Proceedings of ICBioMed 2025 Symposium: AI for Healthcare: Advanced Medical Data Analytics and Smart Rehabilitation
DOI: 10.54254/2753-8818/2025.AU23556

Biomarkers of Alzheimer's Disease: Towards Clinical Implementation

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Abstract: As a common disease in the field of neurology, Alzheimer's disease (AD) causes neurodegeneration. Its pathological features mainly include β-amyloid protein deposition, abnormal phosphorylation of Tau protein which causes neurofibrillary tangles, as well as the following neuroinflammation and synaptic dysfunction. Different pathological features can be identified by detecting different biomarkers. This article summarizes the current common and new biomarkers to diagnose AD. With the diagnostic system centered on Aβ, tau and neurodegeneration, and the gradual development towards blood testing and multimodal integration. However, the clinical application of biomarkers still faces challenges such as standardization, threshold definition, cost and etc. Therefore, future research must prioritize early diagnosis and precise disease period for AD through multimodal biomarker integration, advanced neuroimaging techniques, and focus on longitudinal studies. Focusing on discovering of ultra-early biomarkers, standardizing the blood test and monitoring the influence of biomarkers in targeted therapy dynamically will promote the realization of individualized precision medicine.

Keywords: Alzheimer's disease, Biomarker, Pathological mechanism

1. Introduction

Alzheimer's disease (AD) is a common ailment among seniors and one of the main types of dementia. Patients show clinical symptoms such as gradually losing the ability to memory as well as perform daily activities. In the end progress, it turns out to be long-term memory impairment.

World Alzheimer Report 2024 published in September 2024 demonstrated that the global aging population of quantities of dementia patients is estimated to reach 139 million in 2050. With the progressing of the aging of the population in China, AD will undoubtedly cause serious medical and health problems, and its long-term impact on patients, also their families and even the whole society will cause huge emotional and financial burdens. Due to the insidious onset of AD, the disease exists the problem of mild and unspecific symptoms in the early stages, which are easily overlooked or misdiagnosed, making diagnosis difficult. Currently, there lacks effective drugs for treating or reversing the disease process. Therefore, identify AD as early and accurate as possible is obviously crucial.

The International Working Group added biomarkers into the principles of AD's diagnosis for the first time in 2007, leading to a shift from clinical pathological diagnosis to clinical biological diagnosis. In 2011, NIA-AA proposed a novel framework for AD, categorizing its progression into three distinct clinical stages. The first one was preclinical AD, then mild cognitive impairment due to

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AD and for the last stage was dementia (characterized by significant functional impairment). This staging system revolutionized AD research by emphasizing early biomarker detection and providing a standardized approach for diagnosis and therapeutic development. They also included the preclinical asymptomatic stage into the course of AD, greatly lead the diagnostic window for AD forward [1]. In 2014, IWG released the updated diagnostic criteria IWG-2, which classified AD biomarkers into diagnostic and progressive categories, while emphasizing the importance of imaging techniques, genetic testing, and cerebrospinal fluid markers in AD diagnosis. The criteria also further subdivided the clinical phenotype of AD. These prove that biomarkers are crucial in AD's diagnosis. Therefore, Therefore, this article intends to explore the character of different biomarkers—spanning diagnostic specificity, therapeutic monitoring potential, and prognostic predictive value—for optimizing clinical decision-making in AD management.

2. The core pathological mechanism of AD and its association with biomarkers

AD mainly includes three pathological features, which are Aβ deposition, neurofibrillary tangles (NFTs) caused by abnormal phosphorylation of Tau protein, as well as following neuroinflammation and synaptic dysfunction.

2.1. Aβ deposition

Aβ is a kind of peptide fragments produced by slicing amyloid precursor protein (APP). Those fragments are confirmed as the component of plaques in the AD patients' brain. Its deposition is deemed to the primary reason of this disease. These short peptides are prone to form fiber stacking after several chemical reactions and damages neurons and other nerve cells. This pathology mainly involves significant reduction in the Aβ42/Aβ40 ratio in fluid biomarkers which includes cerebrospinal fluid and blood biomarkers.

2.2. Tau Protein's abnormal phosphorylation and NFTs

Overphosphorylation of Tau protein impairs its ability to stabilize microtubules, leading to neurofibrillary tangles. Once excessive phosphorylation occurs, the self-clearance rate of abnormal Tau will also be affected. Tau inhibits some autophagy physiological processes, leading to its own aggregation and causing an brain ROS level increase [2]. Phosphorylation of subtypes such as p-Tau181 and p-Tau217 is considered as potential biomarkers for AD patients.

2.3. Following neuroinflammation and synaptic dysfunction

Indirect markers of neuronal damage include neurofibrillary light chains (NfL) and synaptic proteins (such as neurotrophin, Ng). NfL is a biomarker of neuroaxonal injury, which correlates with MRI-detected brain atrophy severity. Besides, Ng reflects synaptic loss, and its elevated level is considered as the biomarker of hippocampal volume reduction and memory decline. Although these biomarkers are not AD specific, they have important value in monitoring disease progression and evaluating treatment response.

3. Classification and detection techniques of AD biomarkers

According to their sources and detection methods, AD biomarkers can be mainly divided into four kinds: imaging biomarkers, cerebrospinal fluid biomarkers, blood biomarkers, and emerging biomarkers (Table 1). Each type of biomarker has its own advantages and disadvantages in sensitivity, invasiveness and cost.

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3.1. Imaging biomarkers

Imaging biomarkers can display changes in the patients' brains directly. MRI is helpful to evaluate brain atrophy served as a fundamental tool for assessing brain atrophy patterns, particularly in regions vulnerable to AD pathology, while PET can determine the relationship between specific brain area atrophy and Aβ level changes. For example, Antoine Leuzy et al. found through Tau PET that higher tracer retention was observed in the temporal lobe, medial frontal lobe and inferior parietal cortex of AD patients [3]. Applying structural MRI can find hippocampal volume atrophy in patients' brains. Using 18FDG-PET, researchers observed hypometabolism in patients' brains. Like others, SV2A-PET is used to track SV2A in human brain, which is a useful biomarker for quantifying synaptic loss [4].

However, getting imaging biomarkers is costly and can only be done in specific clinics. Differences in equipment parameters, analysis methods and diagnostic thresholds among different clinics may lead to different results, affecting the reliability of multicenter studies and clinical translation. By the way, the images may be affected by drug side effects, such as after using anti-Aβ monoclonal antibody therapy, amyloid related imaging showed abnormalities, so the related risks should be evaluated before medication [5].

3.2. Cerebrospinal fluid biomarkers

Due to limitations in equipment and price of the above-mentioned imaging biomarkers. Biomarkers based on cerebrospinal fluid (CSF) have been invented to improve sensitivity and convenience in detecting pathological changes related with AD. Among all the CSF biomarkers, the most commonly used markers are Aβ42/Aβ40 and t-Tau detection. Studies utilizing PET imaging as a reference have confirmed that in AD patients, the Aβ42/Aβ40 proportion is significantly reduced, while the level of t-Tau and p-Tau are remarkably rose [6]. Through ELISA, researchers found that those patients had obviously increased Ng level compared with normal individuals [7].

Still, CSF biomarker testing has its own limitations. Since it requires lumbar puncture—an invasive procedure—many patients, particularly older adults and those in primary healthcare settings, are afraid of doing it. This low acceptance rate hinders the feasibility of large-scale population screening and longitudinal monitoring, where repeated CSF sampling would be necessary for tracking disease progression. Thus, blood-based biomarkers were advanced to do blood test.

3.3. Blood biomarkers

Unlike the CSF biomarkers, blood testing has the advantages of noninvasive and easy to repeat, making it a hotspot of research recently. Similar to the trend in CSF, the proportion of plasma Aβ42/Aβ40 also significantly decreased [8]. Yong et al. analyzed the plasma of suspected AD patients and entities with MCI and found compared to AD patients, the enzyme activity of BACE1 was higher in these individuals, which can use as a biomarker to forecast the progress of AD in the prodromal phase [9]. Plasma NfL is also associated with the progression of AD [10]. Higher NfL levels is considered to be associated with the decrease of MCI levels. The popular blood biomarkers recent years are plasma p-Tau181 and p-Tau217, which seems can almost predict whether patients have AD accurately. Currently, scientists are launching research on the real part of tau molecules that anchoring entanglements, attempting to develop a detection method based on blood. T-tau is also one of the important biomarkers of AD in the blood. Meta analysis shows that elevated t-tau is closely related to AD [11]. Compared with p-tau (such as p-tau217), plasma t-tau has weaker specificity associate with AD pathology. But it can be used as a pan biomarker for neurodegeneration to monitor progress or therapeutic response. Besides, researchers discovered some new biomarkers, such as NfL protein and glial fibrillary acidic protein (GFAP), which contribute to further understanding of the

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pathological process and clinical performances of AD. Despite those, some scholars have found that analyzing GFAP in blood directly without CSF analysis can distinguish AD from frontotemporal dementia, with the sensitivity and specificity of 89% and 79% respectively [12].

Although it has less damage to body, the detection of blood biomarkers may be affected by systemic factors, such as Aβ42/40 is affected by renal function and coagulation status. Therefore, false positive may occur in patients with chronic kidney disease. At the same time, factors such as cross platform differences, different operating techniques, and racial differences in detection of Aβ can all affect the results. There are also some obstacles in clinical translation. In addition, some biomarkers (such as p-tau217) have high sensitivity in the preclinical AD stage, but dynamic changes still require long-term cohort validation.

3.4. Other

Besides, there exists some Non-AD copathology and new biomarkers. Vascular dysfunction, as a significant comorbid factor, is typically characterized by reduced vascular constriction [13]. This pathological alteration can lead to inadequate cerebral oxygen supply and impaired nutrient delivery, potentially serving as a biomarker for AD. The detection of total α-synuclein [14] holds important differential diagnostic value, effectively distinguishing diseases like Lewy body dementia from typical AD patients. When focusing on gut microbiome associated biomarkers, Ashwiniriyadarshini Megur pointed out that the most significant changes are the expression of bacteria such as Bifidobacterium brevis, and gut microbiota metabolites (such as short chain fatty acids) may affect AD pathology through the “Gut-Brain-Axis”, but their mechanisms as biomarkers remain to be elucidated [15].

Table 1: AD biomarkers

Biomarkers				Changes	Methods	Ref.
Imaging biomarkers		MRI		temporal lobe atrophy		[16]
		PET	18 FDG-PET	posterior cingulate and temporoparietal hypometabolism		[16]
			Tau-PET	increased tracer retention in supramarginal gyrus, precuneus and lateral occipital lobe		[3]
			amyloid-PET	cortical amyloid β deposition		[16]
			SV2A-PET	regionally decreased synaptic density		[4]
Fluid biomarkers	CSF biomarkers	Aβ		Aβ42、Aβ42/Aβ40 ratio dropped	amyloid-PET	[6]
		Neurogranin (Ng)		selectively increased	ELISA	[7]
		t-tau		usually elevated	Tau-PET	[6]

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Table 1: (continued)

		p-tau	elevated		[6]
	Serum and plasma biomarkers	Aβ	Aβ42/Aβ40 ratio declined	amyloid-PET	[8]
		NfL	significantly increased	Anatomic MRI; FDG-PET	[10]
		GFAP	higher in AD patients	MRI	[12]
		BACE1	elevated	antibody MAB5308	[9]
		p-tau	significantly increased	Tau-PET	[6]
Non-AD copathology and new biomarkers	brain oxygenation dynamics	NVU	reduced	ECG;fNIRS	[13]
		α-synuclein(belongs to CSF); Microbiota–Gut–Brain Axis	increase;selective change		[14,15]

4. Conclusion

By standardizing biomarker related laboratory medicine and discovering new biomarkers, the precision and consistency of AD diagnosis will be enhanced. Also, it remains an achievable goal through methodological advancements. This not only helps to achieve precise determination of biomarkers, but also ensures the reliability and traceability of test results, advancing the elucidation of Alzheimer's disease pathogenesis. Relevant personnel may urgently need to address the following aspects: 1. Establish standardized procedures: Due to various factors, it is necessary to establish standardized testing procedures as soon as possible to improve the clinical value of biomarkers. 2. Clarify the relationship between existing biomarkers: A single biomarker is not perfect for diagnosing AD and determining disease progression. Clarifying the relationship between existing biomarkers and making joint judgments can help with clinical diagnosis and related drug development. 3. Discovery of new biomarkers: By discovering new biomarkers related to AD, we can infer the pathological mechanism of AD and propose solutions based on this. Recently, researchers have suggested that poly glycine arginine protein aggregation may also be a pathological characteristic of AD, and future research directions could consider clearing this protein aggregation.

In the next 5-10 years, AD diagnosis will undergo three major transformations: from single biomarker to multimodal integration, from hospital diagnosis to community screening, and from static assessment to dynamic prediction. By doing continuous technological innovation and clinical translation, it is expected to achieve ultra early accurate diagnosis, almost 10-15 years before symptoms emerge, creating a critical chance for disease modification therapy and ultimately changing the clinical management paradigm of AD. This process requires interdisciplinary collaboration, covering multiple dimensions such as biomarkers development, detection technology optimization, clinical validation, and health economics evaluation and so on. By doing these, we may truly achieve

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a complete transformation chain from laboratory to clinical, benefiting the growing global population of AD patients.

References

[1] *Zhou XR, Gu RJ, Ma RM, et al. Research progress on measurement techniques and standardization of markers for Alzheimer's disease. Quantitative science and technology,2024,68(9):41-50.*

[2] *Haque MM, Murale DP, Kim YK, Lee JS. Crosstalk between Oxidative Stress and Tauopathy. Int J Mol Sci. 2019 Apr 22;20(8):1959.*

[3] *Leuzy A, Chiotis K, Lemoine L, Gillberg PG, Almkvist O, Rodriguez-Vieitez E, Nordberg A. Tau PET imaging in neurodegenerative tauopathies-still a challenge. Mol Psychiatry. 2019 Aug;24(8):1112-1134.*

[4] *Mecca AP, Chen MK, O'Dell RS, et al. In vivo measurement of widespread synaptic loss in Alzheimer's disease with SV2A PET. Alzheimers Dement. 2020 Jul;16(7):974-982.*

[5] *Agarwal, A.; Gupta, V.; Brahmbhatt, P.; Desai, A.; Vibhute, P.; Joseph-Mathurin, N.; Bathla, G. Amyloid-related Imaging Abnormalities in Alzheimer Disease Treated with Anti–Amyloid-β Therapy. RadioGraphics 2023, 43 (9), e230009.*

[6] *Janelidze S, Palmqvist S, Quiroz YT, et al. Phosphotau217 and phospho-tau181 in plasma and CSF as biomarkers for Alzheimer's disease. Alzheimers Dement,2020, 16:e037520*

[7] *Wellington H, Paterson RW, Portelius E, Törnqvist U, Magdalinou N, Fox NC, Blennow K, Schott JM, Zetterberg H. Increased CSF neurogranin concentration is specific to Alzheimer disease. Neurology. 2016 Mar 1;86(9):829-35.*

[8] *Sun Q, Ni J, Wei M, et al. Plasma β-amyloid, tau, neurodegeneration biomarkers and inflammatory factors of probable Alzheimer's disease dementia in Chinese individuals. Front Aging Neurosci. 2022 Aug 18;14:963845.*

[9] *Shen, Y.; Wang, H.; Sun, Q.; Yao, H.; et al. Increased Plasma Beta-Secretase 1 May Predict Conversion to Alzheimer's Disease Dementia in Individuals With Mild Cognitive Impairment. Biological Psychiatry 2018, 83 (5), 447.*

[10] *Cullen NC, et al. Individualized prognosis of cognitive decline and dementia in mild cognitive impairment based on plasma biomarker combinations. Nat. Aging. 2020*

[11] *Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K, Zetterberg H. CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis. Lancet Neurol. 2016 Jun;15(7):673-684.*

[12] *Oeckl P, HOeckl P, et al. Glial Fibrillary Acidic Protein in Serum is Increased in Alzheimer's Disease and Correlates with Cognitive Impairment. J Alzheimers Dis. 2019;67(2):481-488.*

[13] *uliane Bjerkan, Bernard Meglič, Gemma Lancaster, Jan Kobal, Peter V E McClintock, Trevor J Crawford, Aneta Stefanovska, Neurovascular phase coherence is altered in Alzheimer's disease, Brain Communications, Volume 7, Issue 1, 2025, fcaf007,*

[14] *Bousiges O, Philippi N, et al. Differential diagnostic value of total alpha-synuclein assay in the cerebrospinal fluid between Alzheimer's disease and dementia with Lewy bodies from the prodromal stage. Alzheimers Res Ther. 2020 Sep 29;12(1):120.*

[15] *Megur A, Baltriukienė D, Bukelskienė V, Burokas A. The Microbiota–Gut–Brain Axis and Alzheimer's Disease: Neuroinflammation Is to Blame? Nutrients. 2021; 13(1):37.*

[16] *Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, Cummings J, van der Flier WM. Alzheimer's disease. Lancet. 2021 Apr 24;397(10284):1577-1590.*