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MOOD AND BEHAVIORAL DISORDERS IN ALZHEIMER'S DISEASE: CURRENT ISSUES AND TREATMENT

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ABSTRACT

Introduction: In recent years, the rise in population aging and longer life expectancy have led to a higher prevalence of Alzheimer's disease (AD), making it the most widespread form of dementia globally. Despite, the disease being mainly associated with cognitive decline and severe memory loss, there are many behavioral and psychological symptoms of Alzheimer's disease that prevent independent functioning. This introduction highlights the significance of understanding neuropsychiatric symptoms that appear in individuals with Alzheimer's disease which can be very diverse.
Brief description of the state of knowledge: Patients with Alzheimer's disease suffer from a broad spectrum of neuropsychiatric symptoms including depression, aggression, apathy, delusions/hallucinations, abnormal motor behavior, unusual activities, eating disorders, changes in biological rhythms, and sexual dysfunctions. The majority of these symptoms appear in over half of the patients with Alzheimer's disease, posing a serious concern that often leads to hospitalization. Despite the considerable social impact, treatment approaches for these symptoms remain poorly defined. Additionally, the presentation and severity of these symptoms can vary depending on the patient's gender and age of onset.
Summary: In summary, the aim of this review is to outline and highlight the latest knowledge on neuropsychiatric disorders, which occur in patients suffering from Alzheimer's disease, focusing mainly on mood and behavioral symptoms. These symptoms can be classified into various categories based on specific criteria, but what matters most is accurately identifying the disease's signs, as they can sometimes appear before the more typical symptoms of Alzheimer's disease.

KEYWORDS

Alzheimer's Disease, Neuropsychiatric Symptoms, Depression, Behavioral Disorders

CITATION

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Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disease[1,2] and the most common form of dementia in the world[2,3]. There are about 50 million people with AD [1,4,5] and it is more common among women than men. Almost two thirds of AD patients are women, which is primarily due to their longer life expectancy compared to men, as advancing age is the most significant risk factor for the condition. [1]. AD is a complex and progressive disorder leading to severe memory impairment and cognitive decline. Behavioral and psychological symptoms of dementia (BPSD) are often present in patients with AD, constituting a serious challenge to their daily functioning[6]. According to literature, approximately 30-90% of patients with Alzheimer's disease experience behavioral and psychological symptoms of dementia[3,7,8,9]. BPSD are a group of heterogeneous symptoms not involving cognitive functions, which are defined as signs and symptoms of disturbances in perception, thought content, mood and behavior[10]. Xue and Zhang classified BPSD into 8 main categories: delusions, hallucinations, affective disorders (anxiety, depression, apathy, irritability, etc.), aggressive behavior, unusual activities, eating disorders, changes in biological rhythms, and sexual dysfunctions(Li et al, 2012)[4]. BPSD can also be divided into 4 different sub-syndromes: hyperactivity (agitation, disinhibition, irritability, abnormal motor behavior and euphoria), psychosis (sleep disorders and nighttime behavior disorders, delusions, hallucinations), affective (depression and anxiety states) and apathy (apathy and eating disorders)[11].

Materials and Methods

This review presents currently available literature on the topic of neuropsychiatric symptoms in patients with Alzheimer's disease. The PubMed database was searched using different combinations of specific keywords: 'Alzheimer's disease', 'behavioral symptoms', 'neuropsychiatric symptoms', 'mood disorders', and 'depression'. The review focused on papers published since 2018 in English, resulting in a total of 922 articles, of which 31 were selected for their relevance and contribution to the topic at hand.

Description of The State of Knowledge

I. Neuropsychiatric disorders

The prevalence of neuropsychiatric symptoms in patients with Alzheimer's disease is 70-100%[10,12]. The most common symptoms in patients are depression, apathy, delusions/hallucinations, agitation/aggression[3,7,12] anxiety and abnormal motor behavior[7]. Apathy is common in patients with Alzheimer's disease[8,11,13,14], which studies indicate is present in 65% of patients[13]. Apathy appears early and often lasts throughout all phases of the disease. Apathy affects the clinical course of the disease and causes poorer functioning of patients[13]. Delusions in patients with Alzheimer's disease are most often persecutory, including delusions of theft or jealousy. Several disordered psychological processes may contribute to the development of delusions, including attentional bias, attributional bias, jumping-to-conclusions reasoning bias, and mild deficit theory (Nagahama, 2018)[15]. One in three patients develop delusions, and one in six patients develop hallucinations. Delusions occur in a milder form of the disease than hallucinations[16]. In addition to delusions, up to 90% of people with AD experience memory-related false beliefs (false memories), including confabulation (giving false information without being aware of it), intrusion errors, misremembering word lists, false recognition of novel stimuli, and distortions in autobiographical memory(McLachlan et al , 2023)[17]. Patients with Alzheimer's disease are at significantly greater risk of aggressive behavior than healthy individuals[18]. Aggression, agitation, and psychotic symptoms are important because they are the most common reason for hospitalization and institutionalization in Alzheimer's disease patients[3]. The most severe symptoms are irritability, diminished insight, and sundowning[2]. Some neuropsychiatric symptoms are associated with disease severity. In people with mild Alzheimer's disease, the disease may progress more rapidly if delusions, agitation, and abnormal motor behavior are present at diagnosis[19]. A study conducted by Delgado et al indicated that in mild AD, neuropsychiatric symptoms are the best predictors of impairment

in complex activities of daily living[20]. The presence of psychotic symptoms such as delusions, hallucinations, and agitation/aggression is associated with lower mean cognitive scores and faster rates of cognitive decline, whereas the presence of depressed mood is associated with faster rates of dependency. The association between depressed mood and dependency differs by gender and helps predict the trajectory of dependency in men but not in women[12]. When comparing neuropsychiatric symptoms in men and women with Alzheimer's disease, women have a wider range of symptoms. Women are more likely than men to experience irritability, restlessness, hiding things, complaining, and walking/aimlessly wandering, while men are more likely to experience apathy[21]. Studies have shown that taking anticholinergic medications increases the risk of psychosis in patients with neurocognitive disorders[7].

II. Mood disorders

According to clinical studies, the comorbidity of mood disorders in patients with AD can be even over 60%[6]. Numerous studies indicate that symptoms of depression, anxiety and apathy may appear as initial signals of development of AD. However, their appearance in patients who had not previously had them, several months after the diagnosis of dementia, has also been observed[22]. Diagnosis of depression in patients with mild cognitive impairment increases progression to AD. BPSD may therefore be both a signal of the beginning of dementia and a consequence of its progression[22,23,24]. The association between depression and dementia is certainly substantial and complex. However, the diagnostic and treatment criteria for depression in AD still remain unspecified[23]. Among the hypotheses regarding the correlation between AD and depression, there were also some opinions that their occurrence together results from the fact that both disorders share common risk factors, and not from a direct connection between them[25]. Various sources report variable frequency and prevalence of symptoms, which include: agitation, aggression, irritability, lack of inhibitions, fears, depression, apathy, delusions and hallucinations. These symptoms can be divided into 5 groups: mood/affective disorders, hyperactivity, apathy, psychosis and euphoria. Symptoms related to anxiety and depression in this division will constitute the group of affective disorders. Symptoms of hyperactivity according to this classification include aggression, impulsivity, motor hyperactivity. Whereas, hallucinations and delusions are included in the group of psychoses. However, this division is very limited and does not facilitate the use of proven and effective treatment for BPSD[26].

In the conducted studies, the presence of mood disorders in AD was variable, depending on the age at which the patient experienced the first symptoms of dementia. AD associated with early onset is associated with a higher percentage of anxiety and depression in patients. One of the proposed hypotheses suggests that this may be related to the emerging changes in lifestyle and roles, which may be more drastic and more severe in patients with early-onset Alzheimer's. However, the severity of neuropsychiatric symptoms itself seems to be unrelated to the initial age of patients but to the stage of dementia[27]. Quantitative differences in BPSD have also been observed due to gender. Research states that depressive, manic and emotional lability symptoms dominate in women. Men, on the other hand, are most prone to symptoms of apathy and aggression[28]. The phase of AD progression also seems to be important, as symptoms of depression and apathy were among the most common symptoms in the early stages of the disease. Whereas, in the later stages, the patients' agitation increased[6]. Mood disorders may therefore be a factor suggesting to doctors the beginnings of dementia development and should be a signal for further diagnostics[6,22,23]. These disorders are often neglected, which can significantly delay making the correct diagnosis, until more advanced cognitive and behavioral changes develop[22]. Depressive disorders in the elderly often differ in symptoms from those in young people. These disorders in old age are more often associated with a decline in cognitive functions[25]. Such patients often experience a decline in functions such as concentration, learning, and memory. These changes may mask dementia and lull clinicians into a false sense of security. This is an extremely dangerous phenomenon, considering studies suggesting that a diagnosis of depressive disorders in an elderly person may increase the rate of decline in the patient's cognitive functioning[6,23].

III. Treatment

Neuropsychiatric symptoms in patients are variable, and the changes occurring in patients are widespread in different parts of their brains. Loss of neurons in areas such as the hippocampus, brainstem nuclei, and changes in glutamate, acetylcholine, and dopamine transmission probably lead to excessive motor activity and aggression. Inappropriate secretion of GABA and serotonin is associated with symptoms of depression and apathy[28]. There are studies in which disorders in the serotonergic system have been associated with numerous other significant disorders in AD. These dysfunctions impact both the deterioration

of cognitive functions and the patient's affect. The effect of serotonin on mood disorders has been confirmed in numerous clinical studies in AD patients as well as in people without dementia[26]. Currently, we still do not have effective drugs that can cure patients with dementia, a significant part of therapy is based on symptomatic treatment. Due to the complex clinical picture, a common approach to pharmacological treatment is to combine various drugs, including antipsychotics, antidepressants, and mood stabilizers. Some of the neuropsychiatric disorders in dementia (such as depression, apathy, anxiety) are reduced in patients taking donepezil and choline alfoscerate[28]. However, the most commonly used drugs in BPSD are antidepressants, which, due to their low risk of side effects, are considered safe drugs. These drugs include sertraline, trazodone, and escitalopram[28]. Vortioxetine deserves special attention, as its pro-cognitive effects are an additional advantage in AD[23]. Despite its widespread use, the effectiveness of antidepressants in patients with depression and dementia has not yet been unequivocally confirmed. Non-pharmacological therapy is also used to combat the symptoms of mood disorders. Studies show that both patients and their families can benefit from participating in support groups. Patients with AD can also experience a decrease in the severity of depression, anxiety, and irritability symptoms through music sessions. In advanced stages of the disease, participation in psychotherapy is important in coping with mood dysfunction[28].

IV. Sleep disorders

Not only behavioral and psychological disorders but also sleep disorders are more common in patients with AD than in healthy elderly people. Sleep disruptions occur in as many as 71% of patients with AD. Patients with AD have altered circadian rhythms, which is manifested by more awakenings at night, time needed to fall asleep, or waking up too early[29]. Literature describes that not only AD affects sleep, but also sleep disorders contribute to the development of AD[30]. Sleep disorders also increase apathy and depression, accelerate cognitive decline and exacerbate neuropsychiatric disorders in people with AD[10]. The most common sleep disorders in people with AD are insomnia, sleep-disordered breathing, restless legs syndrome, and rapid eye movement (REM) sleep behavior disorder. In a study by Farid Chekani et al, a higher prevalence of agitation/aggression, psychotic symptoms, and anxiety/mood disorders was observed among patients with AD and insomnia compared to patients without insomnia[31].

Conclusions

In conclusion, neuropsychiatric symptoms of Alzheimer’s disease are a significant challenge both for patients and caregivers. Although these symptoms may be the first sign of Alzheimer’s disease, they are frequently overlooked, leading to delayed diagnoses. Understanding these symptoms, particularly in terms of their gender and age-related variations, can aid in earlier detection and intervention. The treatment options for these symptoms remain underdeveloped and poorly defined, with a lack of clear diagnostic and therapeutic guidelines, particularly for conditions like depression in AD. Improved treatment strategies, including both pharmacological and non-pharmacological approaches, are essential for better managing these symptoms and enhancing the care of individuals with AD.

There is an urgent need for further research to better understand the relationship between neuropsychiatric symptoms and Alzheimer’s disease progression. Clearer diagnostic criteria and treatment protocols are necessary to provide more effective care for patients and improve their quality of life.

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