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MINI-REVIEW

Mass spectrometry-driven advances in blood-based biomarkers for Alzheimer's disease: A mini-review

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Abstract

The core pathological characteristics of Alzheimer's disease (AD) are characterized by the deposition of β-amyloid plaques and the formation of tau protein neurofibrillary tangles. Clinical diagnosis predominantly relies on cerebrospinal fluid analysis or positron emission tomography. However, these methods are associated with the risks of invasive procedures and significant cost constraints. Mass spectrometry, with its high sensitivity (reaching the femtogram level) and capability for multiplex detection, facilitates not only the precise quantification of AD biomarkers in blood but also offers a cost-effective solution. This review systematically elucidates the advancements in the clinical application of mass spectrometry technology for risk assessment, early diagnosis, and therapeutic monitoring of AD. It also highlights recent breakthroughs in identifying novel blood biomarkers using mass spectrometry technology and a multi-omics integration strategy.

Keywords: Mass spectrometry; Alzheimer's disease; Blood-based biomarkers; Amyloid β-protein; p-Tau

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1. Background

Alzheimer's disease (AD), a prevalent neurodegenerative disorder, is primarily characterized in molecular pathology by the abnormal extracellular deposition of β-amyloid protein (amyloid β-protein and Aβ), forming senile plaques, and the intracellular aggregation of hyperphosphorylated tau protein (p-tau), leading to the formation of neurofibrillary tangles.[1-3] The diagnosis of AD primarily relies on clinical evaluation, which encompasses medical history collection and physical examination, as well as cognitive screening using tools such as the Mini-mental state examination and Montreal cognitive assessment.[4] To refine the diagnostic process, assess disease severity, and differentiate AD from other forms of dementia, neuroimaging techniques are commonly employed. These include positron emission tomography (PET) and functional magnetic resonance imaging.[5] In the context of AD diagnosis and treatment, biomarkers play a pivotal role in enhancing diagnostic accuracy, monitoring disease progression, and evaluating therapeutic responses. Initially, cerebrospinal fluid (CSF) biomarker analysis was predominantly utilized to reflect the pathological changes associated with AD.[6] However, clinical practice has revealed that traditional CSF detection and neuroimaging

methods face significant limitations due to high costs, restricted availability, and invasive procedures, thereby constraining their application in various scenarios both domestically and internationally.[7,8] In recent years, blood-based biomarker detection for AD has gained momentum and is increasingly being applied in clinical diagnostics and fundamental research.[9,10] Table 1 provides a detailed summary of key biomarkers relevant to AD, including Aβ42/Aβ40 ratio and phosphorylated tau protein variants.

Nevertheless, substantial disparities exist in the accuracy and efficacy of different blood-based biomarker detection methods, posing a major challenge for ongoing clinical investigations.[11,16] At present, immunology-based approaches often encounter issues such as antibody-dependent instability and insufficient determination accuracy, which hinder their clinical utility. Immunoprecipitation-mass spectrometry (IP/MS) technology combines the targeted enrichment capabilities of IP with the high-throughput and precise analytical advantages of mass spectrometry. This method employs specific antibodies to capture and isolate target proteins, followed by mass spectrometry for accurate qualitative and quantitative analysis. Recent head-to-head comparative studies have demonstrated that mass spectrometry techniques exhibit superior detection accuracy compared to conventional immunological methods.[11] Notably, recent advancements in peripheral blood biomarker detection technologies have been acknowledged in international clinical testing guidelines.[17] Unlike invasive procedures, blood-based tests are less stressful for patients and can be performed in various healthcare settings. In addition, they provide a cost-effective solution for disease monitoring and diagnosis, making healthcare more accessible to a wider population.

With the rapid advancement of blood-based biomarker detection technologies for AD, variability in sensitivity and specificity across different detection systems remains a persistent challenge in current clinical studies.[11,16] Mass spectrometry, a powerful analytical technique, plays a crucial role in the detection and quantification of blood-based biomarkers. A detailed analysis indicates that the instability inherent in antibody-dependent immunological methods, as well as the insufficient accuracy of these detection techniques, has significantly hindered their clinical application. The advent of IP/MS technology has overcome these technical limitations by addressing critical issues such as the low abundance of blood-based biomarkers, interference from analogues, and inadequate stability.[11]

This review provides a systematic outline of the innovative mass spectrometry technology system, with a focus on its breakthrough applications in early diagnosis, risk stratification, and disease progression monitoring of AD, and objectively evaluates its translational potential as a clinical efficacy evaluation tool. Ultimately, this paper will propose the strategic value of mass spectrometry technology in clinical detection pathways. In the future, close attention should be paid to the development of mass spectrometry detection technology to provide a technical blueprint for accelerating the implementation of precision medicine in the field of neurodegenerative diseases (Figure 1).

2. Application of mass spectrometry technology in AD detection

The core components of the pathological features of AD are the Aβ peptide segments derived from amyloid precursor

Table 1. Validation of blood-based biomarkers of Alzheimer's disease across several cohorts

Biomarker	Cohort	AUC	Confidence interval	References
Aβ42/Aβ40	The experimental group was composed of 182 healthy controls and 104 patients with MCI from the multi-center BioFINDER cohort in Sweden.	0.86	0.81–0.90	11
	Discovery data set: 121 samples (Japanese National Center for Geriatrics and Gerontology [NCGG]); Validation data set: 111 samples (Australian Imaging, Biomarker and Lifestyle Study of Ageing [AIBL])	0.967 (discovery data) 0.941 (validation data)	0.942–0.992 0.897–0.984	12
	159 samples (longitudinal studies of memory and aging at Washington University)	0.88	0.82–0.93	13
p-tau217	340 samples (Alzheimer's Disease Clinical Trials Association-AHEAD study)	0.92	0.90–0.94	14
	393 samples (obtained from 393 participants of the Alzheimer's Disease Neuroimaging Initiative [ADNI]) and at least 6 plasma isometric samples	0.916	0.887–0.946	15
	135 MCI samples (the Memory Clinic at Skåne University Hospital in Malmö, Sweden)	0.947	0.907–0.987	16

Abbreviations: Aβ40: Amyloid-β40; Aβ42: Amyloid-β42; MCI: Mild cognitive impairment; p-tau217: Phosphorylated tau217 protein; AUC: Area under the curve.

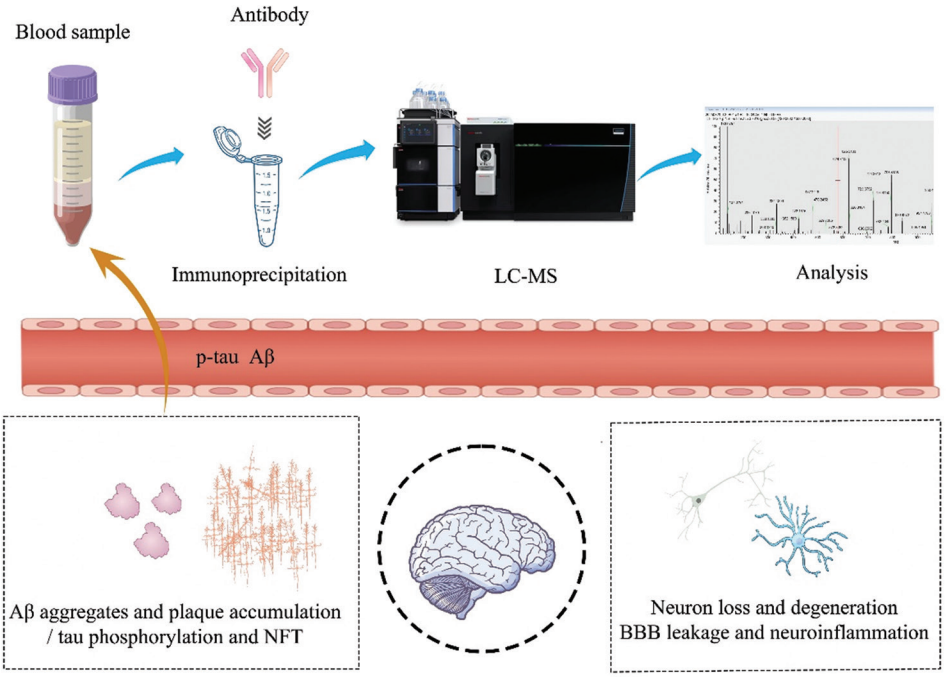

Figure 1. Schematic overview of Alzheimer's disease (AD) pathology, key blood-based biomarkers, and their detection using mass spectrometry. The neurodegenerative process is characterized by Aβ aggregation, tau phosphorylation, and NFT formation, leading to neuronal loss, BBB disruption, and neuroinflammation. Circulating biomarkers such as p-tau and Aβ are extracted from blood samples using antibody-based immunoprecipitation and subsequently quantified by liquid chromatography-mass spectrometry (LC-MS). This workflow enables sensitive detection and analysis of AD-related biomarkers in peripheral blood. Image created by the authors.
Abbreviations: Aβ: Amyloid beta; BBB: Blood-brain barrier; LC-MS: Liquid chromatography-mass spectrometry; NFT: Neurofibrillary tangles; p-tau: Plasma phosphorylated tau.

protein, with lengths of 42 and 40 amino acids (Aβ42 and Aβ40, respectively).[18] It is notable that compared with other Aβ peptides, the 42-amino-acid form of Aβ (Aβ42) is usually observed in neurofibrillary plaques.[19] In the field of blood biomarker detection, the breakthrough development based on immunoprecipitation enrichment combined with high-resolution mass spectrometry has enabled the targeted capture of trace Aβ peptide segments in peripheral blood (with a detection limit of fg/mL level) by specific antibodies.[12,20,21] Combined with isotope internal standard quantification, researchers have successfully constructed a highly sensitive Aβ42/Aβ40 ratio detection system. It has been reported that IP/MS combined with matrix-assisted laser desorption ionization—time-of-flight mass spectrometry shows excellent performance in predicting Aβ load in the brain from blood samples. In particular, the combined biomarkers have shown very high areas under the receiver operating characteristic curve area under the curve (AUC) in two datasets (AUC: 0.967, $n = 121$; AUC: 0.941, $n = 111$).[12] A mass spectrometry study of 158 cases with plasma Aβ42/Aβ40, age, and APOE ε4 status showed high consistency with Aβ PET.[13] In the BioFINDER cohort, 182 participants with normal cognitive function and 104 patients with mild cognitive impairment were compared in experiments on the differences between various methodologies of blood specimens, indicating that plasma IP/MS-WashU Aβ42/40 has higher accuracy (AUC: 0.86) than multiple immunoassay methods (AUC range: 0.69–0.78; $p<0.05$).[11] At present, the inherent advantages of stability and high repeatability in mass spectrometry technology have provided a robust technical foundation for the application of blood biomarkers in AD.

Among various plasma Aβ and tau markers, phosphorylated tau at serine 217 (p-tau217) has emerged as a novel tau marker that outshines others in clinical data, showing greater suitability as a pathological marker for AD. Recently, the updated AD Diagnostic Guidelines by the National Institute on Aging and the Alzheimer's Association have pointed out that the blood diagnostic marker p-tau217 can be used as a diagnostic indicator for AD.[17] In a methodological comparative experiment involving 135 patients diagnosed with mild cognitive impairment, the correlation between the results of plasma p-tau217 detected by mass spectrometry and CSF values was the strongest ($R = 0.891$), outperforming methods such as single molecule array (SimoA). It was clarified that mass spectrometry is superior to

other methodologies in identifying abnormal brain Aβ and progression in patients with mild cognitive impairment.[16] In multiple independent cohort studies, ultrasensitive mass spectrometry quantification of plasma p-tau217 concentrations demonstrated exceptional diagnostic accuracy with an AUC of 0.92. This robust biomarker performance showed strong concordance with corresponding CSF biomarkers and amyloid-PET imaging findings, reinforcing its potential as a reliable peripheral indicator of AD pathology.[14] At the same time, in early risk assessment studies, the plasma biomarker p-tau217 was detected in patients with mild cognitive impairment (n = 304) using mass spectrometry, and it was found to have the strongest correlation with Aβ pathology in mild cognitive impairment (AUC: 0.86).[22] At present, mass spectrometry technology has been widely applied in the research and diagnosis of AD, but for other biomarkers in the blood, such as glial fibrillary acidic protein (GFAP) and neurofilament light chain, there is still a lack of precise detection methods. Therefore, it is necessary to further develop and validate reference methods for standard substances of different plasma biomarkers.

3. Efficacy monitoring of AD through mass spectrometry technology

In the latest research on the treatment of AD, it was found that mass spectrometry technology can not only identify the metabolism of drugs in the blood after medication and dynamically assess the deposition level of amyloid protein in the patient's brain through blood but also has the advantages of clinical economics and the characteristics of minimally invasive detection.

To deeply explore the value of mass spectrometry in the diagnosis and treatment of AD, the research team conducted blind mass spectrometry blood tests using two independent clinical cohorts of AD (from Japan and Australia). The results indicated that mass spectrometry could capture the individual's brain Aβ deposition status to assist in determining treatment strategies.[12] Recently, in a study on the correlation between the efficacy of the modified therapeutic drug donanemab and changes in plasma biomarkers, mass spectrometry assessment of p-tau217 and GFAP levels in the plasma of the drug group and the placebo group showed a significant correlation with drug treatment.[23] At the same time, mass spectrometry detection of plasma p-tau217 can be used to evaluate the eligibility of early AD patients for disease-modifying treatments.[24] Based on the foundation of prior research, mass spectrometry technology demonstrates potential capabilities for both qualitative and quantitative assessment of clearance targets in modified therapeutic drugs. However, we must recognize that the mechanism of action of AD drugs is synergistic, and efficacy evaluation of targeted treatment approaches in AD through mass spectrometry needs to be validated through clinical cohort studies.

4. Innovative biomarker discovery based on a mass spectrometry platform

During the AD diagnosis process, although the traditional biomarker system centered on the Aβ protein and tau protein has shown excellent performance in the pathological diagnosis of AD, it still has limitations in the fields of differential diagnosis and early risk assessment of the disease. Mass spectrometry technology not only enables precise quantitative analysis of target substances but also exploits its powerful non-targeted analysis capabilities to explore innovative mechanisms. Relevant studies have found that through mass spectrometry analysis of proteins of human brains, changes in 173 proteins were revealed in AD patients, involving 17 regulatory pathways.[25] Recently, a non-targeted mass spectrometry proteomics exploration based on a 2000-large-cohort AD plasma biomarkers discovered a series of candidate markers such as chloride nucleotide-sensitive channel 1A gene (*CLNS1A*), cysteine-rich secretory protein LCCL domain-containing 2 gene (*CRISPLD2*), and Golgi phosphoprotein 3 (*GOLPH3*).[26] In addition, through IP/MS technology, microtubule-binding region containing residue 243 (eMTBR-tau243) fragments with low internalization were successfully isolated and quantified from plasma.[27] Through clinical comparison, this indicator was verified to be applicable for early diagnosis, treatment monitoring, etc. The exploration of innovative biomarkers for AD expands the coverage of existing biomarkers to fulfill more precise clinical needs. However, the results of scientific research experiments cannot be directly applied to clinical practice. Therefore, larger-scale samples and multi-center cohort clinical validation and investigation work need to be carried out in the future.

5. Conclusion and perspectives

With high selectivity and sensitivity, mass spectrometry provides a powerful clinical tool for analyzing complex diseases like AD. Innovative blood biomarker detection methods using integrated antibody enrichment, sample pretreatment, and advanced mass spectrometry have revolutionized early AD prediction, diagnosis, and personalized treatment strategies (Figure 1). By optimizing mass spectrometry platforms across clinical and research settings, this technology continues to solidify its critical role in AD biomarker discovery and precision medicine development, positioning it as an increasingly vital tool in neurodegenerative disease management.

Previous studies have investigated the application of mass spectrometry in AD. Nevertheless, future research should prioritize standardized cross-platform integration to broaden its clinical applicability. Despite the high specificity and sensitivity of mass spectrometry, the absence of traceable reference materials and quality control products considerably hinders its advancement. Consequently, developing internationally recognized standard substances and reference methods stands as a pivotal task for future research. At present, only a limited number of institutions in the world are capable of developing mass spectrometry-based detection methods for core biomarkers of AD. Aside from that, there is an urgent need to enhance the training of clinical laboratory personnel, facilitate the clinical translation of technology, and construct a mass spectrometry-based validation system along with reference thresholds that are applicable to large-scale, multi-ethnic populations.

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Conflict of interest

The authors declare that they have no competing interests.

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Ethics approval and consent to participate

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Consent for publication

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