ORIGINAL RESEARCH PAPER

Health Science.

DEPRESSION IN ALZHEIMER'S DISEASE: CAUSE OR CONSEQUENCE? AN UPDATING REVIEW

KEY WORDS: Depression, Alzheimer's disease, Serotonin.

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ABSTRACT

Introduction: Alzheimer's disease is a neurodegenerative dementia characterized by memory impairment, decreased abilities, and behavioral problems and directly affects the quality of life of patients and caregivers. **Objective:** This review sought to highlight the pertinent literature-reported aspects of Alzheimer's disease and its correlation with depression and serotonin. **Methods:** A literature survey of articles related to Alzheimer's disease, depression, and serotonin published in the PubMed, SciELO, and Science Direct databases between 2008 and 2015, was conducted. **Results:** A total of 128 articles were initially identified; 16 articles were selected for this study. **Conclusion:** The review of the literature shows that Alzheimer's disease and depression are closely associated.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a progressive and incapacitating decay of cognitive and neuropsychiatric manifestations, personality alterations, and, consequently, changes in behavior and the social and functional life of affected elderlies[1,2,3]. There is no elucidated cure.

The changes in the AD patient tend to be slow and are displayed through transformations in reasoning, language, attention difficulties, spatial-temporal orientation, behavioral disorders, insomnia, agitation, apathy, and mood disorders. Because they occur slowly, the initial symptoms are confused with the physiological process of aging; the worsening of disease signs occasionally leads to disease detection. This difficulty of diagnosis results from disease heterogeneity and stage among patients[4].

Initially, loss of recent memory occurs while remote memories are preserved for a certain period; this status depends on the existing cognitive reserve based on lifestyle and environmental factors to which the patient is susceptible. The more active a patient is, the less intellectual decline and disease worsening is observed[4,5].

AD is caused by the reduction of bioamides present in the locus coeruleus, raphe nuclei, and substantia nigra. Hereditary factors and neurobiological elements trigger the coexistence of depression and AD. Other conditions such as cognitive impairment and physical illnesses, as well as social aspects can trigger depression in AD and can interfere with well-being and personal autonomy[6,7].

The loss of brain cells in AD is highly selective and concentrated in lesions in the cortex and some subcortical regions, mainly the amygdala, hippocampus, and brainstem. These lesions result from extracellular deposits of the -amyloid protein that generate senile plaques, which reduce the number of neurons and, consequently, lead to brain atrophy and subsequent reduction in neurotr ansmitter synthesis and nerve conductivity[8].

Depression is caused by neurobiological dysfunctions of the monoaminergic system, hyperactivity in the hypothalamic-pituitary-adrenal axis, decreased brain-derived neurotrophic factor (BDNF), and genetic predisposition[9].

The neurochemistry of depression has been extensively investi gated in the search for treatment options. Serotonin or 5-hydroxytryptamine (5-HT) is the neurotransmitter targeted by antidepressants and anxiolytics that acts predominantly as agonist or antagonist and affect several pathways in this neurotran smitte r's metabolism[10].

Serotonin is a neurotransmitter that is the product of L-tryptophan hydroxylation and carboxylation and is degraded by the monoamine oxidase enzyme. It originates primarily in the dorsal and median raphe nuclei located in the brain stem and mesencephalon, which emits nerve fibers into other brain regions. This neurotransmitter has a modulating effect on the psychic activity and is used as a biomarker for depression[10,11].

Selective Serotonin Reuptake Inhibitors (SSRIs) are tricyclic antidepressants used to treat depression; they are reported to be safer, more specific, and more effective than other antidep ressants, but are dose-dependent and subject to prescription errors12. When SSRIs are used for the treatment of severe depression, they may be responsible for preventing suicides[13].The literature has conflicting reports about the efficacy of SSRIs; therefore, neurobiological studies have been conducted to improve the understanding of this drug therapy.

This study aimed to use literature references to clearly and succinctly present the aspects pertinent to Alzheimer's disease and its correlation with depression and serotonin.

METHODOLOGY

This review was prepared between September and December of 2015 and based on literature published during 2008 to 2015 sin PubMed, SciELO, and Science Direct. The following descriptors were used: Alzheimer's, dementia, depression, Alzheimer's and depression, Alzheimer's and cognition, depressive symptoms, L-tryptophan and depression, and L-tryptophan. Articles that contemplate AD and depression were included in the study. Articles that did not report the neurodegenerative effects of Alzheimer's and their relationship with depression were excluded.

The study included original articles, bibliographic reviews, and case reports.

RESULTS

A total of 128 articles were initially identified; of these, 16 were selected for analysis; three were original articles.

Table 1 summarizes the original articles evaluated in the study.

TABLE 1 - Summary of reviewed original articles

Author (es)	Sample	Adopted therapy	Evaluated parameters	Evaluation instrument	Results
Bremenkamp15	50 patients with a probable diagnosis of AD.			Personal information questionnaire; Clinical Dementia Staging (CDS), Functional Activities Questionnaire (FAQ), and Neuropsychiatric Inventory (NPI) in its two Subscales.	Mainly neuropsychiatric alterations of motor behavior, apathy, and agitation were identified.
Geerlings MI, den Heijer T, Koudstaal PJ, Hofman A, Breteler MMB17	503 people, aged 60-90, without dementia but with a history of depressive episodes.			Center for Epidemiologic Studies Depression Scale (CES-D).	134 subjects (26.6%) reported a history of depression; individuals with early-onset depression had an increased risk for AD.
Briones A, Gagno S, Martisova E, Dobarro M, Aisa B, Solas M, Tordera R, Ramírez MJ19	Rats were submitted to chronic moderate stress (CMS) for the selection of vulnerable or stress-resistant rats.			Forced swimming test and object recognition test for cognitive deficits.	After CMS, 40% of rats were resistant to the development of anhedonia. The group stressed with anhedonia showed a significant increase in time of immobility in the forced swimming test, cognitive deficits, synaptophysin reductions, phosphorylated PKB, and phosphorylated ERK1/2 expression in the hippocampus.

DISCUSSION

Baquero and Martín14 reported that neurodegenerative diseases are usually related to affective disorders, loss of disposition, and a sensation of discomfort. Because of the similarity in characteristics, Alzheimer's disease can be confused with depression, and vice versa, which makes accurate diagnosis necessary. Sleep disorders and feeling of loss are common in depression; however, these symptoms may also be present in AD, and may or may not be associated with mood alteration. Depressive symptoms may predispose to dementia; however conversely, these may be the consequence of self-perceived cognitive deterioration.

According to Bremenkamp15, neuropsychiatric dysfunctions are frequent and considered a major problem in Alzheimer's disease; 98% of patients present behavioral alterations depending on the disease subtype and encephalic region involved. These alterations can be represented by hyperactivity, psychosis, affective symptoms, and apathy. Among these alterations, manifestations in motor performance and apathy are the most constant, and agitation is the most serious.

According to Silva and Andrade16, serotonergic pathways in depressive conditions are diminished by the depletion of tryptophan in the diet or by a decrease in platelet imipramine receptors. Variations in mood and anxiety responses follow tryptophan depletion because serotonin is one of the main neurotransmitters regulating neuroendocrine functions, motor activity, and cognition.

Research by Bremenkamp15, Baquero, and Martín14 note affective alterations and social isolation; however, they separately report the presence of motor manifestations and sleep disorders, respectively. Regardless of the presence or absence of motor or psychological symptoms, these authors report the presence of emotional disorders that are related to depression and AD; according to Silva, Andrade16, these symptoms are due to a decrease in serotonin.

According to Geerlings17 and Caraci18, depression and AD, when associated, present a complex pathophysiology; it is still uncertain whether depression is the causal factor or the consequence of cognitive decline. Prolonged stress increases the circulation of corticosteroids, induces depressive symptoms, compromises the hippocampal region, and ultimately affects executive and memory functions. In addition, these authors suggest that the reduced synthesis of neurotrophic factors, present in neural modulation and synaptic plasticity, can be found in both dementia and depression.

Briones19 and Maes20 suggest that the existence of neuroinflammation, deregulation of neurotransmitters, and changes in neuroplasticity in AD might also be present in depression.

Geerlings17, Caraci18, Briones19, and Maes20 observed similar findings regarding the regeneration of the central nervous system; this impairment is due to the interference of neutrophil and inflammatory factors that perpetuate an inflammatory cycle and prevent neural plasticity from occurring in the cortex. The clinical manifestations of AD would be minimized if these factors could be controlled.

Wuwongse, Chang, and Law21 investigated the synaptic degeneration and protein degradation related to depression and dementia. These authors also observed that damage in the presynaptic compartment modifies the recycling of synaptic vesicles, negatively affecting their function. Therefore, they concluded that the degeneration of synapses was linked to these diseases and that the antidepressants used in the study were beneficial in the treatment of depression and AD because they attenuated presynaptic damage. Other factors such as neuroinflammation, oxidative stress, and neurotransmitter dysregulations should also be considered.

The process of senescence is influenced by serotonin and neuroplasticity impairment and involves synaptic degradation and cortex degeneration. Thus, the degradation of synapses is reported as one of the main predisposing factors to these dysfunctions. Concomitantly, other factors may be associated with the triggering of AD and depression.

CONCLUSION

There are several elements that can trigger AD and depression, such as decreased serotonin, changes in synaptic clefts, neuroinflammation, and neuroplasticity. These can cause both motor and neuronal manifestations in addition to a prevalence of affective symptoms. Although both diseases are closely related, their causes or consequences are not yet well-defined since a reduction in neurotransmitters or serotonin in depression may intensify AD, while the serotonergic pathways present in the hippocampus affect the self-perception of dementia and may predispose to depression.

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