolism [63].

In the delirium, through the humoral pathway, cytokines have indirect inhibitory effects on the central cholinergic system (interleukin-2, IL2), the forebrain (prostaglandin-mediated actions of IL1) or in a more complex interplay (IL6, tumor necrosis factor α or TNFα, IL8, IL1 receptor antagonist or IL1RA, IL10) [64-68]. Through the neural pathway, cytokines activate primary afferent nerves (such as the vagus nerve) and modify CNS functioning [69].

The inflammatory response to surgery in patients with hip fracture is characterized by a significant increase of TNFα (after the first hour) and IL-6 and IL-10 (after the first day), predicting for adverse post-operative outcomes (mortality and complications) [70, 71].

The increased secretion of cortisol is the central event of the stress reaction, as a result of cognitive (conventional senses) and non-cognitive (inflammatory cytokines from the immune system) stimuli. Glucocorticoids on cerebral cells (e.g., neurons and astrocytes) are relevant for brain functioning, but they result in damaging effects when excessive (hippocampal neurotoxicity), with possible implications for delirium [72-77]. It is noteworthy that hypothalamus-pituitary-adrenal (HPA) axis hyperactivity has been described in AD, in relation to the hippocampal damage, with a loss of the glucocorticoid receptors and of the negative feedback on the HPA axis itself [78-81]. Moreover, cortisol levels during the stress reaction to hip fracture and surgery have important metabolic effects. Neurosteroids produced within the CNS are also significant modulators of GABAergic transmission [82]. Data are scanty about the activity of the homeostatic systems in AD patients with hip fracture [77], but these factors may be associated to adverse events and poor surgical outcomes; we therefore suggest to consider them as an essential part of the clinical assessment in AD. Our preliminary observation in AD patients after surgery for osteoporotic hip fracture (without neuroactive treatments, such as antidepressant, cholinesterase inhibitors, glutamate antagonist or antipsychotics) showed a marked increase of urinary diurnal (8 am-8 pm) and nocturnal (8 pm-8 am) cortisol after the stress condition (5.4 ± 3.5 days after the hip fracture surgery), with a significant inflammatory response (demonstrated by an increase in the C-reactive protein) [83] Fig. (**3a**).

The neurotrophins are trophic factors for neuronal cells. Brain Derived Neurotrophic Factor (BDNF) promotes neuronal maintenance, survival and synaptic plasticity, with resulting protective effects in AD [84]. We found reduced serum BDNF levels in AD patients after hip fracture surgery [79] Fig. (**3b**). It has to be pointed out that BDNF levels in AD patients are commonly lower than in controls [85, 86]. Therefore, the osteoporotic hip fracture and the related surgery induced a marked alteration of the neuroendocrine-immune parameters (BDNF and cortisol) in AD, synergistically and inversely involved in the clinical course of the patients. Further studies are necessary in order to confirm the BDNF and cortisol involvement and to evaluate the role of these modifications on cerebral functions (worsening of cognition and appearance of delirium) and clinical out-comes (risk of infections and mortality) in a larger group of subjects.

Neuronal damage by oxidative stress has been demonstrated by the increase of thiobarbituric acid-reactive substances (marker of lipid peroxidation) occurring during sepsis, with or without a disruption in the blood-brain barrier and it may be associated with delirium [87-89]. Two opposite hypothesis proposed delirium as the result of a global or a limited CNS failure [18]. The former hypothesis consist of systemic vascular-metabolic effects on neuron (such as hypotension and/or decrease of glucose and oxygen supply); the latter hypothesis suggests a localized damage in susceptible neuronal area (the basal ganglia and thalamus, Purkinje cells and the hippocampal pyramidal neurons) [18, 90].

In the majority of cases, the pathophysiology of delirium is complex, multi-factorial and incompletely understood [10]. Age-related brain changes predispose older subjects to have delirium during situations that should be better tolerated in younger individuals. Systemic inflammation after injury and surgery is recognized as a trigger for delirium, particularly in elderly demented patients.

DIAGNOSTIC CRITERIA AND TOOLS

The first two steps in the prevention of post-operative delirium are the careful evaluation of predisposing factors and the earliest diagnosis when delirium occurs. Since the AD patients have a high risk for post-operative delirium, a screening for AD has to be included in pre-operative geriatric assessment [91].

The available tests for rapid cognitive screening are Mini Mental State Examination (MMSE) (age and education corrected cut-off <24), Clock Drawing Test (CDT) (equivalent score 0, cut-off ≤7.56), Mini-Cog Test (cut-off <1-2 recalled words + abnormal CDT or 0 recalled words), Short Portable Mental Status Questionnaire (SPMSQ) (cut-off <8), Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (cut-off >4) and, recently, Cognitive Disorder EXamination (CODEX, cut-off ≤3) [92-100].

Two main neurotransmission disorders are investigated: the deficit of central cholinergic transmission (typically, the patient affected by AD) and the deficit of central dopaminergic transmission (typically, the patient with Parkinson's disease, PD).

After the brief cognitive evaluation, a specialized physician must evaluate the presence of delirium.

According to Diagnostic and Statistical Manual of Mental Disorders (DSM5), the delirium has been described as a severe disorder characterized by an acute, fluctuating attention deficit, with change of an additional cognitive domain (memory, orientation, language, visuospatial ability and perception). The disturbance must not be the result of another neurocognitive disorder and it must not be occurring in the presence of coma (where the level of arousal is very decreased) [101-104]. The physician must detail the delirium directly resulting from substance intoxication/withdrawal or medication-induced and the level of activity (hyperactive, hypoactive and mixed) [101].
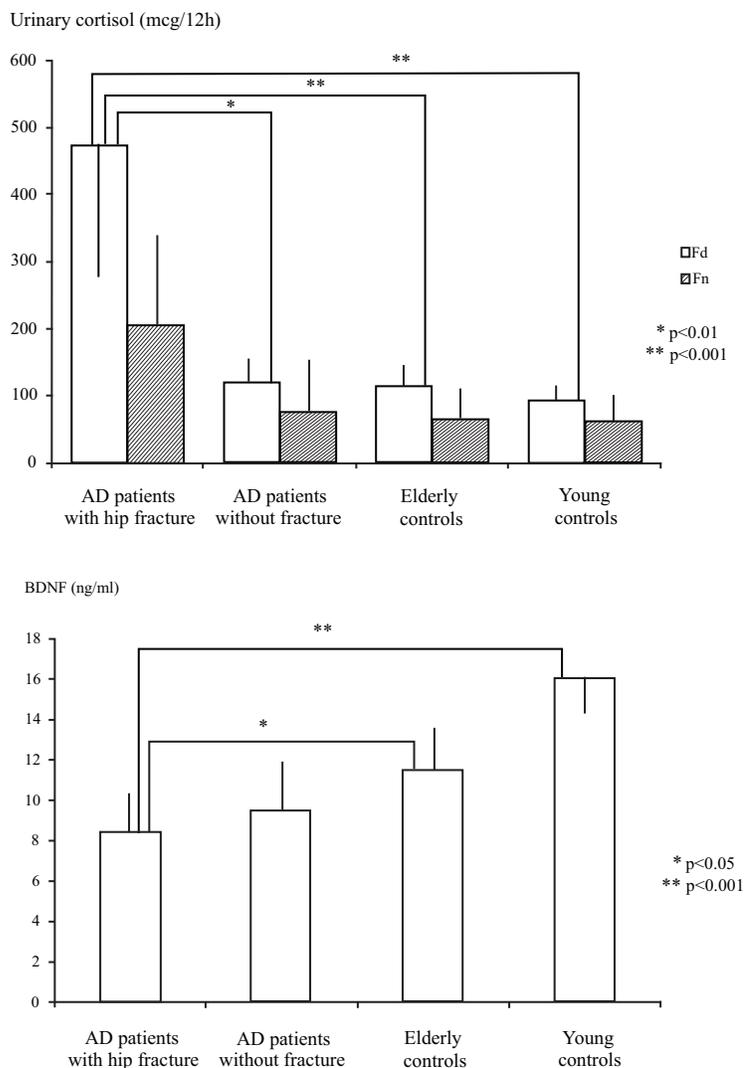
Urinary cortisol (mcg/12h)

BDNF (ng/ml)

Fig. (3). The urinary diurnal (Fd) and nocturnal (Fn) cortisol (**3a**) and serum BDNF (**3b**) in AD patients with (n=5) and without hip fracture (n=6), elderly (n=8) and young (n=6) controls (AD=Alzheimer's disease).

Despite the importance of an early diagnosis and treatment of delirium, it is currently under-recognized in clinical settings. The presence of delirium should be investigated by a specialized physician (or nurse), every day from the admission to the hospital, particularly after the operation, using a standardized method.

A well-known scale for delirium is Confusion Assessment Method (CAM). For a diagnosis of delirium by CAM, there must be present an acute onset, a fluctuating discourse, inattention and disorganized thinking or altered consciousness [105]. Other scales are Delirium Observation Screening Scale (DOS, cut-off ≥3), Delirium Rating Scale-Revised-98 (DRS-R-98, total score cut-off>18, severity score cut-off >15) to monitor the severity of delirium, and Intensive Care Delirium Screening Checklist (ICDSC) scale to define the subsyndromal delirium (score of 1-3, of a maximum of 8) [105-109]. The Delirium Symptom Interview (DSI) may be useful to identify the subtype of delirium [110]. Hyperactive delirium is a subtype of delirium characterized by heightened arousal, restlessness, agitation or aggressiveness; on the contrary, hypoactive delirium is characterized by quietness, withdrawal and sleepiness [111]. The Neelon and Champagne (NEECHAM) confusion scale allows a rapid assessment by nurses (cut-off ≤24) [112].

A new testing apparatus and methods has been developed for determining a user's ability to sustain attention, in the determination of the presence or absence of delirium [113]. Mobility can be measured with the warn accelerometer-based sensor, helping to make the differential diagnosis between the subtype of delirium [114]. A semi-automated, continuous and objective delirium monitoring system has been recently developed [115].

With regards to pharmacological risk factors, four scoring scales have been developed to evaluate the anticholinergic drug burden: Anticholinergic Risk Scale (ARS), Anticholinergic Drug Scale (ADS), Anticholinergic Burden scale (ACB) and anticholinergic component of Drug Burden Index (DBI) [116-120]. From a laboratory point of view, a functional competitive binding assay has been developed to

measure the serum anticholinergic activity (SAA) against central muscarinic receptors [121, 122].

The more the diagnosis of delirium will be correct and specific, the more the treatment will be adequate and effective.

TREATMENT OPTIONS FOR DELIRIUM

Environmental strategies appear to be useful in the treatment of delirium, including: - appropriate lighting, with blinds open in the day and reduced lighting during the night, in order to minimize patient's disorientation; - quiet environment, especially at the rest times, with reduction of noise and disturbance by the staff; - family and caregiver involvement; - avoiding of room changes; - assistance in the use of hearing and visual aids, when necessary.

A recent invention has been developed for controlling lighting conditions in a hospital room, according to a predetermined schedule, with a circadian rhythm to reduce delirium incidence [123].

In the older population with hip fracture, a wide range of treatments explored the beneficial effects of pharmacological supports, based on the above described pathophysiological mechanisms of delirium. The results are not always significant, because the samples are small and heterogeneous, limiting the evaluation of the efficacy/safety of therapies [124].

Most trials compared potent dopaminergic blockers (haloperidol 0.5-1 mg) with other typical or atypical antipsychotics (chlorpromazine, risperidone, clozapine, olanzapine, quetiapine, ziprasidone and aripiprazole) [125-128]. In chronic administration, olanzapine induces overweight, glucose and lipid increase (especially triglycerides) with diabetes mellitus and it may be linked to a high rate of cardiovascular diseases and a shorter life span [129]. Clozapine is less used for the agranulocytosis risk. Atypical antipsychotics may stimulate hypothalamic AMP-protein kinase (AMPK) through H1 receptor antagonism, suggesting a possible mechanism for their metabolic effects.

A double-blind, randomized, placebo-controlled trial (MIND-USA, Modifying the Impact of ICU-Induced Neurological Dysfunction-USA) is under investigation to study the role of antipsychotic treatment for delirium in susceptible patients, with regards to safety and, in particular, evaluating the incidence of arrhythmias, extrapyramidal symptoms and mortality, during one year, between three groups (haloperidol, atypical antipsychotic ziprasidone and placebo).

Regarding the cholinergic transmission, two therapeutic strategies examined how to potentiate it by increasing anabolic pathways (citicoline or cytidine diphosphate-choline) or by reducing catabolic reactions (acetylcholinesterase inhibitors, such as donepezil 5 mg) [130, 131]. The citicoline did not prevent or reduce the incidence of delirium after surgery [130]. In the small trial in elective total hip replacement, the incidence of delirium was not ameliorate by donepezil, however there was a consistent trend suggesting possible benefits [131].

The cholinergic receptor agonist (physostigmine) could be employed in the anticholinergic drug toxicity with delir-

ium, but peripheral (respiratory, gastrointestinal and cardiac) collateral effects limits its use [132]. Muscarinic M1 receptor positive allosteric modulators have been developed in order to treat AD and schizophrenia [133]. The modulators of the nicotinic α7 Ach receptors are recent targets for cognitive enhancement [134].

The GABAergic transmission can be increased in patient with delirium by the use of benzodiazepines (preferring the short-acting medications with no active metabolites, such as lorazepam 0.5-1 mg) [135]. Gabapentin has an inhibitory action mediated, and not, by GABA-ergic neurotransmission, that may be useful in delirium [136]. Compounds with GABA-B positive allosteric modulation (enhancers) have been developed to treat or prevent anxiety, depression, epilepsy and schizophrenia [137].

The DA antagonists and the GABA agonists are the two main options of treatment for delirium. Typical antipsychotic drugs (chlorpromazine and haloperidol) induce extrapyramidal side effects including Parkinson-like symptoms and tardive dyskinesia. Atypical antipsychotics induce extrapyramidal side effects with lower intensity, antagonize D2 dopamine receptors and also have antagonist activity at the 5-HT2A receptors [138]. The typical DA antagonists with anticholinergic properties have to be excluded from the treatment of delirium in AD patients. Therefore, the atypical DA antagonists are usually preferred in AD patients. GABA agonists are not a first choice in AD patients, since these drugs may induce paradoxical responses. In subjects with delirium and deficits in dopaminergic transmission, such as the patients with PD, the GABA agonists and the atypical DA antagonists are commonly preferred.

With regards to other kinds of treatment, GABA receptor-B positive allosteric modulators (enhancers) are useful in alcohol-withdrawal delirium [139]. Selective GABA A.alpha.5 negative allosteric modulators have proposed for conditions related to excessive GABAergic inhibition [140].

Melatonin (3 mg in the evening for 5 consecutive days, starting within 24 hours after admission) did not reduce the incidence of delirium within 8 days from admission [141].

A retrospective, not randomized or blinded, study suggested that the brain entry of phenylalanine could be decreased by L-tryptophan, improving MMSE score and sleep/wake cycle, and reducing benzodiazepines use in delirium [142]. Branched-chain amino acids could also reduce the entry of tyrosine and phenylalanine into the CNS, in the care of delirium [143]. A substituted 2-amino-3-(sulfonyl)-pyrazolo-[1, 5-a]-pyrimidine has been developed with 5-HT.sub.6 receptor antagonism, and it plays a role in treatment of AD, Huntington's disease and schizophrenia [144].

With regards to the glutamatergic transmission, specific kynurenergic agents (kynurenine aminotransferase II or kynurenine 3-monooxygenase inhibitors) could be developed to reduce potentially harmful consequences [63]. Substituted bicyclic alkoxy pyrazole analogs and related compounds have been developed with positive modulatory actions on the metabotropic glutamate receptor (mGluR5), in order to treat disorders associated with glutamatergic neurotransmission dysfunction [145].

A neurotrophic peptide having an amino acid sequence of VGDGGGLFEKKL, similar to Ciliary Neurotrophic Factor (CNTF), is a survival factor for various neurons and it can rescue cognition [146]. Ibudilast, a pharmacologic phosphodiesterase inhibitor, interferes with the microglial pathways of activatory signaling and the subsequent neuroinflammation [147].

In conclusion, the orthogeriatric collaboration and support may improve the cure and outcomes of elderly patients after hip fracture [148, 149]. Since delirium is common among elderly subjects with hip fractures and comorbid dementia and it is associated with a poor prognosis after surgery, specialized therapies may help to optimize the postoperative care for this frail group of patients, with particular regard to the prevention/treatment of delirium.

Further studies are necessary in order to determine the best model of integrated approaches combining environmental and pharmacological strategies in the treatment of delirium, with a close collaboration between the orthopedic and geriatric team.

CONCLUSIONS

The orthogeriatric collaboration and support may improve the cure and outcomes of elderly patients after hip fracture [148, 149]. Since delirium is common among elderly subjects with hip fractures and comorbid dementia and it is associated with a poor prognosis after surgery, specialized therapies may help to optimize the post-operative care for this frail group of patients, with particular regard to the prevention/treatment of delirium.

CURRENT & FUTURE DEVELOPMENTS

The current area of research is improving the evaluation of the clinical parameters for the prevention and diagnosis of delirium, by the means of clinical scales (ten diagnostic tools), chemical testing (serum anticholinergic activity) and instrumental methods (accelerometer-based sensors or semi-automated monitoring systems).

Further studies are necessary in order to determine the best model of integrated approaches combining environmental and pharmacological strategies in the treatment of delirium, with a close collaboration between the orthopedic and geriatric team.

CONFLICT OF INTEREST

No potential conflicts of interest or financial contributions were present for the manuscript preparation.

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