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NEW BLOOD BIOMARKERS FOR THE DIAGNOSIS OF ALZHEIMER'S

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Abstract: Objective: To identify and evaluate recent advances in the discovery of blood biomarkers for early diagnosis and monitoring of the progression of Alzheimer's disease, highlighting their clinical potential, sensitivity, specificity and feasibility for large-scale use. **Methods**: Bibliographic review carried out in the PubMed database using the search strategy: (Alzheimer's Disease) AND (Early Diagnosis) AND ((Biomarkers) OR (Blood Biomarkes)). It resulted in the selection of 19 articles from a total of 468 initially identified, based on strict inclusion and exclusion criteria **Review**: The potential usefulness of plasma biomarkers such as Tau protein, NFL, and beta-amyloid peptides (Aβ42 and Aβ40) is highlighted), which were shown to reflect the pathological processes of the disease and offer a less invasive diagnostic approach. Furthermore, technologies such as mass spectrometry and antibody-based assays have been identified as essential for advancing the accurate identification of these biomarkers. **Final considerations**: We highlight the need for more research to validate the clinical applicability of these biomarkers in different populations and stages of the disease, with the aim of integrating them effectively in the diagnosis and monitoring of Alzheimer's disease.
Keywords: Alzheimer's Disease; Early Diagnosis; Biomarkers.

INTRODUCTION

Alzheimer's disease is a complex neurodegenerative disorder characterized by progressive loss of memory and cognitive ability. As the leading cause of dementia, it is estimated to affect more than 78 million people globally by 2030 (AlMansoori et al., 2024). This disease is marked by the accumulation of beta-amyloid plaques outside cells and neurofibrillary tangles containing the tau protein inside brain cells. The transition of these substances from a soluble to an insoluble form, although not yet fully understood, is often explained by

the amyloid hypothesis, which suggests an alteration in amyloid metabolism resulting in the formation of these plaques and the subsequent neurodegenerative cascade. Abnormal hyperphosphorylation of tau protein also contributes significantly to pathogenesis, interfering with axonal transport and culminating in synaptic dysfunction and neuronal death (Álvarez-Sánchez et al., 2023).

Although the accumulation of amyloid plaques can be detected using positron emission tomography (PET) or cerebrospinal fluid (CSF) analysis, the high costs and invasive nature of these methods limit their clinical application. In contrast, blood biomarkers emerge as a less invasive, more economical and accessible alternative (Pan et al., 2023). It is essential to perform screening in the early stages of mild cognitive impairment associated with Alzheimer's disease, as each stage of the disease is characterized by specific biomarkers that serve as diagnostic criteria. Studying these molecular mechanisms and developing biomarkers at different stages of Alzheimer's disease progression are crucial to laying the foundation for more targeted and personalized therapies, strengthening precision medicine (Wang et al., 2023).

Considered one of the main causes of mortality among the elderly, the incidence of Alzheimer's disease is increasing, particularly with the increase in global life expectancy (Wang et al., 2023; Silva-Spínola et al., 2024). The development of tests based on blood biomarkers has the potential to accelerate diagnosis in the preclinical phase of the disease, acting as a non-invasive monitoring tool (Suridjan et al., 2023). To date, given the irreversibility of the disease and the absence of effective diagnostic therapies, many low-risk patients undergo invasive procedures that do not necessarily identify those most likely to be amyloid positive (Suridjan et al., 2023).

Recently, the use of blood biomarkers has become viable due to the development of highly sensitive tests. Studies such as that of Pan et al. (2023) investigated the predictive ability of plasma biomarkers, such as APP669-711/Aβ1-42 and Aβ1-40/Aβ1-42, and their combinations, to detect patients with amyloid-β positive or negative brain status. Researchers have also found evidence that plasma biomarkers can accurately predict brain amyloid-β burden, highlighting their potential for cost-effective and scalable population screening (AlMansoori et al., 2024).

This study aims to identify and evaluate recent advances in blood biomarkers for the early diagnosis and monitoring of Alzheimer's disease, emphasizing their clinical potential, sensitivity, specificity and feasibility for large-scale use.

METHODOLOGY

Bibliographic review developed according to the criteria of the PVO strategy, an acronym that represents: population or research problem, variables and outcome. Used to prepare the research through its guiding question: "Which new blood biomarkers have potential for the early diagnosis and monitoring of Alzheimer's disease?". The searches were carried out through searches in the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. Search terms were used in combination with Boolean terms through the following search strategy: (Alzheimer's Disease) AND (Early Diagnosis) AND ((Biomarkers) OR (Blood Biomarkes)). From this search, 468 articles were found, subsequently submitted to the selection criteria. The inclusion criteria were: articles in English; published in the period from 2023 to 2024 and which addressed the themes proposed for this research, as well as studies such as systematic reviews, meta-

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analysis, longitudinal observational studies, case-control studies, experimental studies and clinical trials, available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. After applying the inclusion and exclusion criteria, 19 articles were selected to form the collection of this study.

DISCUSSION

The diagnosis of Alzheimer's Disease (AD) traditionally relies on clinical methods, including detailed history, physical examination, cognitive assessments such as the Mini-Mental State Examination (MMSE) and magnetic resonance imaging or computed tomography. However, these methods can be complemented or even supplanted by less invasive and more accessible alternatives (Wang et al., 2023). The emergence of blood biomarkers is part of this context as a promising approach, reflecting fundamental pathophysiological processes of the disease. Currently, a variety of biomarkers have been studied, both in cerebrospinal fluid (CSF) and plasma. CSF collection, although informative, is invasive and less preferred compared to plasma analysis, which offers a less invasive and potentially more viable alternative on a large scale (Zabala-Findlay et al., 2023). Biomarkers currently associated with AD include neurofilament light (NFL), Tau protein and its phosphorylated isoforms (t-Tau and p-Tau), as well as inflammatory biomarkers such as proinflammatory cytokines, interleukins (IL-10 in particular), the chemotactic protein of monocytes (MCP-1), and others. New candidates, such as the SIRT1 protein, GFAP, SNAP25, UCHL-1, and the Aβ42/Aβ40 and NFL/Aβ42 ratios, are being investigated for possible inclusion in diagnostic panels.

For a better understanding of Alzheimer's disease biomarkers, it is important to recognize that it is characterized by a progressive neurodegenerative process, with distinct features such as the accumulation of extracellular amyloid plaques, intraneuronal neurofibrillary nodes and brain atrophy resulting from axonal degeneration. Biomarkers implemented in clinical practice include imaging tests and fluid-based markers, with cerebrospinal fluid (CSF) being the main methodology for analysis. In this fluid, beta-amyloid peptides, such as Aβ42 and Aβ40, t-tau and phosphorylated isoforms of tau protein, such as p-tau 181, p-tau 231 and p-tau 217, are evaluated in this fluid, in addition to inflammatory and cell activation markers. glial cells, such as NF-L, a cytoskeletal protein highly expressed in reactive astrocytes, and other markers such as UCH-L1 and SNAP25 (Wojdała et al., 2023).

Blood plasma presents itself as a less invasive and more accessible alternative, allowing analyzes similar to those of CSF. In particular, variants of the p-tau protein (p-tau 181, p-tau 231 and p-tau 217) have stood out in plasma due to their accuracy in identifying the neuropathological process and because they are predictors of cognitive decline.

The characteristic pathological changes of Alzheimer's disease (AD) begin decades before the first clinical symptoms appear, emphasizing the importance of early detection for effective therapeutic interventions and improving patients' quality of life (Baldini et al., 2022; Zhou et al., 2023; In this context, detection technologies and methods are crucial, with mass spectrometry (MS) and antibody-based assays being pillars of current proteomics methodology (Jain et al., 2023; Kang et al., 2023; Weiner; Blennow; Zetterberg; Gobom, 2023;

The AD biomarkers can be measured in cerebrospinal fluid (CSF) using fully automated analytical platforms, representing a non-invasive prognostic screening tool with great potential. However, current studies are small scale, which requires more rigorous validation studies to confirm their effectiveness (Silva-Spínola et al., 2024). With the aim of developing techniques that detect biomarkers early and less invasively, blood biomarkers are being considered to prevent the onset of symptoms through early diagnosis (KASTELAN et al., 2023).

Mass spectrometry has emerged as a powerful tool for identifying biomarkers associated with AD, enabling the analysis of biological samples such as CSF and blood for early markers of the disease (Kang et al., 2023; Weiner; Blennow; Zetterberg; Gobom, 2023; An et al., 2024). On the other hand, antibody-based assays such as single molecule array (SIMOA) offer a less invasive and more affordable alternative for analysis. Recent studies have demonstrated that lower concentrations of Aβ42 or the Aβ42/Aβ40 ratio in plasma are associated with the presence of cerebral amyloidosis, as measured by PET (Kang et al., 2023). Although differences in Aβ levels between individuals with and without amyloidosis are smaller in plasma compared to CSF, measuring Aβ in plasma may be useful for screening in primary care and clinical trials, reducing the need for more invasive tests such as PET scans. amyloid or CSF testing (Kang et al., 2023; Chimthanawala; Haria; Sathaye, 2024). However, the development and application of these technologies for early detection of AD face significant challenges. Biological variability and disease heterogeneity can make it difficult to identify consistent biomarkers across different patient populations. Furthermore, validation of the identified biomarkers requires large-scale longitudinal studies to confirm their effectiveness in predicting the development of AD over time (Weiner; Blennow; Zetterberg; Gobom, 2023; Chimthanawala; Haria; Sathaye, 2024).

Studies have shown promising results: a systematic review involving 15,646 participants indicated that the Tau protein and its N-terminal fragment can detect significant differences between individuals with Alzheimer's and healthy controls, as well as p-tau231 (Álvarez-Sánchez et al., 2023; Zabala-Findlay et al., 2023). Furthermore, p-tau181 has demonstrated the ability to differentiate between individuals with subjective cognitive decline, mild cognitive impairment, and AD patients, strengthening its utility as a diagnostic biomarker (Wang et al., 2023). The NFL biomarker has also emerged as a valuable tool for screening AD patients. Although research into plasma biomarkers shows high sensitivity and a promise of greater accessibility due to lower cost, challenges remain. There is still a lack of well-established protocols, and the specificity and reliability of the tests need to be rigorously validated (Álvarez-Sánchez et al., 2023).

Recent studies, such as that by Wojdała et al. (2023), carried out a retrospective cohort comparing patients at different stages of Alzheimer's Disease with a control group without cognitive deficits and a group with Frontotemporal Dementia, showing that plasma biomarkers have a strong association between values for all protein parameters, especially for the detection of GFAP Protein values using plasma material, indicating that the plasma method allows effective discrimination for diagnosis and differentiation of the Alzheimer's spectrum.

Furthermore, a study conducted by Brum et al. (2023) quantified biomarkers present in plasma samples in a group of European individuals between 40 and 60 years old, considering their lifestyles and health

status for 10 consecutive weeks. This study highlighted a difference between the classes of biomarkers, which may vary depending on the context in which they are used, showing greater interference in the dosages of Aβ42 and Aβ40 proteins. Additionally, miRNAs, known as non-coding RNAs that regulate mRNA translation and are associated with neurodegenerative processes, emerge as promising biomarkers. They are present in both CSF and plasma, highlighting the presence of deregulated miR-34a, both in cerebrospinal fluid and plasma, which proves its role in neuroprotection (Pereira et al., 2023).

FINAL CONSIDERATIONS

The emergence of blood biomarkers for the early diagnosis of Alzheimer's disease represents a significant evolution in the detection and monitoring of this neurodegenerative condition. Advances in biomarkers such as neurofilament light (NFL), Tau protein, and beta-amyloid peptides (Aβ42 and Aβ40) have the potential to transform the diagnostic paradigm by providing less invasive and more accessible methods.

Early identification of the disease through these biomarkers can revolutionize management and intervention, allowing for more effective and personalized therapeutic approaches. However, despite these promising innovations, the clinical application of blood biomarkers still faces challenges related to test validation in large-scale multicenter studies and the interindividual variability of biomarkers. Added to this, the complexity of the disease requires more studies to validate and implement these biomarkers in clinical practice. Future research must focus on validating these markers in larger and diverse populations to confirm their efficacy and feasibility.

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