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DEVELOPMENT OF ALZHEIMER'S DISEASE AND THE ORGANIC CHANGES INVOLVED IN THE PROCESS

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative condition characterized by the accumulation of amyloid-beta peptide (Aβ) in the brain. The first clinical signs are related to the loss of recent memory, as the disease progresses, other areas are affected, such as attention, verbal fluency, visuospatial skills and difficulty in carrying out routine activities. Loss of consciousness, lucidity and motor coordination are visible in the advanced stages of the disease. These symptoms can be accompanied by behavioral disorders such as aggression, depression and hallucinations. Genetic predisposition plays an important role in the development of the disease, with mutations in genes such as APP, PS1, PS2 and ApoE4 related to the development of the disease. Furthermore, factors such as neuroinflammation, oxidative stress, and injuries to cholinergic neurons contribute to neurodegeneration. Metals such as zinc, copper and iron play important roles in the pathology of AD, being able to influence the production and accumulation of proteins related to the disease. Vitamin B12 deficiency is also associated with increased risk of Alzheimer's due to elevated homocysteine levels, and can cause brain damage. AD treatment is mainly medication and aims to minimize disease disturbances, stabilize cognitive and behavioral impairment and maintain daily functional capacity. Current research is focused on understanding the mechanisms of AD, such as abnormal metabolism of tau protein and β-amyloid, inflammatory response, cholinergic damage, and free radicals, to develop effective treatments that can halt or modify the course of the disease. New therapeutic and preventive strategies are being developed, along with improved methods of early diagnosis, representing a significant advance in the fight against this important public health issue.
Keywords: Alzheimer's, Pathogenesis, Diagnosis, Treatment.

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease, in which it directly affects the brain with the accumulation of beta-amyloid peptide, mainly in the areas of the medial temporal lobe and neocortical structures. According to Breijyeh Z. et al. Currently, around 50 million people are affected by Alzheimer's in the world, mainly elderly people, and it is believed that the number of people doubles every 5 years, showing a constant increase in cases [3]. Currently, there is no exact definition to explain what causes the disease to progress, but it is known that genetic inheritance and advanced age are conditions that influence the development of the disease and that become significant over the years [3,1].

The first clinical aspects are presented by a cognitive decline that initially affects the practice of routine activities, learning and recent memory, and as the pathology evolves, there is greater neurological involvement, leading to an increase in cognitive changes, which may affect abilities. visuospatial disorders, language function, changes in personality or behavior and even motor function causing slow gait, requiring daily monitoring by family members or health professionals. During this process, it is common for changes in mood, behavior and even the development of depression to be noticed in 40-50% of patients due to the loss of their autonomy [2,5,8].

The diagnosis of the disease is based on several behavioral assessments that analyze the individual's loss of cognitive capacity, language functions and motor tasks. The use of neuroimaging and monitoring of biomarkers aids in diagnosis [8,13,18].

One of the main treatments is based on cognitive therapies, with the aim of reversing the processes that lead to dementia, and prophylactic approaches, which consist

of delaying the onset of cognitive loss. Many patients with mild to moderate AD showed positive results in the combination of cognitive rehabilitation therapies and drug treatments, this association helped to stabilize and even slightly improve cognitive and functional deficits, even though they were progressive in the progression of the disease. Drug treatments, such as the use of antidepressants, are also used with the aim of treating secondary manifestations, such as depression, which affects a large proportion of patients with AD, also with the aim of controlling motor agitation, aggressiveness and other factors that can result from the worsening of the disease [2,6,4,15].

MATERIAL AND METHODS

This study is based on a literature review with the aim of analyzing the risk factors for the development of the disease, the clinical manifestations presented with the progression of the pathology, the forms of diagnosis and the main treatments currently used.

This is qualitative research into the development of the disease. A survey of 21 scientific productions was carried out between the years 2000 and 2022 in relation to Alzheimer's, aiming to understand the material produced in the area during periods of increase in the disease. The data included in this study were taken from scientific articles published in the Scientific Electronic Library Online (Scielo) and PubMed databases with the keywords "Alzheimer" "Patogenesis" "Diagnosis" and "Treatment", using basic Boolean resources to combine the words mentioned (Figure 1).

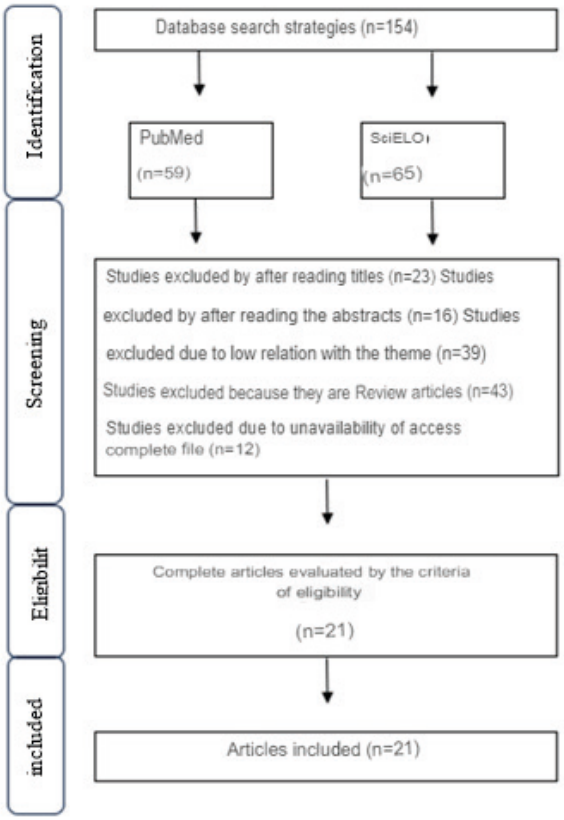

Figure 1: flowchart of articles used in the present study.

RESULTS

Alzheimer's disease is characterized neuropathologically by neuronal losses due to the accumulation of amyloid-β peptide (Aβ) in cortical areas of the brain, together with hyperphosphorylation and aggregation of tau protein, which form filaments within neurons that condense into neurofibrillary tangles, generating neurodegeneration [8,9]. Neuropathological changes developed over the course of the disease include two types of lesions, positive and negative lesions. Positive lesions are characterized by the accumulation of neurofibrillary tangles, amyloid plaques and other deposits that affect the brain. On the other hand, negative lesions are related to neural loss and, consequently, brain atrophy. Other factors such as neuroinflammation, oxidative stress and damage to cholinergic neurons can also cause neurodegeneration[3].

Lei et al. (2021) analyzed that brain zinc is related to the regulation of β-amyloid peptide (Aβ), this is linked to its role in the secretases that produce this peptide, in vitro studies analyzed that zinc inhibits the activity of b-secretase.

For this reason, with the increase in zinc, there is a limitation in the production of Aβ, however, on the other hand, it has been seen that zinc can directly bind to the TAU protein, consequently generating neurotoxicity [9]. Another factor analyzed was the reduction in cellular copper, which is directly associated with the production of Aβ. This change causes copper to concentrate with other metals in amyloid plaques, altering the distribution of copper in the brain tissue affected by the disease. Another element that can contribute to the pathology in several ways is iron, its action can drive the formation of plaques and cerebrospinal tangles, it has also been seen that iron promotes the aggregation of Aβ, thus promoting neuronal toxicity [5,9]. The interaction of these metals with amyloid plaques generates the production of hydroxyl radicals, favoring oxidative stress and the generation of amyloid fibers with greater aggregation and resistance to removal [4].

Another cause associated with the increasing risk of developing Alzheimer's and neurological changes is vitamin B12 deficiency, the lack of this vitamin generates high levels of homocysteine, leading to brain damage due to oxidative stress, increasing the influx of calcium and subsequently apoptosis of neurons. [3].

Currently, genetic factors are directly associated with the development of the disease, studies evaluated by Smith et al. (1999) reported that one third of cases of AD patients presented an autosomal dominant monogenic inheritance pattern [16]. The APP gene is responsible for encoding the amyloid precursor protein, mutations in this gene are directly associated with the early onset of AD. Therefore, the amyloid hypothesis has been one of the most accepted today, suggesting that Alzheimer's disease is the result of altered expression of APP or aggregation of Aβ, caused by mutations in APP, leading to an imbalance between the production and clearance of Aβ. Other cases are associated with the genes that lead to early-onset AD are the presenilin 1 (PS1) and presenilin 2 (PS2) genes. On the other hand, the ApoE4 gene, which is linked to b-amyloid metabolism, is related to the development of late-onset AD [16,17,7,14].

Another association with the pathology of Alzheimer's disease is neuroinflammation, which directly affects nerve cells. It has been proven that cells such as microglia, astrocytes and even neurons play important roles in the aggregation of amyloid beta (Aβ) protein and neuronal death, leading to increased expression of many inflammatory components [19].

The AD symptoms are related to progressive declines that in the long term affect the individual's memory, language, reasoning, sense of time, personality and behavior. This decline results in the loss of abilities to perform basic routine activities [20]. As a result, it has been observed that depressive disorders frequently affect individuals with AD, especially geriatrics, who are affected by mood disorders, apathy, a feeling of worthlessness which, when combined with a family history, can trigger depressive disorders [5].

As the disease progresses, other symptoms such as loss of muscle tone and ease of mobility mainly affect elderly people with advanced stage AD. The need for daily monitoring means that many of these elderly people require caregivers. Studies by Luzardo et al. (2006) demonstrated that caregivers are preferably spouses, who live with the elderly person and who have emotional, conjugal

or parent-child closeness, the support often from just one or a few family members makes it difficult both to care for the elderly and the burden on caregivers, due to this factor, the work of health professionals, especially nurses, contribute significantly to family guidance and patient care [11].

The early diagnosis of Alzheimer's is essential so that pharmacological and therapeutic treatment can begin with a focus on delaying the progression of the disease. It is necessary to initially assess the patient's clinical and pathophysiological conditions, analyze biomarkers (beta-amyloid protein and tau protein) from cerebrospinal fluid (CSF), neuroimaging assessment and neuropsychological tests, which are based on identifying cognitive impairments [12,10].

Currently, the use of CSF biomarkers has been one of the main means of diagnosing and monitoring its progression. Biomarkers are evaluated to visualize the accumulation of tau protein in the CSF. High levels of this protein are associated with disease progression, as, its presence is a strong marker of neuronal damage.

The evaluation of direct Aβ biomarkers of AD pathology and total and hyperphosphorylated T proteins (Thr181 and Thr231) for analysis of intracellular neurofibrillary tangles is also carried out. Other ways to confirm the diagnosis of Alzheimer's are magnetic resonance imaging (MRI) to evaluate anatomical changes that occur with the presence of AD and proton emission tomography (PET) with the use of molecular imaging to track the spread of Aβ protein and of the microtubule tau protein [8,18,20].

Another form of diagnosing AD is based on tests applied to patients for neuropsychological assessment, such as tests to assess language, memory, attention and executive functioning[13].

Research testing the use of new medications that help treat or even reduce the risk of developing the disease has been the focus of many researchers today. Zheng et al. (2022) evaluated the use of metformin and its action in diabetic and non-diabetic individuals, as it is known that dementia is associated with many factors, one of which is high blood sugar, which is caused in diabetic individuals [21]. Metformin is a hypoglycemic drug therapy for hyperglycemic control in diabetic individuals. In this study it was observed that the use of metformin genetically proxies leads to a 15% reduction in the risk of Alzheimer's and the maintenance of cognitive function in the general population, it was also seen that there was a reduction in the incidence of dementia in diabetic individuals [6, 21].

Treatments using medication are focused on delaying the progression of the disease, pharmacological treatment is currently based on the use of cholinesterase inhibitors (I-ChE), their use is based on increasing the synaptic availability of acetylcholine through the inhibition of its catalytic enzymes, acetyl and butyrylcholinesterase, the use of N-methyl-d-aspartate (NMDA) receptor antagonists such as memantine is also indicated, its action has an effect on glutamatergic neurotransmission, the use of chelating agents and MPA is also recommended that act on the relationship between metal ions and amyloid plaques. Other means of treatment used are antioxidants, such as vitamin E, which treat the cognitive symptoms of AD and the use of estrogen replacement agents that act to release neurotransmitters and increase cerebral blood flow. Treatment for secondary conditions caused by AD, such as depression, is based on controlled antidepressants [6,4,15,20].

Other forms of treatment are based on therapies that improve activities and interactions that are lost due to complications caused by the disease. One of the cognitive

rehabilitations is reality orientation therapy (OR), it has been used with the focus on creating environmental stimuli so that the individual develops verbality, attention and social interaction during treatment, a variation of this therapy is Reminiscence therapy focuses on stimulating the retrieval of information in the patient through photos, music, games and memories related to the individual's life [2].

DISCUSSION AND CONCLUSIONS

It must be considered that Alzheimer's disease is a progressive neurodegenerative disease and that there is no cure currently available, only treatments to relieve symptoms and reverse factors that are related to the worsening of the disease. The use of drugs and cognitive therapies are the most effective treatment methods, they aim to treat neurodegeneration, with the greatest focus on targeting the Aβ cascade and also on the cognitive development of patients with the use of cognitive therapeutic treatments. The treatment of AD directly depends on early diagnosis and medical monitoring to assess disease progression [3,2,8].

The genetic factor is currently considered the main pathogenesis of AD, the PSEN1, PSEN2 and APP genes play an important role in the development of the disease among other factors such as endogenous metal ions such as copper, zinc and iron also contribute to neurodegeneration and Aβ aggregation[3,9].

Currently, we know that the cognitive decline caused by the progression of the disease is inevitable, AD is associated with aging and familial genetic inheritance presenting an autosomal dominant type of inheritance [7]. Knowledge for early diagnosis is an important resource for early detection of the disease, management and treatment of dementia. It has been reported that carriers of the gene for the development of early-onset AD have the beginning of accumulation of the β-amyloid peptide (Aβ) 16 years before the onset of mild cognitive impairment and 21 years before the first clear signs of dementia [8]. For this reason, much current research studies new alternative strategies to inhibit the early mechanism of the disease, associated with better diagnostic alternatives, presenting great development in the discovery of new therapeutic and preventive medications, as well as new methods of cognitive rehabilitation therapies for this condition. important public health problem [3,1].

REFERENCES

1- Bondi, M. W.; Edmonds, E. C.; Salmon, D. P. Alzheimer's Disease: Past, Present, and Future. **Journal of the International Neuropsychological Society**, v. 23, n. 9-10, p. 818–831, out. 2017.

2- Bottino, C. M. C. et al. Reabilitação cognitiva em pacientes com doença de Alzheimer: Relato de trabalho em equipe multidisciplinar. **Arquivos de Neuro-Psiquiatria**, v. 60, n. 1, p. 70–79, mar. 2002.

3- Breijyeh, Z.; Karaman, R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. **Molecules**, v. 25, n. 24, p. 5789, 8 dez. 2020.

4- Falco, A. D. et al. Alzheimer's Disease: Etiological Hypotheses And Treatment Perspectives. **Química Nova**, v. 39, n. 1, 2016.

5- Forlenza, O. V. Transtornos depressivos na doença de Alzheimer: diagnóstico e tratamento. **Revista Brasileira de Psiquiatria**, v. 22, n. 2, p. 87–95, jun. 2000.

6- Forlenza, O. V. Tratamento farmacológico da doença de Alzheimer. **Archives of Clinical Psychiatry** (São Paulo), v. 32, n. 3, p. 137–148, 2005.

7- Fridman, C. et al. Alterações genéticas na doença de Alzheimer. **Archives of Clinical Psychiatry** (São Paulo), v. 31, n. 1, p. 19–25, 2004.

8- Hane, F. T. et al. Recent Progress in Alzheimer's Disease Research, Part 3: Diagnosis and Treatment. **Journal of Alzheimer's Disease**, v. 57, n. 3, p. 645–665, 10 abr. 2017.

9- Lei, P.; Ayton, S.; Bush, A. I. The essential elements of Alzheimer's disease. **Journal of Biological Chemistry**, v. 296, p. 100-105, 1 jan. 2021.

10- Lindeboom, J.; Weinstein, H. Neuropsychology of cognitive ageing, minimal cognitive impairment, Alzheimer's disease, and vascular cognitive impairment. **European Journal of Pharmacology**, v. 490, n. 1-3, p. 83–86, abr. 2004.

11- Luzardo, A. R.; Gorini, M. I. P. C.; Silva, A. P. S. S. DA. Características de idosos com doença de Alzheimer e seus cuidadores: uma série de casos em um serviço de neurogeriatria. **Texto & Contexto - Enfermagem**, v. 15, n. 4, p. 587–594, dez. 2006.

12- Mantzavinos, V.; Alexiou, A. Biomarkers for Alzheimer's Disease Diagnosis. **Current Alzheimer Research**, v. 14, n. 11, 6 out. 2017.

13- Nitrini, R. et al. Diagnóstico de doença de Alzheimer no Brasil: avaliação cognitiva e funcional. Recomendações do Departamento Científico de Neurologia Cognitiva e do Envelhecimento da Academia Brasileira de Neurologia. **Arquivos de Neuro-Psiquiatria**, v. 63, n. 3a, p. 720–727, set. 2005.

14- Selkoe, D. J. Alzheimer's Disease: Genes, Proteins, and Therapy. **Physiological Reviews**, v. 81, n. 2, p. 741–766, 1 abr. 2001.

15- Sereniki, A.; Vital, M. A. B. F. A doença de Alzheimer: aspectos fisiopatológicos e farmacológicos. **Revista de Psiquiatria do Rio Grande do Sul**, v. 30, n. 1, 2008.

16- Smith, M. DE A. C. Doença de Alzheimer. **Revista Brasileira de Psiquiatria**, v. 21, n. suppl 2, p. 03–07, out. 1999.

17- Tcw, J.; Goate, A. M. Genetics of β-Amyloid Precursor Protein in Alzheimer's Disease. **Cold Spring Harbor Perspectives in Medicine**, v. 7, n. 6, a024539, 21 dez. 2016.

18- Tiwari, S. et al. Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. **International Journal of Nanomedicine**, v. 14, n. 1, p. 5541–5554, jul. 2019.

19- Tuppo, E. E.; Arias, H. R. The role of inflammation in Alzheimer's disease. **The international journal of biochemistry & cell biology**, v. 37, n. 2, p. 289–305, 2005.

20- Weller, J.; A, B. Current Understanding of Alzheimer's Disease Diagnosis and Treatment. **F1000Research Faculty Rev**, v. 7, p. 1161, jul. 2018.

21- Zheng, J. et al. Evaluating the efficacy and mechanism of metformin targets on reducing Alzheimer's disease risk in the general population: a Mendelian randomisation study. **Diabetologia**, v. 65, n. 10, p. 1664–1675, 29 jul. 2022.