

# DELIRIUM IN CANCER PATIENTS

**Gabriela Zarie, Simona Tamasan**

## REZUMAT

În contextul dezvoltării noului domeniu al psiho-oncologiei, articolul sumarizează datele recente legate de manifestările, fiziopatologia și managementul clinic al deliriumului, o patologie cu o înaltă incidență în spitalul general, dar în special în secțiile oncologice. De asemenea, se subliniază importanța abordării interdisciplinare a acestui sindrom și faptul că intervenția psihiatrului de legătură poate fi de ajutor în toate cazurile, dar mai ales în cazul pacienților agitați, cu delirium hiperactiv.

**Cuvinte cheie:** delirium, stare confuzională acută, cancer, psihiatrie de legătură

## ABSTRACT

In the context of the new developed domain of Psycho-Oncology, the review summarizes recent literature on the manifestations, pathophysiology and clinical management of delirium, pathology with a high incidence in general hospital, but especially in oncological units. It also highlights, the importance of interdisciplinary approach of this syndrome, and that the intervention of a liaison psychiatrist can be helpful in all cases, especially in agitated patients with hyperactive delirium.

**Key Words:** delirium, acute confusional state, cancer, liaison psychiatry

## BACKGROUND

Delirium represents an acute consciousness, cognition, perception and behavior disturbance and the synonyms used in general hospital for it are acute confusional state, acute cognitive dysfunction, and toxic metabolic encephalopathy. Typical there is acute onset, fluctuant course and attention disturbance. It occurs in 10–30% of general hospital patients.<sup>1</sup> In cancer patients 42% were found with delirium by Lawlor.<sup>2</sup> In Centeno's study (2004) 26% to 44% of cancer patients admitted to hospital or hospice had delirium, and over 80% of all advanced cancer patients eventually experience delirium in their final days.<sup>3</sup> In advanced cancer, delirium is a multifactorial syndrome where opioid appear as factor in almost 60% of episodes; frequently, it is under diagnosed or misdiagnosed as dementia, depression, an inherent feature of cancer outcome, or a characteristic of advanced age.<sup>4,5</sup>

Delirium impact to medical personnel and family is significant due to difficulty in cooperation with a disoriented person, eventually agitate, which can present hallucinations or deeply disturbed behaviour imposing use of force or some actions opposed to the patient's will.<sup>6,7</sup>

## PATHOGENESIS

Pathophysiology of delirium has not been studied much and is not well understood. It is particularly complex in cancer patients. We attempted to make an overview of the main modern etiopathogenesis hypothesis of delirium :

a. **Hypothesis of cerebral oxidative metabolism depletion** which determines directly or indirectly (hypoxia, energetic deficiency) disturbances of neurotransmitters release and uptake. The rule would be amynergic hyperactivity (dopamine, serotonin, norepinephrine, L – glutamate) or reduction of cholinergic neurotransmission (it could explain "anticholinergic delirium" caused in elderly persons by a variety of anticholinergic drugs).<sup>8,9</sup> By Van der Maast, delirium develops as a consequence of plasmatic tryptophan reduction, and serotonergic function reduction respectively and phenylalanine increase, with amynergic cerebral hyper synthesis of dopamine and norepinephrine type.<sup>10</sup>

<sup>1</sup> Timisoara Municipal Hospital, <sup>2</sup> Timisoara Clinical Emergency County Hospital

Correspondence to:  
Dr. Gabriela Zarie, 1-3 Murgurilor Str., Timisoara, Tel. +40-744-635099  
Email: gabizar@rdslink.ro

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- **Acetylcholine** – takes an essential function in delirium's pathogenesis. A well-known source of confusional states is anticholinergic medication. Patients with cholinergic transmission deficiency, like those with Alzheimer disease, are particularly susceptible to these kind of states (cholinergic deficiency and cerebral metabolism reduction, both present in demented patients could be considered types of "cerebral insufficiency"). In postoperative delirium patients, serum anticholinergic activity is increased.<sup>11</sup>

- **Dopamine** – in delirium, there is an excess of dopaminergic activity which explains the symptomatic improvement occurred in antipsychotic drugs administration (Haloperidol or other neuroleptics with dopaminergic blocking effect).<sup>9</sup>

- **Serotonin** – studies on humans and animals have demonstrated that serotonin is increased in patients with hepatic encephalopathy and septic delirium. Hallucinogenic drugs as LSD act like serotonergic receptors agonists. Serotonergic agents could also cause delirium. Plasma amino acid disturbances (large neutral amino acids – LNAA) – increase in phenylalanine concentration and decrease in serum tryptophan, alters cerebral levels of serotonin, produces neurotoxicity or both.<sup>12</sup>

- **Gamma-amino butyric acid (GABA)** – high levels of GABA (amino acid inhibitor) were reported in patients with hepatic encephalopathy, related to increased serum ammonium and glutamine which are GABA precursors (hypoactive delirium). Low serum GABA levels were found in patients with delirium caused by alcohol and benzodiazepine withdrawal, (hyperactive delirium).<sup>13</sup>

**b. Inflammatory hypothesis.** Increase in cytokines cerebral secretion (interleukine – 1 released by cells in infectious, inflammatory or toxic insults and interleukine – 6 released in head trauma and cerebral ischemia) affects cerebral neurotransmission systems and frequently associates delirium.<sup>14</sup>

**c. Stress reaction and hormone regulation hypothesis.** Psychosocial distress and sleep deprivation facilitates delirium onset due to hypothalamic-hypophiso-corticosuprarenalian axe disturbance in response to stress, especially in elderly demented people.<sup>15</sup> Hyperactive delirium was correlated with high levels of melatonin, a pituitary hormone related to the biological regulation of the circadian rhythms and hypoactive delirium with low levels of melatonin.<sup>16</sup>

**d. Neuropathogenesis hypothesis.** As generalized superior cortical dysfunction it associates slow - wave activity on electroencephalographic recordings. Final common anatomic way for different etiologies

of delirium would be represented by alterations in prefrontal cortex, anterior right thalamus and temporo – parietal medial cortex. Final common way is responsible for central symptoms (disorientation, cognitive deficits, reversal of the sleep – wake cycle thought disorganization, language abnormalities) while other symptoms (delusions, hallucinations, illusions, affective lability) could appear in connection to delirium ethiology.<sup>17</sup>

### **Particular causes of delirium in cancer patients**

Delirium is often of multifactorial causes and can be due either with direct effects of cancer on the central nervous system (CNS) (primary brain tumours, metastatic spread) or to indirect CNS effects of the disease or treatments (medications, radiations, electrolyte imbalance, dehydration, metabolic encephalopathy due to failure of a vital organ or system, infection, vascular complications, paraneoplastic syndromes and pre-existing cognitive impairment or dementia).<sup>18,19</sup>

Narcotic analgesics such as levorphanol, morphine sulphate and meperidine are common causes of confusional states, particularly in the elderly and terminally ill. The presence of both cognitive impairment and delirium frequently is misdiagnosed or missed. Potential risk factors include neuropathic and incidental pain, opioid tolerance, somatization of psychologic distress, and a history of drug or alcohol abuse. Elevation of opioid metabolites with renal impairment may contribute to cognitive dysfunction.<sup>20</sup>

Chemotherapeutic agents known to cause delirium include methotrexate, fluorouracil, vincristine, vinblastine, bleomycin, BCNU (carmustine), cisplatin, asparaginase, procarbazine, and the glucocorticosteroids. Exposure to opioids, corticosteroids, and benzodiazepines is independently associated with an increased risk of delirium in hospitalized cancer patients.<sup>21</sup> Except for steroids most patients receiving these agents will not develop prominent CNS effects. The spectrum of mental disturbances related to steroids includes minor mood lability, affective disorders (mania or depression), cognitive impairment (reversible dementia), and delirium (steroid psychosis). Symptoms usually develop within the first weeks on steroids, but in fact can occur at any time on any dose. The disorders are rapidly reversible upon dose reduction or discontinuation.<sup>13</sup>

Postoperative delirium is a common complication associated with significant morbidity and mortality among cancer patients. Causes are multifactorial, some of predisposing factors being: advanced age, pre-

existing cerebral illness, and poor preoperative status. Precipitant factors are infection, myocardial ischemia, hypoxia, metabolic imbalances, and anticholinergic medication.<sup>22</sup>

Delirium occurs in about 50% of patients receiving stem cell transplantation, and presentations are atypical: psychomotor and sleep-wake cycle disturbances began rapidly and persisted, whereas cognitive symptoms continued to worsen throughout much of the episode. Most (86%) of the psychomotor disturbances were of a hypoactive subtype. However hallucinations and delusions were rare.<sup>23</sup> Alcohol withdrawal can be a cause for agitation and restlessness in terminal cancer patients even 6-12 month after alcohol cessation.<sup>24</sup>

## **DIAGNOSIS**

Diagnosis of delirium is a clinical one but associates paraclinical investigations and laboratory tests.<sup>25</sup> The reason for asking a psychiatric evaluation is different between the different departments of the general hospital: medical doctors seem to detect preferential affective symptoms while surgeons seem to remark especially perceptual and behavioral disturbances. Affective disorders are more frequent in women while cognitive disorders are encountered more frequently in men.<sup>26</sup> Due to patients' confusion, data obtained from caregivers could be important in relation to disorientation episodes, abnormal behavior and hallucinations. Delirium should be always suspected when appear acute or subacute deterioration of behavior, cognition or function including treatment compliance, especially in elderly, demented or depressed patients.<sup>27</sup> Essential symptoms are clouding of consciousness, difficulties in maintaining or focusing attention, disorientation and reversal of the sleep – wake cycle, low insight, impaired judgement, neurologic symptoms (dysphasia, dysarthria, tremor, asterixis in hepatic encephalopathy and uremia, motor abnormalities). Some of the patients could present visual hallucinations or persecutory delusions, while others could become suicidal or homicidal.

Criteria for Delirium due to a General Medical Condition as described in American Psychiatric Associations (APA) Diagnostic and Statistic Manual of Mental Disorders, DSM-IV were: (A) Disturbance of consciousness (reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention, (B) Change in cognition (such as memory deficit, disorientation, language disturbance, or perceptual disturbance) that is not better accounted for by a preexisting, established or evolving dementia,

(C) The disturbance develops over a short period of time (usually hours to days) and tend to fluctuate and tend to fluctuate during the course of the day, (D) There is evidence from the history, physical examination, or laboratory findings of a general medical condition judged to be etiologically related to the disturbance. A complete physical evaluation including mental state examination, vital signs monitoring (temperature, blood pressure, breath), is mandatory.<sup>28</sup>

**Differential diagnosis** has to be made with: depression (cognitive impairment without clouding of consciousness), dementia (the two of them coexist but differ in the type of onset and in length of evolution), and psychosis (psychotic symptoms appear in both entities but there is no previous history of psychosis in delirium).<sup>29</sup>

## **GENERAL TREATMENT PRINCIPLES**

First rule in delirium's treatment is early detection and identifying and solving the underlying cause.<sup>30</sup> The treatment of delirium in the dying cancer patients is unique because: (1) the etiology of terminal delirium is often multifactorial or may not be found; (2) when a distinct cause is found, it is often irreversible (such as hepatic failure or brain metastases; (3) the consultants focus is usually on the patients comfort, and ordinarily helpful diagnostic procedures that are unpleasant or painful (e. g., computer tomography, lumbar puncture) may be avoided.<sup>13</sup>

Delirium management implies supportive therapy from caregivers and family (reorientation techniques like calendars, clocks and family photos; stable, quiet and well lighted environment) and pharmacological treatment. Psychiatric consultation may be indicated for the management of behavioral problems like agitation and aggressive behavior. Pharmacotherapy is indicated when patient is excessive agitated, anxious, insomniac, psychotic, or potentially dangerous for him/her or others. Even if perceptual problems could determine agitation, fear, combative behavior, constant observation is preferred, avoiding as much as possible physical restraint.<sup>31</sup>

### **Medication**

Prevention has to be the main goal in the management of at risk patients because delirium associates, frequently, unfavorable evolution and high costs. Patients at risk must be carefully monitored while hospitalization and surgical procedures. Clinicians should become familiar with practical prescriptions in elderly patients by low doses administration and

avoidance of delirium causative medication.<sup>31</sup>

Parenteral hydration is on debate, concerning hydration status and the prolongation of life in patients with advanced cancer.<sup>20</sup>

In case of manifest delirium, neuroleptics are the most frequently used medication. Classic high potency neuroleptics as Haloperidol are useful but could determine many adverse neurological effects as extrapyramidal symptoms, neuroleptic malignant syndrome, and tardive dyskinesia. Doses should be maintained as low as possible in order to minimize the adverse effects. Initial doses could be repeated up to patient's sedation, and then they are adjusted and discontinued step by step, until they are completely stopped. Modern antipsychotics like Risperidone, Olanzapine, Quetiapine and Amisulpride determine resolution of symptoms with minimal adverse effects. Nevertheless, they could produce proarrhythmic secondary effects by prolonging QT interval. Initial doses should be higher than the maintenance ones, with lower dose in elderly patients. Paradoxical and hypersensitivity reactions may also occur.<sup>32-37</sup>

Short acting sedatives may be administered with neuroleptics only in patients who tolerate lower doses of either medication or have prominent anxiety or agitation. Benzodiazepines necessitate caution in administration because they may cause respiratory depression, or increase the risk of accidents, especially in elderly patients. The most desirable is Lorazepam, due to its short acting and lack of active metabolites; in addition, it can be administered in both i.m. and i.v. forms; it is contraindicated in severe respiratory insufficiency; caution also needed in elderly patients, limited pulmonary reserve, myasthenia gravis, organic brain syndrome, or Parkinson disease.<sup>31</sup>

In terminal cancer patients with hypoactive delirium, cognitive function could be improved with Methylphenidate. Postoperative delirium could be prevented by preoperative administration of Piracetam. Also cholinesterase inhibitors Donepezil and Rivastigmine were successfully used in these cases.<sup>11,38-39</sup>

Successful management of opioid-induced delirium requires either dose reduction or a change of opioid, in addition to addressing other reversible precipitants such as dehydration or volume depletion. In patients with advanced disease, an optimal management approach requires careful clinical assessment, identification of risk factors, objective monitoring of cognition, maintenance of adequate hydration, and either dose reduction or switching to a different opioid. Opioid rotation from morphine to

fentanyl may be effective in alleviating delirium and pain in cancer patients with morphine-induced delirium. On the other hand switching from transdermal fentanyl to oral methadone, improves the balance between analgesia and side effects in patients with cancer.<sup>24</sup>

## CONCLUSIONS

Delirium represents a brain response to injuries, imbalances and pharmacological agents in cancer patients. The liaison psychiatrist in the oncology settings is likely to encounter delirium as a common major psychiatric complication of cancer. Proper assessment, diagnosis and management are important in minimizing morbidity and improving quality of life.

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