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Use of biomarkers in the early detection of Alzheimer's disease

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Abstract

In 1906, Alois Alzheimer described the disease bearing his name, a progressive neurodegenerative pathology with high prevalence. This condition is characterized by progressive cognitive impairment, particularly memory loss, resulting from the degeneration and death of neurons in cortical and subcortical regions. Late diagnosis remains one of the main factors negatively impacting the prognosis of patients with Alzheimer's disease (AD). Evidence from studies using positron emission tomography (PET) and cerebrospinal fluid (CSF) analysis indicates that neuropathological changes associated with AD begin up to 20 years before the onset of clinical symptoms. This study aims to present the growing role of biomarkers in the early detection of Alzheimer's disease, emphasizing their importance in identifying early pathological changes before the appearance of clinical symptoms. This review seeks to investigate the use of biomarkers in the early detection of Alzheimer's disease, focusing on articles from the last five years, both national and international. The methodology will be conducted systematically and structurally. The development of biomarkers for Alzheimer's disease has advanced considerably, providing essential tools for the prevention, diagnosis, and monitoring of disease progression. Among the most studied biomarkers are Beta-Amyloid and phosphorylated Tau protein, which serve as biological indicators of the underlying pathological processes of the disease. These biomarkers can be measured objectively; however, obtaining this information often requires invasive methods, such as the collection of cerebrospinal fluid (CSF) to quantify protein levels. Phosphorylated Tau protein (p-tau), for instance, has proven particularly useful when combined with other biomarkers, offering a more accurate evaluation of the pathology. The integration of protein, genetic, and lipid biomarkers, together with new measurement platforms, will likely be essential in transforming the clinical approach to AD, providing a more comprehensive understanding of the disease from its early stages to its more advanced phases.

Keywords: Biomarkers; Alzheimer's disease; Early detection; β-amyloid; tau; CSF; PET; Functional magnetic resonance imaging

1. Introduction

In 1906, Alois Alzheimer described the disease that bears his name, a progressive neurodegenerative pathology with high prevalence. This condition is characterized by progressive cognitive impairment, especially memory loss, resulting from the degeneration and death of neurons in cortical and subcortical regions. These areas are directly associated with complex cognitive functions, such as memory, language, and emotional regulation (GOMES, SILVA & GUERRA, 2023).

The pathophysiology of Alzheimer's disease (AD), although not yet fully understood, is widely associated in late-onset cases with the presence of the ε4 allele of the apolipoprotein E gene (APOE4). Additionally, β-amyloid biomarkers and hyperphosphorylated tau protein, deposited in the cerebral cortex, play a central role in the pathogenesis of the disease, serving as significant indicators for staging and clinical progression (FILHO, 2022).

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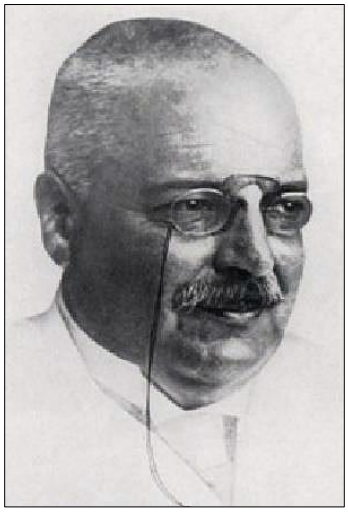
Late diagnosis remains one of the main factors negatively affecting the prognosis of patients with Alzheimer's disease (AD). Evidence from studies using positron emission tomography (PET) scans and cerebrospinal fluid (CSF) analysis indicates that neuropathological changes associated with AD begin up to 20 years before the onset of clinical symptoms. Consequently, in most cases, the diagnosis is made in advanced stages of the disease, when significant neurodegenerative damage has already occurred, limiting therapeutic possibilities due to the irreversibility of the pathological process (GOMES, SILVA & GUERRA, 2023).

Globally, the diagnosis of Alzheimer's disease remains largely based on clinical evaluation. However, various studies have focused efforts on developing biomarkers, both imaging and biofluid-based, to enhance diagnostic accuracy. Specific biomarkers for neurodegenerative diseases are indispensable, particularly for enabling early detection of the disease before symptom onset. Additionally, these markers play a crucial role in monitoring disease progression and evaluating the effectiveness of pharmacological treatments (BRASIL, 2021).

Thus, the objective of this study is to present the growing role of biomarkers in the early detection of Alzheimer's disease, emphasizing their importance in identifying early pathological changes before the appearance of clinical symptoms.



Source Public domain, via Wikimedia Commons.

Figure 1 Alois Alzheimer, German neuropathologist and psychiatrist responsible for the first diagnosis of the disease.

2. Methodology

This review aims to investigate the use of biomarkers in the early detection of Alzheimer's disease, focusing on articles published in the last five years, both national and international. The methodology will be conducted systematically and in a structured manner.

Original studies, systematic reviews, and meta-analyses published in the last five years that examine the use of biomarkers for the early detection of Alzheimer's disease were included. The focus was on biomarkers in biofluids (cerebrospinal fluid and blood) and biomarkers analyzed through imaging techniques (such as PET and functional magnetic resonance imaging).

The search was conducted in scientific databases such as PubMed, Scopus, Web of Science, Google Scholar, LILACS, and other relevant sources, using specific keywords such as "biomarkers," "Alzheimer's disease," "early detection," "β-amyloid," "tau," "CSF," "PET," "functional magnetic resonance imaging," among others.

The research was systematically conducted, utilizing combinations of keywords and Boolean operators (AND, OR) to refine the results. The search included articles in English, Portuguese, and Spanish.

The review incorporates both national and international data, allowing for a global and local perspective on advancements in the field.

The selection process was conducted in two stages: in the first stage, article titles and abstracts were evaluated; in the second stage, full articles were read to ensure they met the inclusion criteria.

Relevant data were extracted, including the type of biomarker investigated, detection methods, characteristics of the studied population, main results, and implications for the early diagnosis of Alzheimer's disease.

The discussion highlights recent advances in both national and international studies, emphasizing the most promising biomarkers for early detection, the challenges faced, and future prospects for clinical implementation.

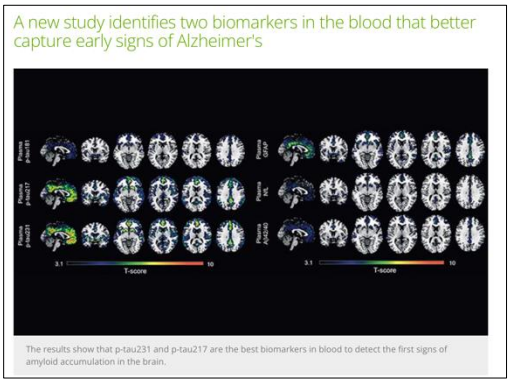
3. Literature Review

Alzheimer's disease (AD) is a chronic and progressive neurodegenerative disorder characterized by the deterioration of cognitive functions and the manifestation of behavioral symptoms that negatively impact the individual's functional capacity. Although it represents the most prevalent form of dementia and one of the leading causes of cognitive decline in the elderly, AD remains widely underdiagnosed, particularly in its early stages. Early diagnosis is especially challenging in individuals who, although not exhibiting full-blown dementia, show signs of subjective cognitive decline (SCD) or mild cognitive impairment (MCI), conditions that may precede the more evident clinical manifestations of the disease (COELHO et al., 2024).

The development of biomarkers for Alzheimer's disease has advanced significantly, providing essential tools for the prevention, diagnosis, and monitoring of disease progression. Among the most studied biomarkers are Beta-Amyloid and phosphorylated Tau protein, which serve as biological indicators of the underlying pathological processes of the disease. These biomarkers can be objectively measured, but obtaining this information often requires invasive methods, such as cerebrospinal fluid (CSF) collection, to quantify the levels of these proteins. Phosphorylated Tau protein (p-tau), for instance, has proven particularly useful when combined with other biomarkers, offering a more accurate assessment of the pathology (FILHO, 2022).

Additionally, other proteins have been identified as efficient in classifying the different stages of the disease, demonstrating robust performance in determining the severity of cognitive impairment. The combination of Beta-Amyloid and p-tau, in particular, has shown high efficacy in the early detection of the disease and in predicting its progression, allowing for the identification of individuals in the initial stages, prior to the appearance of more evident clinical symptoms (DANTAS et al., 2024).

In terms of accessibility, the combination of Beta-Amyloid and p-tau has been widely studied and applied in clinical settings, mainly due to its relative availability and ease of implementation in diagnostic practices. The use of these biomarkers in clinical contexts facilitates the continuous monitoring of the disease, enabling a more effective and personalized approach to patient care. Additionally, it serves as a crucial tool for the development of targeted therapies (FERREIRA, 2021).



Source: Brain Research Center, 2022.

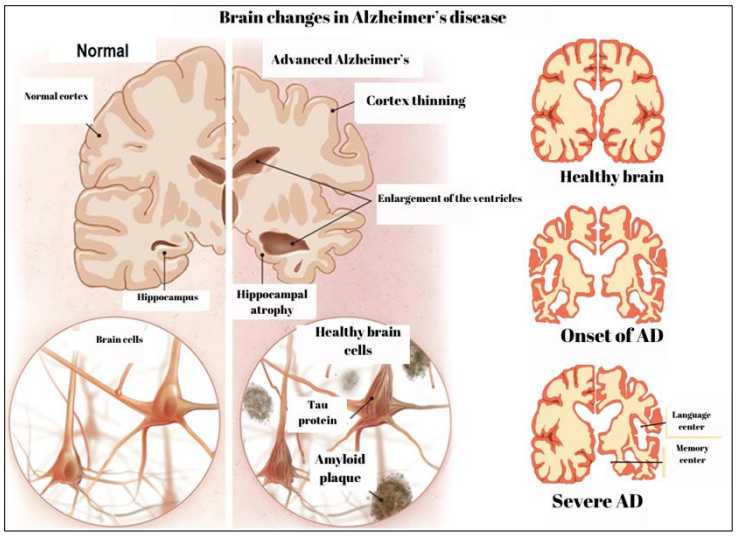
Figure 2 Figure caption to the figure

Studies of structural neuroimaging, such as brain magnetic resonance imaging (MRI), allow for the evaluation of hippocampal volume, a brain region commonly affected in the early stages of the disease. Functional neuroimaging, through techniques such as 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), enables the

visualization of cerebral metabolic activity and, consequently, the detection of functional changes associated with the progression of the pathology (SILVA et al., 2024).

Furthermore, other PET modalities, such as amyloid PET and tau PET, have proven effective in identifying and quantifying the pathological proteins associated with AD, contributing to early diagnosis and disease monitoring over time. The use of these technologies, which provide detailed information about pathological processes in the brain, is essential for identifying individuals in the early stages of the disease, prior to significant clinical manifestation (ASSIS et al., 2024).

Understanding the pathophysiology of Alzheimer's disease, which involves the deposition of abnormal proteins such as Beta-Amyloid and tau, in addition to the impairment of neuronal networks, is crucial for diagnosis and the development of therapies. Early detection of the disease is vital as it allows for the implementation of therapeutic strategies to slow disease progression and improve patients' quality of life (GOMES, SILVA & GUERRA, 2023).



Source: Gamcheolou Korean Medical Clinic, 2021.

Figure 3 Figure caption to the figure

3.1. Diagnosis by PET-CT

With technological progress over the years, new techniques have been developed and improved to assist in the diagnosis and monitoring of neurodegenerative diseases. Among these techniques, positron emission tomography (PET) and computed tomography (CT) stand out, using detailed images to identify pathophysiological changes related to various diseases. These diagnostic tools are non-invasive, extremely accurate, and allow for quantitative analysis of biological processes essential in the human brain (FERREIRA, 2021).

PET, widely recognized as a cutting-edge imaging technology in nuclear medicine, has become indispensable in several medical fields, including oncology, cardiology, and neurology. In the field of neurodegenerative diseases, its application has gained prominence by enabling the early detection of metabolic changes in the brain, as well as assisting in the differential diagnosis between different types of dementia. PET is also crucial in monitoring disease progression and evaluating therapeutic response, providing functional and metabolic images essential for understanding the underlying pathological processes (SANTOS; TAMELINI; ROMANO, 2024).

When integrated with computed tomography (CT), PET achieves an even higher level of diagnostic accuracy, combining functional and metabolic information with detailed anatomical data. CT provides structural images that allow for the identification of the location, size, and morphology of lesions or brain changes, complementing the functional data provided by PET. This combined approach increases diagnostic accuracy and specificity, allowing for a more comprehensive and detailed analysis of the brain. This integration is especially useful in managing conditions like Alzheimer's disease by offering a complete view of the structural and functional changes associated with neurodegeneration (OLIVEIRA; RABI, 2023).

Moreover, the combination of these technologies has stood out in the early detection of brain changes associated with neurodegeneration, often before the emergence of significant clinical symptoms. This ability to identify metabolic and structural changes in the early stages enables earlier therapeutic interventions, increasing the chances of delaying disease progression and improving the quality of life for patients. Thus, the integration of PET with CT represents a milestone in diagnosing neurodegenerative diseases, providing a more efficient and accurate approach to tackling the challenges of these complex conditions (CAMBRAIA et al, 2024).

Proper patient preparation is a crucial step to ensure the quality of the images obtained and minimize the presence of artifacts that may compromise the interpretation and analysis of the results. Initially, it is essential for the patient to be advised to avoid strenuous physical activities within 24 hours prior to the examination, as physical effort can interfere with metabolism and affect the results. Additionally, a minimum fasting period of 4 hours before the procedure is necessary, allowing metabolic processes to stabilize during the examination (FERREIRA, 2021).

In patients who have difficulty remaining still, such as anxious or restless individuals, the administration of muscle relaxants or sedatives may be indicated. This immobility is crucial, as even small movements can create artifacts that compromise the precision of the images and diagnostic analysis. After the initial preparation, a dose of a radioactive substance, usually a radiotracer such as fluorodeoxyglucose (18F-FDG), is administered intravenously. This substance has an affinity for metabolically active regions, allowing metabolic changes to be detected (FERREIRA, 2021).

After the injection, the patient must remain at complete rest, preferably in a quiet environment with minimal sensory stimulation, for a period of 30 to 60 minutes. This time is necessary for the radiotracer to be properly distributed and absorbed by the body, ensuring the quality and accuracy of the image capture. Only after this rest period is the patient taken to the procedure room, where they will be positioned on the equipment for image acquisition. During the examination, it is essential that the patient remains completely still to ensure the clarity and reliability of the obtained data, allowing for a more precise analysis of the brain's metabolic and structural state (SANTOS; TAMELINI; ROMANO, 2024).

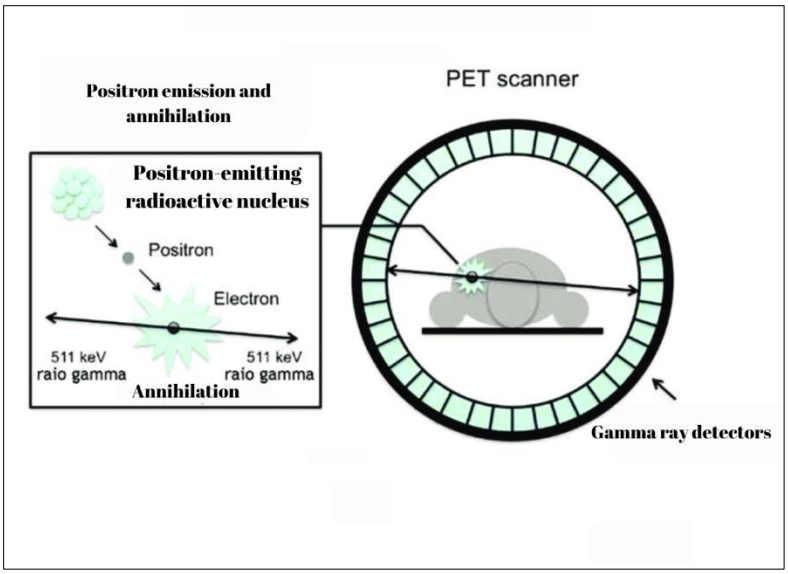
Recent studies have demonstrated the effectiveness of the PET/CT technique in diagnosing Alzheimer's disease (AD). A study published in 2017 developed and validated a new Alzheimer's dementia score based on FDG-PET images, achieving an area under the curve (AUC) of 0.78 in distinguishing individuals on a trajectory toward AD from those not progressing to AD. Additionally, the score showed promising performance in predicting the conversion of mild cognitive impairment to AD, with AUCs of 0.81, 0.80, and 0.77 for conversion windows of 2, 3, and 5 years, respectively (MATANÓ et al, 2023).

These findings indicate that PET/CT can increase diagnostic accuracy in complex cases, identifying early brain metabolic changes characteristic of AD. Consequently, the use of this technique can lead to more effective therapeutic interventions, improving the prognosis and quality of life for patients (MATANÓ et al, 2023).

In the PET-CT technique, different biomarkers are used to detect metabolic, structural, and functional changes in the brain. Most of these biomarkers are composed of isotopes of carbon, oxygen, and fluorine, which have radioactive properties and are used as tracers in the examination. Among the most common radioisotopes in Alzheimer's disease (AD) investigation are carbon-11 (^{11}C) and fluorine-18 (^{18}F), which have relatively short half-lives. These half-lives are designed to ensure patient safety while allowing precise detection during the examination (BRASIL, 2021).

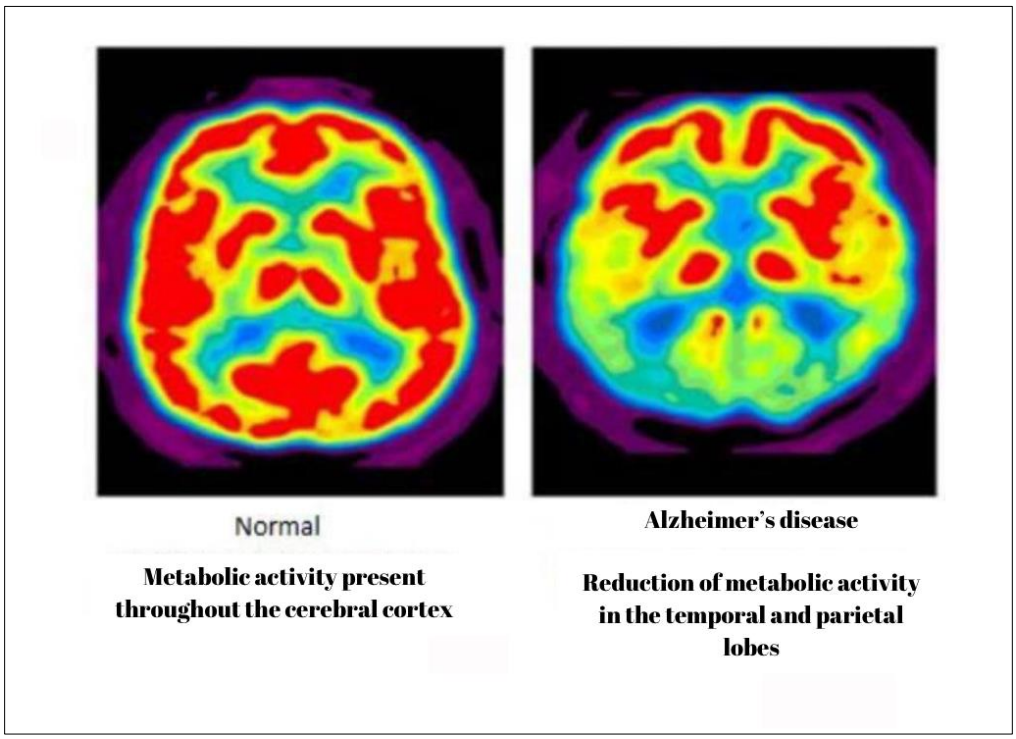
These radioactive elements emit positrons as they decay, a process known as beta-plus decay. The positrons quickly interact with the electrons in the body, resulting in annihilation that releases two high-energy photons in opposite directions. This radiation is captured by PET detectors, which process these signals to create detailed three-dimensional images. These images display variations in color and brightness, reflecting differences in the metabolic or structural levels of brain regions (FERREIRA, 2021).

The use of biomarkers such as ^{11}C and ^{18}F is essential for the early identification of brain changes typical of AD, such as the deposition of beta-amyloid plaques and neurofibrillary tangles of tau protein. Additionally, these tracers provide valuable information about brain metabolism, enabling the differential diagnosis between different types of dementia and monitoring disease progression. This technological advancement has revolutionized how neurodegenerative diseases are evaluated and treated, offering more precise and robust data for clinical practice (SANTOS; TAMELINI; ROMANO, 2024).



Source: GUIO; DORSCH, 2021.

Figure 4 Diagram of the functioning of a Positron Emission Tomography (PET) scanner



Source: SANTOS; TAMELINI; ROMANO, 2024.

Figure 5 Image of the PET imaging biomarker

4. Biomarkers

Biomarkers play an essential role in identifying specific biological processes within the body, enabling the evaluation of diseases, prognosis prediction, and monitoring of pathological conditions. In the case of Alzheimer's disease (AD), it is crucial for these biomarkers to accurately identify the molecular changes associated with the disease, targeting specific molecules that exhibit characteristic modifications (MATANÓ et al., 2023).

In the context of AD, biomarkers need to be highly sensitive and specific to detect abnormalities related to the disease. The tau protein, which normally functions to stabilize the microtubules of neurons, is one of the main targets. When hyperphosphorylated, tau forms toxic clusters that affect neuronal function and contribute to the neurodegeneration observed in AD. This modification of tau, which results in the formation of neurofibrillary tangles, is a distinctive feature of the disease and is directly associated with cognitive decline (COELHO et al., 2024).

Another key biomarker in AD is the beta-amyloid protein, which tends to accumulate and form amyloid plaques in the brain. These plaques, or senile plaques, are typical pathological signs of AD, and their excessive deposition in neurons interferes with cellular communication and induces inflammatory processes that contribute to neuronal death. Detection of beta-amyloid plaques is essential for early diagnosis and monitoring disease progression (GOUVEIA et al., 2021).

With the use of biomarkers like tau and beta-amyloid, imaging techniques such as positron emission tomography (PET) can visualize these brain changes. The radioisotopes used for this purpose are specially developed in nuclear medicine laboratories, as they are not commercially available. These radiopharmaceuticals are prepared specifically for each examination, ensuring high accuracy in results (SANTOS; TAMELINI; ROMANO, 2024).

Therefore, the use of biomarkers, such as the detection of hyperphosphorylated tau and beta-amyloid plaques, represents an important tool for the early diagnosis of AD and for monitoring therapeutic efficacy. The combination of different biomarkers can significantly improve diagnostic accuracy, enabling earlier and more effective therapeutic interventions (SANTOS; TAMELINI; ROMANO, 2024).

A	T	N
Amiloide-β (Aβ)	Tau	**Neurodegeneration**
PET for amyloid plaques or CSF for (A-beta42 or A-beta42/A-beta40 ratio)	**PET for neurofibrillary tangles in the parenchyma or CSF for Tau or phosphorylated Tau**	**Cortical or hippocampal volume**

Source: MOREIRA; MOREIRA, 2020.

Figure 6 ATN system (cerebrospinal fluid biomarkers)

In the 1990s, the diagnosis of Alzheimer's disease (AD) was made late, based on exclusion criteria, without the use of biomarkers. However, the recognition of beta-amyloid (Aβ) and tau proteins as central to AD pathology paved the way for the development of biomarkers. The presence of extracellular Aβ, even without cognitive impairment, was identified as an early change, associated with an increased risk of dementia, and its monitoring in the blood showed potential for detecting the disease before clinical diagnosis (FILHO, 2022 & OLIVEIRA et al., 2021).

The Aβ42/Aβ40 ratio, combined with the ApoE ε4 genetic variant, has shown high accuracy in identifying early pathological changes. Additionally, neurofilament light chain (NfL) is a promising biomarker for monitoring axonal damage, although its low specificity limits its use. Clusterin, involved in the formation of Aβ plaques, is also under investigation, but it has sensitivity limitations (FILHO, 2022 & OLIVEIRA et al., 2021).

Recent research indicates that biomarkers in exosomes and antiphospholipid autoantibodies may assist in early detection, with studies suggesting the possibility of identifying AD up to 10 years before the onset of symptoms. Faster and more sensitive methods, such as electrochemical assays, show promise for the early diagnosis of AD. These advances offer hope for less invasive and more accessible diagnoses (FERREIRA, 2021 & OLIVEIRA et al., 2021).

Genetic biomarkers are considered one of the most promising approaches for the early diagnosis of Alzheimer's disease (AD), due to their practicality, resilience, and low cost. Circulating microRNAs (miRNAs) have gained prominence as they regulate gene expression and are stable in the blood, protected by exosomes and other molecules. MiRNAs such as miR-9, miR-125b, and miR-191-5p are the most promising, but further research is needed for their practical application (OLIVEIRA et al., 2021).

Moreover, transcriptomics, which analyzes gene expression at the RNA level, has proven to be more effective than genotyping or DNA sequencing in identifying risks for complex diseases like AD. The combination of miRNAs and transcriptomics offers a new direction for more accessible and accurate AD diagnoses (OLIVEIRA et al., 2021).

Plasma levels of lysophosphatidylcholine, choline plasmalogen, and platelet-activating factor increase with aging and progression to Alzheimer's disease (AD), making them potential biomarkers for the early stages of the disease. Additionally, metal imbalances such as manganese, aluminum, lithium, and copper, which cross the blood-brain barrier, may trigger biochemical and behavioral changes associated with AD. Monitoring these biomarkers can assist in early diagnosis and understanding disease progression (OLIVEIRA et al., 2021).

Research on Alzheimer's disease (AD) biomarkers has advanced considerably in recent years, particularly with fluid biomarkers being widely used for diagnosis and monitoring disease progression. Currently, the most common biomarkers in cerebrospinal fluid (CSF) are total tau, phosphorylated tau, and beta-amyloid (Aβ) levels, which indicate pathological changes in the brain, such as Aβ plaque formation and tau tangles, characteristic of AD (OLIVEIRA et al., 2021).

However, the continuous development of new measurement techniques, such as mass spectrometry and advanced molecular imaging, along with a deeper understanding of AD's pathophysiological mechanisms, has led to the identification of new biomarkers. These new markers aim to more accurately reflect various aspects of AD neuropathology, including inflammation, neuronal damage, and changes in brain connectivity. Moreover, emerging biomarkers such as miRNAs, proteins associated with lipid metabolism, and inflammatory mediators are being explored to provide a more comprehensive view of the disease, enabling earlier diagnoses and more effective therapeutic strategies.

5. Conclusion

Research on biomarkers in Alzheimer's disease (AD) has evolved significantly in recent years, expanding our understanding of pathological mechanisms and enhancing early diagnosis and disease monitoring. The identification of biomarkers in cerebrospinal fluid, such as total tau, phosphorylated tau, and Aβ, has been crucial in understanding the neurodegenerative changes underlying AD, objectively revealing the presence of Aβ plaques and tau tangles, which are key characteristics of the disease. However, the limitations of accessibility and invasiveness of these biomarkers have driven the search for more practical and non-invasive alternatives, such as genetic and lipid biomarkers.

Genetic biomarkers, including microRNAs and transcriptomic expressions, have shown great potential, providing insights into biochemical and epigenetic changes associated with AD. Additionally, biomarkers related to metal and lipid imbalances, such as increased lysophosphatidylcholine and plasmalogen, may play key roles in early detection and in understanding pathological changes in the brain. The combination of these biomarkers, along with the use of more sophisticated measurement technologies, promises not only to improve diagnostic accuracy but also to facilitate the implementation of personalized therapeutic approaches.

Therefore, advancements in the identification and validation of biomarkers for AD offer a promising future for faster, more accurate, and accessible diagnoses, with significant impact on early intervention, prevention, and treatment of the disease. The integration of protein, genetic, and lipid biomarkers, alongside new measurement platforms, will likely be essential in transforming the clinical approach to AD, providing a more comprehensive view of the disease from its early stages to the more advanced stages.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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