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Advances in Early Biological Diagnostic Markers for Alzheimer's Disease

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Abstract: Alzheimer's disease(AD) denotes a progressive neurodegenerative disorder, predominantly identified by the abnormal buildup of β-amyloid (Aβ) and tau proteins in the brain. Despite the absence of a definitive cure, identifying the disease early is essential for slowing its advancement and enhancing the well-being of patients. Traditional diagnostic approaches, however, typically fail to detect brain changes until symptoms are evident, underscoring the importance of biomarker studies in achieving earlier detection of AD. This review focuses on the principal biomarkers linked to Alzheimer's disease, emphasizing those present in cerebrospinal fluid (CSF) and blood, and evaluates their potential role in facilitating early detection. While conventional CSF markers, including Aβ42, total tau, and phosphorylated tau, are commonly employed, their invasive nature and high costs pose challenges to widespread use. More recently, research on blood-based indicators has emerged as a significant area of interest, with markers like neurofilament light chain (NFL) and plasma tau showing substantial promise for diagnosis. This paper also explores how these biomarkers could illuminate the underlying mechanisms of AD, improve diagnostic reliability, and support timely interventions, while anticipating future advancements in the discovery of new diagnostic tools.

Keywords: Alzheimer's disease, early diagnosis, biomarkers

1. Introduction

As the global population ages, Alzheimer's disease (AD), a degenerative neurological condition, has emerged as the primary contributor to dementia [1]. The main pathological features of the disease involve the buildup of β-amyloid (Aβ) plaques in the cerebral cortex and hippocampus, alongside the aberrant phosphorylation of tau proteins, resulting in neurofibrillary tangles. These alterations often take place silently, without overt symptoms, yet they are closely associated with the steady decline in cognitive abilities among those affected. With the global population aging, the prevalence of Alzheimer's disease is sharply increasing, presenting significant challenges to healthcare systems.

Although there is currently no effective cure, timely detection and treatment are vital to slow illness advancement and enhance patient well-being. However, existing clinical diagnostic tools, such as neurocognitive assessment and imaging, often show pathological changes only after the disease has manifested itself clearly, making it difficult to achieve a truly early diagnosis. Traditional biomarkers such as Aβ, total tau protein (t-tau), and phosphorylated tau (p-tau) in cerebrospinal fluid (CSF), although widely used in the diagnosis of the disease [2], these methods usually have limitations such as being highly invasive, costly, and burdensome to patients.

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Recent advances in Alzheimer's research have prioritized non-invasive biomarkers for early diagnosis. In particular, the study of blood markers has become a new research hotspot due to its convenience and low invasiveness. Blood biomarkers such as neurofilament light chain (NFL) and plasma tau proteins [3]. These indicators exhibit a significant association with the pathological transformations seen in Alzheimer's. Identifying such markers could not only facilitate earlier detection of these changes but also offer a potential biological foundation for early intervention strategies targeting the disease.

This study seeks to explore the primary biomarkers linked to Alzheimer's disease, analyzing critical indicators found in both cerebrospinal fluid and blood samples. By evaluating their diagnostic potential, the paper will investigate how these markers contribute to early detection and shed light on underlying disease mechanisms, and development of future therapeutic options. At the same time, we analyze the limitations of existing markers considering the current research trends and look forward to the future direction of research and development of novel markers. Through a comprehensive understanding of Alzheimer's disease biomarkers, this paper aims to provide theoretical support for early diagnosis and intervention of the disease and to promote its application in clinical practice.

2. AD recognition criterion

The early recognition of AD experienced four stages. In 2007, the International Working Group (IWG) included biomarkers in the diagnostic criteria for AD for the first time [4], marking the shift from clinicopathologic to clinical-biologic diagnosis and establishing a sequential disease course for AD that includes three phases: preclinical, prodromal, and dementia. This earliest biomarker-based criterion proposes key biomarkers such as structural magnetic resonance (MR) imaging changes, changes in cerebrospinal fluid levels of Aβ and tau proteins (including P-tau, and T-tau), and specific PET imaging manifestations. Later in 2011, the NIA-AA diagnostic criteria published by the National Institute on Aging (NIA) and the Alzheimer's Association (AA) categorizes the biomarkers of AD into markers reflecting amyloid deposition or neuronal damage [5-7].

In 2014, the IWG updated the IWG-2 diagnostic criteria for AD [8], categorizing biomarkers into diagnostic markers, which reflect AD-specific pathological changes, and progression markers, which reflect disease severity and progression, and emphasizing the combined use of biomarkers to reduce the limitations of a single marker and to improve diagnostic accuracy. In 2018, the NIA-AA proposed the ATN framework to include amyloid (A), tau protein (T), and nerve damage (N) as key pathological markers of AD, further advancing the progress of precision diagnosis and individualized treatment of AD [9]. This is a comprehensive system that maps the connections between traditional Chinese medicine findings and Alzheimer's biomarkers, offering a way to track how each patient's condition evolves as the disease progresses. This latest recognition framework recognizes that abnormalities in amyloid markers are the earliest detectable neuropathological changes in AD.

3. Advances in neuroimaging markers

Neuroimaging has become an increasingly vital tool in the diagnosis of Alzheimer's disease (AD), propelled by continuous progress in medical imaging and computational software. It not only enables the assessment of brain changes across structural, functional, and molecular levels but also is key to AD's qualitative assessment, volume assessment, changes in brain function, and prognosis. Common imaging techniques include structural magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), and positron emission tomography (PET).

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3.1. Structural imaging

The atrophy of the hippocampus and medial temporal lobe is a key characteristic of Alzheimer's disease [10]. The study found that structural MRI, especially T1-weighted images, can accurately evaluate atrophy in these regions by hippocampal volume score (MTA). In AD patients, the hippocampal regions atrophy at a significantly faster rate, this is particularly evident during the mild cognitive impairment (MCI) stage, as noted by Keith et al [11]. reported hippocampal atrophy rates of approximately 3.0% per year in MCI patients, escalating to about 5.1% per year among dementia patients. Additionally, studies by Kilimann [12] et al. and Capizzano et al. [13] have also shown significant volume reductions in several brain regions including the hippocampus and amygdala, which are critical for memory and emotion processing. Research demonstrates a clear link between structural brain changes and cognitive deficits in individuals with attention deficit disorder (ADD). Neuroimaging studies reveal significant volume loss—with the hippocampus shrinking by 26-27% and the entorhinal cortex diminishing by 38-40%—which correlates strongly with impaired memory and executive functioning. These findings indicate that measuring regional brain atrophy could serve as a reliable diagnostic tool for predicting disease progression and treatment outcomes in ADD patients. The severity of these anatomical changes appears to mirror the extent of neurological impairment, offering clinicians an objective way to assess the disorder's impact.

3.2. Functional imaging

Blood oxygen level dependent-functional MRI (BOLD-fMRI) assesses brain activity by detecting localized changes in the ratio of deoxyhemoglobin to oxyhemoglobin, reflecting neuronal activation. Resting-state functional MRI (rs-fMRI) captures spontaneous neural activity in the absence of external tasks, identifying intrinsic functional networks such as the default mode network (DMN). The study showed that AD patients exhibited diminished temporal activity within the default mode network, specifically the posterior cingulate cortex and significant abnormalities of localized spontaneous activity in the resting state, which were consistent with the localized brain areas of Aβ deposition.

3.3. PET/SPECT

Fluorodeoxyglucose positron emission tomography (FDG-PET) effectively measures cerebral glucose metabolism, offering highly sensitive insights into synaptic activity. FDG-PET utilizes positron-emitting radiolabeled glucose analogs to image neuronal metabolic function. Alegret [14] et al. found that AD patients typically exhibit significant hypometabolism in temporoparietal regions, correlating strongly with impaired cognitive function and neurodegenerative changes. In mild cognitive impairment (MCI), reduced cerebral blood flow in the middle and posterior cingulate gyrus and reduced blood flow in these regions may be an early marker of the transition from MCI to AD.

18F-FDG PET responds to changes in brain function by measuring the rate of glucose metabolism in the brain. 11C-PIB PET can specifically bind to Aβ in the brain, and Aβ imaging can detect senile plaques with a sensitivity of 86% ~100% and a specificity of 92%~100%, and the positive results of Aβ imaging are closely correlated with the patient's age and the apolipoprotein E4 allele [15]. Combining FDG-PET and amyloid PET enhances diagnostic accuracy; initiating with FDG-PET to identify regions of hypometabolism followed by amyloid PET to confirm plaque presence provides robust diagnostic precision for Alzheimer’s disease [16].

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4. Cerebrospinal fluid biomarkers

In recent years, cerebrospinal fluid (CSF), which provides a direct reflection of pathophysiological alterations within the central nervous system (CNS), has been increasingly recognized as a critical focus in research on Alzheimer's disease (AD). In 2016, Jack and his team at the Mayo Clinic proposed a classification system for biomarkers, dividing them into categories of amyloid deposition (A), Tau pathology (T), neurodegeneration, and markers related to neuronal injury (N), which together constitute the AT(N) biomarker framework [17]. Currently, Aβ 42, tau protein and Phosphorylated tau protein (p-tau) levels in cerebrospinal fluid have been extensively studied as one of the key classical biomarkers for Alzheimer's disease (AD) [18].

Amyloid-beta 42 (Aβ42) is one of the central biomarkers in Alzheimer's pathology. Its concentration progressively decreases in the CSF as AD advances, reflecting the transfer of Aβ42 from the cerebrospinal fluid to the brain to form amyloid plaques. Early stages of AD, a decrease in Aβ42 is usually accompanied by a change in Aβ40 levels, and a decrease in the Aβ42/Aβ40 ratio is considered to be one of the earliest biomarkers of AD [19]. Several studies have shown that a decrease in the Aβ42/Aβ40 ratio can be detected before the onset of clinical symptoms and has more diagnostic value than changes in a single level of Aβ42 [20] .

Tau protein is crucial for keeping neuronal microtubules stable and sturdy. However, in Alzheimer's disease (AD), tau gets excessively phosphorylated, which leads to the formation of neurofibrillary tangles – a telltale sign of the disease and a major characteristic. Elevated total tau protein (t-tau) is usually associated with neuronal damage and neurodegeneration, whereas phosphorylated tau protein (p-tau) reflects tau protein pathology. Palmqvist [21] et al. found that the best indicators for identifying Mild Cognitive Impairment (MCI) and AD were the cerebrospinal fluid AB42/total tau protein ratio and AB42/p-tau ratio. -tau ratio. The t wo primary forms of tau protein used diagnostically are total tau protein (t-tau), indicative of neuronal damage and degeneration, and phosphorylated tau protein (p-tau), which specifically reflects tau-related pathological change [22]. An analysis conducted by Olsson [23] and colleagues revealed that both total tau protein and phosphorylated tau (p-tau) in cerebrospinal fluid exhibit a robust correlation with Alzheimer's disease (AD) and are effective in distinguishing AD patients from healthy individuals: cerebrospinal fluid total tau protein (mean ratio 2.54%, 95% *CI*: 2.44-2.64), p -tau (mean rate 1.88%, 95% *CI*: 1.79-1.97). A retrospective evaluation by Oboudiyat [24] et al. suggested that cerebrospinal fluid total tau protein and p-tau index could be used as a predictor of AD and could identify non-amnesic AD in non-amnesic dementia.

5. Blood biomarkers

Despite being prime biomarkers for diagnosing Alzheimer's Disease, CSF Aβ and tau proteins are hindered by the invasiveness of lumbar punctures in widespread clinical use patient discomfort, compliance issues, and the high cost associated with PET/SPECT imaging. Consequently, blood biomarkers are increasingly valued for their minimal invasiveness, simple collection, and higher patient compliance.

The most studied blood biomarkers include classical CSF biomarkers (Aβ42, Aβ40, Aβ42/Aβ40 ratio, p-Tau181, p-Tau217, p-Tau231), Neurofilamentlightchain (NfL), Neurogranulin, neuron-derived exosomes, neuron-enriched extracellular vesicles, GFAP, myeloid triggered receptor 2 (TREM2), monocyte chemotactic protein 1 (MCP1), and several pro-inflammatory and anti-inflammatory cytokines, including IL-1β, IL-2, IL- 6, IL-10, and IL-18[25,26] Additionally, the p-tau proteins (especially p-tau181 and p-tau181) and p-tau231 (p-tau231 and p-tau231) are associated with a wide range of cytokines. tau181 and p-tau217), another important marker of AD, are closely associated with tau protein neuroprogenitor fiber tangles because of concentration changes in the

blood. Elevation of p-tau181 in the blood usually occurs before changes in cerebrospinal fluid and PET imaging, suggesting that p-tau181 may be one of the key markers for the early detection of Alzheimer's disease (AD) [27]. Studies have demonstrated that p-tau181 shows strong diagnostic value in patients with familial Alzheimer's disease (AD) and mild cognitive impairment (MCI), providing early warning signals that can aid in early intervention. Similarly, p-tau217 has exhibited increased sensitivity in several studies, particularly for diagnosing early-stage AD. The amyloid proteins Aβ42 and Aβ40 are among the first and most extensively studied blood biomarkers for Alzheimer's disease. In AD patients, the hallmark pathological changes include the deposition of Aβ plaques and neurofibrillary tangles, which begin to accumulate 10 to 20 years prior to the appearance of clinical symptoms [28,29]. Studies have shown that decreased blood Aβ42 levels are highly correlated with amyloid load in the brain, and its diagnostic accuracy is comparable to that of cerebrospinal fluid Aβ42 and is therefore considered a competitive early biomarker. It has been suggested that high levels of Aβ40 and Aβ42 are present in the plasma of AD patients, and more studies have observed high levels of Aβ in the plasma of non-demented older adults as well. Schupf et al. [30] observed that older adults with high baseline levels of plasma A burgundy had a 3-fold higher risk of developing AD than other older adults. In addition to Aβ and tau proteins, neurofilament protein light chain (NfL) has gained widespread attention as a marker of axonal damage in the early diagnosis of AD. Mattsson [31] showed that NfL levels are significantly showed in the blood of AD patients and are closely associated with cognitive decline. Elevated NfL is not only associated with neurological damage in AD but also reflects the disease process progression, therefore, as a non-invasive detection tool, NfL is important in the monitoring of AD.

6. Conclusion

AD is a global problem. And it is increasing with the trend of global aging. AD is difficult to diagnose because the early symptoms are insidious and difficult to detect. The majority of patients receive a diagnosis during the intermediate or advanced phases of the condition. Based on the current difficult situation of drug development for the treatment of middle and late-stage AD. Prompt detection and treatment of Alzheimer's significantly impacts disease management and enhances well-being. Detection of AD biomarkers is an important means confirm diagnosis AD. Pinpointing Indicators of Alzheimer's (AD) serves as a crucial method for verifying its diagnosis and can aid in clarifying the disease’s pathogenic mechanisms, which is highly significant for facilitating early detection and intervention. However, there are limited biomarkers available for clinical diagnosis. Therefore, research to find suitable biomarkers for AD should be promoted, including the search for new biomarkers and further validation of the utility of potential biomarkers. Blood is convenient to collect, easy to obtain, and more acceptable to patients compared to cerebrospinal fluid, and more potential biomarkers are currently found in the periphery. However, their exact diagnostic efficacy and specificity need to be further tested. It is also important to improve the existing detection methods and develop more advanced, perfect, and sensitive means to assist in the search for AD biomarkers.

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