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ALZHEIMER'S DISEASE: DIAGNOSTIC INNOVATIONS AND APPLICATIONS IN CLINICAL PRACTICE

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative condition that results in loss of memory and other cognitive functions. It is characterized by the presence of amyloid plaques and tau tangles in the brain, as well as the degeneration of cholinergic neurons. Early diagnosis of AD is essential for effective management, and biomarkers play a central role in assessing the disease. Amyloid PET and cerebrospinal fluid biomarkers have shown promise for identifying pathological changes associated with AD. However, the combination of biomarkers with detailed clinical assessment remains necessary for an accurate diagnosis. Research into new treatments continues to be an active area, aimed at improving patients' quality of life and slowing down the progression of the disease.
Keywords: Alzheimer's disease, early diagnosis, biomarkers, amyloid PET, tau, neurodegeneration.

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia in the world, accounting for approximately two thirds of all dementia cases. With the increase in the proportion of elderly people in the global population, the incidence of this disease is likely to rise considerably in the coming years. Characterized by a progressive neurodegenerative process, AD results in neuropathological changes, including the formation of beta-amyloid plaques and neurofibrillary tangles containing tau proteins. These changes are directly associated with the loss of neurons and synapses, as well as changes in neurotransmitters, neuroinflammation and reactive astrogliosis, leading to cognitive impairment. (DUBOIS et al., 2023)

Clinically, AD manifests itself gradually and insidiously, with memory loss and other cognitive functions being the most obvious symptoms. However, the disease can present different clinical phenotypes, with the amnesic form being the most common. In this

form, episodic memory loss, initially associated with recent events and conversations, is the main symptom, evolving into difficulties with judgment, thinking and language. The non-amnesic form, on the other hand, can start with behavioral changes, language difficulties and visual problems, and over time all patients tend to present with global cognitive impairment and motor symptoms. (DUBOIS et al., 2023; KNAPSKOG et al., 2021)

Typically, amnesic syndrome is characterized by difficulties in learning and remembering recently acquired information, which is assessed using semantic clues. Patients suffering from this syndrome usually show a low capacity for spontaneous recall and a reduction in total recall, which suggests that the information is not adequately stored and that it is not retrieved effectively (DUBOIS et al., 2023).

Despite the severity of the clinical picture, AD still has no treatments capable of modifying its course. The pharmacological interventions available focus on relieving symptoms, but do not alter the progression of the disease. However, there is growing evidence that preventive measures, such as promoting healthy habits in middle age, can potentially delay the onset of the disease in up to 40% of cases. This includes controlling risk factors such as hypertension, obesity, diabetes, depression, social isolation and lack of physical activity. (KNAPSKOG et al., 2021)

Diagnosis is still challenging due to the pathobiological heterogeneity of the disease, which results in distinct clinical presentations, such as the logopenic, corticobasal and posterior cortical atrophy variants. The co-occurrence of AD with other neurodegenerative diseases, such as vascular diseases and other neurological conditions, makes diagnosis even more complex. Often, the diagnosis is only made after a long period of symptoms, when cognitive impairment is already considerable. Therefore, early detection and careful monitoring of patients are key to implementing more effective treatments and improving the quality of life of affected individuals. (DUBOIS et al., 2023)

There is a range of variation in the severity of cognitive impairment in individuals with AD, which defines different phases throughout the development of the disease. These phases include: the preclinical phase, with detectable biomarkers of AD pathology but no obvious or subtle cognitive impairment; the prodromal phase, with mild cognitive impairment related to AD; and mild dementia and those stages of moderate to severe dementia caused by AD (DUBOIS et al., 2023).

It is important to note that research into non-pharmacological interventions, especially those based on psychological and biochemical aspects, has been gaining prominence. Studies indicate that these approaches can help slow down the progression of the disease and improve patients' emotional well-being. However, to date, there is no single, proven therapeutic method for treating AD. (BEATA et al., 2023) In view of the above, this study aims to identify the main diagnostic innovations in AD, their biomarkers and their application in clinical practice.

METHODOLOGY

The methodology of this study is a bibliographic review of articles published in the last five years, located in the PubMed database, with the aim of summarizing the most recent information on diagnostic innovations in Alzheimer's disease (AD). The descriptors "Alzheimer's Disease" and "Diagnosis" were used to select the articles. The inclusion criteria covered original studies, reviews and clinical trials that discuss innovations in the diagnosis of AD, from biomarkers to neuroimaging techniques, with a focus on the latest technological discoveries. The exclusion criteria were strict, disregarding articles that did not meet the inclusion requirements, such as those that were not available on PubMed or that did not directly address diagnostic advances in AD.

The selection of articles was conducted through a detailed search in the established periods, with an emphasis on studies that address the different diagnostic modalities, including molecular, metabolic and neuroimaging biomarkers. The publications were analyzed in order to assess the impact of new technologies, such as amyloid PET, tau PET, structural magnetic resonance imaging and cerebrospinal fluid biomarkers, on early diagnosis and the differentiation of typical and atypical AD phenotypes. The systematic approach followed the guidelines to guarantee the reproducibility of the study and the transparency of the process, with the collection, analysis and synthesis of the evidence in an organized and rigorous manner, providing a comprehensive overview of recent advances in Alzheimer's disease diagnostic methodologies.

RESULTS AND DISCUSSION

Alzheimer's disease (AD) is a neurodegenerative condition characterized by the progressive death of cholinergic neurons in the basal forebrain, which results in increasingly severe cognitive deficits. This degenerative process is associated with abnormal deposits of proteins, such as amyloid peptides and hyperphosphorylated tau protein, which constitute the fundamental histological markers of the disease. The formation of senile plaques, composed mainly of amyloid peptides, and the presence of neurofibrillary tangles of tau protein are crucial pathological signs for the diagnosis of AD. In addition, the degeneration of key neurotransmitter systems, such as the cholinergic system, has a substantial impact on cognitive function, with the loss of nicotinic acetylcholine receptors being an important factor in the progression of the disease. (BEATA et al., 2023; DUBOIS et al., 2023)

The pathogenesis of AD also involves a series of complex pathophysiological mechanisms. Among the main associated factors are oxidative damage, dysfunction of the neurotransmitter systems, and hyperphosphorylation of the tau protein, as well as alterations in the metabolism of the beta-amyloid peptide. Research also suggests that electromagnetic radiation can influence the transmission of neurotransmitter signals in the brain, playing a relevant role in the etiology of the disease. However, the literature still lacks a complete understanding of how these factors interact to promote the onset and progression of AD. (BEATA et al., 2023)

In terms of diagnosis, advances in biomarkers have been a major focus of research. Pathophysiological biomarkers, such as amyloid PET and tau and amyloid concentrations in cerebrospinal fluid (CSF), have been key to characterizing the underlying pathology of AD and allowing differentiation between the different clinical phenotypes. However, it is important to note that although there are promising biomarkers, none of them can yet provide a definitive or individualized diagnosis of AD, especially in atypical cases. (BEATA et al., 2023)

Molecular and metabolic biomarkers are of great importance for the diagnosis of AD, especially in the context of differentiating between typical and atypical phenotypes. Amyloid PET remains the most validated imaging biomarker, with high sensitivity and specificity for detecting amyloid plaques in the brain, one of the central pathological signs of AD. Positron emission tomography with FDG-PET has demonstrated hypometabolism in specific brain regions, such as the temporal and parietal lobes, in AD patients, making it easier to distinguish the disease from other forms of dementia. (BEATA et al., 2023; DUBOIS et al., 2023)

Although FDG-PET provides valuable information on the brain's metabolic activity, structural magnetic resonance imaging (MRI) has proven more useful in the longitudinal assessment of AD progression, with gray matter atrophy being a significant indication of neurodegeneration. The use of serial MRI may be particularly useful for monitoring therapeutic

efficacy in clinical trials, offering an accurate means of assessing brain volume loss over time. (BEATA et al., 2023)

CSF biomarkers, such as tau and Aβ concentrations, are also important for the early diagnosis of AD, with decreased levels of Aβ42 in the CSF being indicative of amyloid deposition in the brain. The Aβ42/Aβ40 ratio and the presence of pTau have been shown to be particularly useful in distinguishing AD from other neurodegenerative conditions, such as frontotemporal dementia. (BEATA et al., 2023)

While current biomarkers offer valuable insights into the underlying pathology of AD, the combination of these diagnostic tools, together with a detailed clinical assessment, remains essential for accurate diagnosis and effective management of the disease. (DUBOIS et al., 2023)

CONCLUSION

Diagnosing AD is a complex process, especially due to the possibility of atypical presentations that mimic other forms of dementia. The use of biomarkers has proved to be a valuable tool for differential diagnosis, but their use alone is not enough to guarantee diagnostic accuracy. They should always be complemented by a detailed clinical assessment, since a positive result does not necessarily imply the manifestation of symptoms throughout life. In addition, the inappropriate use of these biomarkers, particularly in asymptomatic patients, can have adverse psychological and clinical impacts.

Current treatment for AD is based on the use of cholinesterase inhibitors (rivastigmine, donepezil and galantamine) for mild and moderate cases, and memantine for more advanced stages. Although memantine has a milder side-effect profile, the combination of both treatments is rarely recommended due to the potential increase in adverse effects. In parallel, there is promising research into disease-modifying therapies (DMTs), which aim to reduce the deposition of amyloid plaques and prevent the phosphorylation of the TAU protein. However, the efficacy of these treatments has not yet been fully established, representing a significant challenge due to the long pre-clinical period of AD.

In addition to the drug approach, non-pharmacological strategies play a crucial role in reducing the risk of dementia at a population level. Preventive measures, such as regular physical activity, a balanced diet and control of cardiovascular risk factors, combined with psychological interventions - including MARKS therapy, which has shown modest benefits in slowing cognitive and functional decline - are fundamental in the management of AD.

Advances in the use of biomarkers not only facilitate earlier and more accurate diagnosis, but also allow for the personalization of treatment. However, practical challenges such as cost, accessibility and clinical applicability still need to be overcome. Integrating these biomarkers into clinical practice, along with specialized psychological support for patients and families, can significantly improve the prognosis and quality of life of affected individuals. Thus, the improvement of diagnostic tools, coupled with the continuous development of new therapies, opens up promising prospects for the prevention and effective treatment of AD.

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