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Review Article

About Delirium in Cancer Patients

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Abstract

The number of cancer survivors grows, the scope of care broads from treating the disease alone to managing cancer-related symptoms, including comorbid mental health disorders. Many cancer patients have delirium, this is often fatal problem. The review presents the data about epidemiology, risk factors, pathogenesis, clinical-diagnostic and treatment aspects.

Key words: cosmetic product; dermo cosmetics; skin care; active substances

Introduction

According to latest estimates of the global cancer burden, in 2022 there were 20 million new cancer cases. As a result of the demographic development, their prevalence is expected to double during the next 10 years. Cancer is a leading cause of death. It accounted for nearly ten million deaths worldwide (around 15% of all deaths) in 2020 (72.5% more than in 1990). For patients, caregivers, and families, going through cancer can be a devastating experience with many stresses and emotional upheavals. Because cancer is potentially life-threatening, the psychological impact of its diagnosis on patients has been an important aspect of clinical oncology.

Meanwhile the number of survivors continues to grow, not just because of earlier detection and treatment, but also because of revolutionary new therapies. This changes the landscape from a terminal illness to more of a chronic illness with periods of remission and exacerbation of symptoms. This perspective on neoplasms has broadened the scope of care from treating the disease alone to managing cancer-related symptoms at different stages of the disease trajectory including mental disorders.

On psychiatric consultation of 546 cancer patients there was revealed that 54% of the referrals were diagnosed as having adjustment disorders, 15% delirium and 9% major depression [1]. The results showed elevated risk of comorbid common mental health disorders among persons who at the time of the study were undergoing treatment for cancer across all countries studied compared with either cancer survivors or cancer-free respondents.

Delirium. Epidemiology.

Cancer patients often have delirium, particularly ones with far-advanced disease. The term *delirium* derives from the Latin word *delirare* (*lira* is Latin for "furrow or track" and the prefix *de* means "down, out of, or away"), which means to deviate from a straight line or "out of the furrow" [2].

Delirium is the most common and serious neuropsychiatric complication in cancer patients with advanced illness [3]. It is an often-fatal problem affecting up to 50% of hospitalized seniors, and costing over $164 billion (2011) per year in the United States and over $182 billion (2011) per year in 18 European countries [4]. This disorder is included on the patient safety agenda [5] and has been increasingly targeted as an indicator of healthcare quality for seniors.

Delirium has been defined as a disorder of global cerebral function characterized by disordered awareness, attention, and cognition. The term *acute confusional state* has also been used to describe this syndrome which is, in addition, associated with behavioral manifestations; the condition sometimes referred to as terminal restlessness probably represents a terminal delirium. Occurrence rates range from 28% to 48% in patients with advanced cancer on admission to hospital or hospice. Variability in reported rates and clinical outcomes most likely reflects sampling from different clinical settings or different stages in the clinical trajectory of cancer, in addition to inconsistency in diagnostic terminology. Elderly patients who develop delirium during a hospitalization have an estimated 22% to 76% chance of dying during that admission. Approximately 90% of these patients will experience delirium in the hours to days before death.

Risk factors

The delirium is multifactorial, especially in the setting of advanced cancer. The development of delirium involves the complex inter-

relationship between a vulnerable patient with multiple predisposing factors and exposure to noxious insults or precipitating factors. These factors include: -
The direct impact of cancer on the central nervous system (CNS). The systemic inflammatory response may result in a cascade of local (brain) neuroinflammation, triggered by inflammatory cytokines, leading to endothelial activation, impaired blood flow, and neuronal apoptosis. There is correlation between levels of circulating cytokines at diagnosis and specific types of cognitive dysfunction.

- The indirect CNS effects related to systemic complications of cancer such as organ failure (e.g., hepatic or renal failure), metabolic or electrolyte disturbance (e.g., hypoglycemia, hypercalcemia, hyponatremia, or dehydration), infection, and paraneoplastic syndromes.

Despite the very limited systematic study of risk factors for delirium in patients with cancer, risk factors have been identified in general medical patients (some of them with cancer) and include severe illness, level of comorbidity, advanced age, prior dementia, hypoalbuminemia, infection, azotemia, and psychoactive medications. The level of risk is proportionate to the number of risk factors present. Cancer is particularly prevalent in the elderly population. Many patients with cancer, particularly those with advanced disease, are likely to have a high level of baseline vulnerability. Such vulnerability leaves them predisposed to precipitants. Early identification of risk factors reduces the occurrence rate of delirium and the duration of episodes.

Main pathogenetic aspects

It is likely that the quest for a single cause or mechanism for delirium will remain unanswered. Rather, accumulating evidence suggests that several different sets of interacting biological factors result in disruption of large-scale neuronal networks in the brain, leading to acute cognitive dysfunction. Among these factors' neurotransmitters, inflammation, physiologic stressors, metabolic derangements, electrolyte and genetic disorders are mentioned. A relative cholinergic deficiency and/or dopamine excess are the key neurotransmitters.

Clinical experience and previous studies demonstrate that delirium susceptibility varies between individuals. Delirium in some patients reflects disease of the brain (as in encephalitis or certain types of strokes). But for many patients with delirium, it seems to be best to think about it as a manifestation of frailty, cognitive impairment, vision or hearing impairment, and comorbidity. Less than 10% of patients with a PS of 0–2 was diagnosed as having delirium, as opposed to more than 40% of patients with a PS of ≥3. With its acute onset in response to noxious insults, delirium may help to shed light on cognitive reserve; that is, the brain's resilience to withstand external factors. In this context, delirium may serve as a marker of the vulnerable brain with diminished reserve capacity. Delirium is typically the manifestation of a severe cerebral disorder in a vulnerable patient, subjected to noxious insults or precipitating factors. Older adults are frail when they have several interacting medical and social problems that give rise to a loss of redundancy in their homeostatic capacity and, thus, an inability to withstand stress [6].

Brain and cognitive reserve concepts developed from observations that some individuals demonstrate less cognitive impairment than others with comparable brain injury or neuropathology. Cognitive and brain reserve concepts represent important new conceptualizations to capture this vulnerability to delirium.

The poor outcomes of delirium cut across all its causes, and persist even when controlling or stratifying by underlying causes. Thus, the outcomes may be attributable to the presence of the delirium itself, and not simply to the underlying causes. This conclusion is further supported by evidence that delirium of all causes (and its associated adverse effects) is preventable through targeted multicomponent risk factor interventions. Extrapolating the concept of reserve to delirium, an acute confusional state, may allow us to elucidate fundamental aspects of reserve and provide a unique opportunity to advance the field.

Clinical Presentation. Diagnostics

The clinical features of delirium are numerous and encompass a variety of neuropsychiatric symptoms common to other psychiatric disorders. These features include prodromal symptoms (restlessness, anxiety, sleep disturbance, and irritability); rapidly fluctuating course; reduced attention (easily distractible); altered arousal; increased or decreased psychomotor activity; disturbance of the sleep-wake cycle; affective symptoms (emotional lability, sadness, anger, or euphoria); altered perceptions (misperceptions, illusions, poorly formed delusions, and hallucinations); disorganized thinking and incoherent speech; disorientation as to time, place, or person; and memory impairment (difficulty registering new material).

Neurologic abnormalities may be present during delirium, including cortical abnormalities (dysgraphia, constructional apraxia, dysnomic aphasia); motor abnormalities (tremor, asterixis, myoclonus, and reflex or tone changes); and electroencephalogram abnormalities [3].

The diagnosis of delirium should be considered in any patient with cancer demonstrating an acute onset (hours to days) of agitation or uncooperative behavior, personality change, impaired cognitive functioning, altered attention span, fluctuating level of consciousness, or uncharacteristic anxiety or depression. This diagnosis is frequently missed and poorly documented.

The core clinical criteria for this diagnosis:

- A disturbance of consciousness with reduced clarity of awareness and attention deficit.
- Other cognitive or perceptual disturbances.
- Acuity of onset (hours to days) and fluctuation over the course of the day.
- The presence of an underlying cause such as a general medical condition (e.g., hypoxia or electrolyte disturbance), medication, a combination of etiologies, or indeterminate etiology.

Other associated noncore clinical criteria features include sleep-wake cycle disturbance, delusions, emotional liability, and disturbance of psychomotor activity. The latter forms the basis of classifying delirium into three different subtypes:

1. Hypoactive that generally been found to occur with hypoxia, metabolic disturbances, and anticholinergic medications.

2. Hyperactive that is correlated with drug intoxication, or medication adverse effects.

3. Mixed, with both hypoactive and hyperactive features.

It's hypoactive type that has higher rates of incidence and mortality in patients with far-advanced cancer. Delirium presenting with hypoactive subtype, irreversible etiologies, and greater cognitive impairment is often associated with death within a period of days to weeks.

In the medically ill, delirium can interfere significantly with the recognition and control of symptoms such as pain. Uncontrolled pain can cause agitation, however, in the presence of a clear sensorium, delirium is an unlikely explanation. Patients with delirium use a significantly greater number of "breakthrough" doses of opioids at night compared with patients without delirium due to sleep wakefulness cycle reversal. On the other hand, agitation due to delirium may be misinterpreted as uncontrolled pain, resulting in inappropriate escalation of opioids, potentially exacerbating delirium [7]. Medical staff and family members may attribute a functional cause to some of the early, prodromal, and more subtle signs of delirium such as increased anxiety, restlessness, and

emotional lability. Failure to recognize delirium is particularly likely if the patient is encountered in a transient lucid phase, which can commonly occur as part of the fluctuating nature of delirium.

Delirium and dementia have some shared clinical features such as disorientation and impairment of memory, thinking, and judgment. Dementia, however, typically appears in relatively alert individuals; disturbance of consciousness is not a common feature. In elderly patients with cancer, delirium is often superimposed on dementia, giving rise to a particularly difficult diagnostic challenge. The diagnosis is more apparent when some features of delirium, especially cognitive impairment, persist. Dementia is often then the most likely explanation for a persistent or residual cognitive deficit.

Regular cognitive screening facilitates the diagnosis of delirium in cancer patients. Instruments that have favorable psychometric properties and are brief enough to allow repeated administration in cancer patients include:

- The Mini-Mental State Examination (MMSE) screens for cognitive impairment and requires active patient participation in assessment.
- The Confusion Assessment Method (CAM) screens for cognitive impairment but does not require formal patient participation.
- The Memorial Delirium Assessment Scale (MDAS) has been validated as having diagnostic and severity rating potential. This scale allows prorating of scores when a patient cannot actively participate in testing for reasons such as dyspnea or fatigue.

In family's delirium is usually the harbinger of impending death; this syndrome seriously challenges the ability to grant a loved one's wish to die at home; it is distressing for all concerned. Determining and securing the best care setting for the dying patient with delirium is complex; there are controversies regarding the goals of management, including appropriate assessment and pharmacological and nonpharmacological approaches. Delirium clearly has a recognized association with the dying phase, but many episodes of delirium are reversible; such reversal is consistent with the goals of care; therefore, the standard management approach in these patients is to search for and treat the reversible precipitants of delirium. An etiology is discovered in fewer than 50% of terminally ill patients with delirium. However, studies in patients with earlier stages of advanced cancer have demonstrated the potential utility of a thorough diagnostic assessment. 68% of delirious cancer patients experienced improved symptoms upon discovery of an etiology and institution of treatment, despite a 30-day mortality rate of 31%. Delirium was more likely to reverse when dehydration could be corrected and when opioids or psychoactive medications were reduced or discontinued when possible. Irreversibility of delirium was associated with major organ failure and hypoxic encephalopathy. Reversibility of delirium was highly dependent on the etiology: hypercalcemia was judged reversible in 38%; medications in 37%; infection in 12%; and hepatic failure, hypoxia, disseminated intravascular coagulation, and dehydration each in less than 10% [8].

Medical and Psychosocial Care

There is evidence that nonpharmacological interventions to management may result in faster improvement in delirium and slower deterioration in cognition, although no effects on mortality or health-related quality of life compared with usual care. Such interventions include oxygen delivery, fluid and electrolyte administration, ensuring bowel and bladder function, nutrition, mobilization, pain treatment, frequent orientation, use of visual and hearing aids, and environmental modifications to enhance a sense of familiarity.

Multicomponent approaches are most effective for both prevention and treatment. Stopping unnecessary medications, reversing metabolic abnormalities, treating the symptoms of delirium, and providing a safe environment open the list of priorities. Agents known to cause delirium include corticosteroids, CT agents, biological response modifiers, antidepressants, benzodiazepines, opioids, and anticholinergic agents. In a small trial of 20 cancer patients who developed delirium while being treated with morphine, rotation to fentanyl reduced delirium and improved pain control in 18 patients. To limit the potential for drug interactions, medications that are no longer useful or that are inconsistent with the goals of care should be stopped.

Treatment with antipsychotic or sedative medications is often essential to control the symptoms of delirium. Meanwhile, no medications have been approved by the US FDA for treatment of delirium.

The neuroleptic haloperidol is still considered the drug of choice for the treatment of delirium in the patient with cancer due to its efficacy, relative safety, and versatility (e.g., few anticholinergic effects, minimal cardiovascular adverse effects, lack of active metabolites, and availability in different routes of administration). However, only 0.5% to 2% of hospitalized cancer patients receive haloperidol for symptoms of delirium and only 17% of terminally ill patients receive any antipsychotic drugs for agitation or delirium [9].
Consensus guidelines recommended initial doses in the range of 1 to 2 mg every 2 to 4 hours as needed (to 4 mg orally, intravenously, or subcutaneously) and lower starting doses, such as 0.5 mg every 4 hours as needed, in elderly patients.

Risperidone is an atypical antipsychotic with fewer extrapyramidal side effects than haloperidol. It's available in oral tablet and liquid formulations; dosing begins at 1 to 2 mg per day in two divided daily doses that are titrated, if necessary, to a total daily dose of 4 to 6 mg per day.

Olanzapine, another atypical antipsychotic oral formulation is used with an initial dose range of 2.5 to 10 mg and a mean of 3 mg per dose in two daily doses to 20 mg orally at night. It's also reported to have antiemetic and possibly analgesic properties.

Lorazepam (0.5–1 mg orally or parenterally) is used along with haloperidol in patients with delirium who are particularly sensitive to extrapyramidal side effects. Another exception is midazolam, a very short-acting benzodiazepine, which is given by continuous subcutaneous or intravenous infusion in doses ranging from 30 to 100 mg over 24 hours. Midazolam is used to achieve deep sedation, especially in a terminal hyperactive or mixed delirium when agitation is refractory to other treatments. Therapeutic intervention results in delirium reversal, or at least improvement, in 30% to 75% of episodes.

Safety measures include protecting patients from accidents or self-injury while they are restless or agitated. The use of restraints is controversial; other strategies include having family members or sitters at the bedside to prevent harm.

In the last days of life, the ideal goal of delirium management is a patient who is comfortable, not in pain, awake, alert, calm, cognitively intact, and able to communicate coherently with family and staff. When delirium is a consequence of the dying process, the goal of care may shift to providing comfort through the judicious use of sedatives, even at the expense of alertness

The most challenging clinical problem is management of the dying patient with a terminal delirium that is unresponsive to standard neuroleptics, whose symptoms can only be controlled by sedation to the point of a significantly decreased level of consciousness. Before undertaking interventions such as midazolam or propofol infusions, in which the goal is a calm, comfortable, but sedated, unresponsive patient, the clinician must first have a discussion with the family (and the patient if he or she appears to have the capacity during lucid moments) to elicit concerns and wishes for the type of care that best honors a desire to provide comfort and symptom control during the dying process.

The clinician should describe the optimal achievable goals of therapy as they currently exist. Family members should be informed that the goal of sedation is to provide comfort and symptom control, not to hasten death. They should also be told to anticipate that sedation may result in a premature sense of loss and that they may feel their loved one is in some sort of limbo state, not yet dead, but no longer alive in the vital sense.

The distress and confusion that family members can experience during such a period may be ameliorated by including the family in the decision-making process and emphasizing the shared goals of care.

Our experience includes the results of evaluation 5873 patients (men 2984, women 2889, mean age 65.4 ± 5.2 years). They were examined at home because their condition precluded a standard examination in a medical facility.

They had variety of malignancies, the commonest being breast, lung, colorectal & skin cancers. The patients were cIassified as having mental comorbidity based on clinical judgment which was added with routine tests if necessary.

Mental disorders were detected in 2601 (44.3% of total cohort); in this group nosologic prevalence was as follows: depression & other mood disturbances 942 cases (36.2%), cognitive impairments - 544 (20.9%), delirium (hyperactive, hypoactive & mixed) 1079 (41.5%), other disorders - 36 (1.4%). The most difficult for differentiating were cases when delirium superimposed on dementia (58 patients). The delirium's fluctuating consciousness permitted it to set apart from dementia. During final days of life, the delirium prevalence increased.

Conclusion

Improving the quality of care requires recognition and addressing patients' distress, mental disorders and supportive care needs during treatment and after care. Thus, psychosocial and psycho-oncological support services considerably contribute to improving the quality of life of patients as a central outcome criterion of oncological care. It is clear that a more personalized approach to supporting the psychological health of people with cancer is needed. Some people may not want or require support or treatment, others will be able to self-manage, and some may have more complex needs that require more intensive follow-up and support. At diagnosis, the psychological health of patients should be considered alongside their physical health and sources of support offered. Needs and symptoms may also change over time. Being mentally aware is a preference reiterated by seriously ill patients.

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