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EDITORIAL

Early Diagnosis of Alzheimer's Disease: Moving Toward a Blood-Based Biomarkers Era

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Introduction

Alzheimer's disease (AD) is the most common type of dementia in the aging population characterized by a progressive decline of cognition that brings a significant burden for patients and society. The exact pathogenesis of AD is still elusive.[1] AD progresses along a continuum from the preclinical stage, mild cognitive, and then dementia stages. Converging lines of evidence from research studies reveal that underlying pathological changes due to AD exist in the decades before symptom onset.[2] However, a large portion of patients remains undiagnosed at the early stages of AD in clinical practice. The early and accurate identification of AD underlying pathology is fundamental for the diagnosis, disease monitoring, and management of AD patients. Notably, early diagnosis of AD is a critical step forward for the clinical trial, which facilitates the development of disease-modifying therapies. In recent years, immense affords have been made to illustrate the early pathological changes of AD.[3] Progress in fluid biomarkers and image analyses facilitates the early and accurate diagnostic process for AD. Based on the evidence of several core pathological changes of AD, including amyloid-β (Aβ) deposition, phosphorylated tau (p-tau), and neurodegeneration, a research framework for AD defining was proposed in 2018.[4] However, positron emission tomography (PET) and cerebrospinal fluid (CSF) biomarkers evaluations have several limitations, including high cost, insufficient accessibility, and invasiveness, stint them as a first-line AD diagnostic evaluation. Emerging blood-based biomarkers are an exciting development in this field, since they may provide a convenient, cost-effective, and less invasive screening tool.[5]

Current Situation of AD Early Diagnosis

AD has been considered as a continuous biological continuum that is identified by several kinds of biomarkers. In 2011, the National Institute on Aging and Alzheimer's Association (NIA-AA) proposed diagnostic guidelines for AD, including the pre-symptomatic and symptomatic stages of AD.[6] In 2018, the NIA-AA further proposed a research framework to biologically define AD by AT(N) biomarker profiles.[4] The research framework listed validated biomarkers of AD pathology include: Aβ and p-tau PET; the CSF concentration of Aβ42; the CSF Aβ42/Aβ40 ratio; the CSF concentrations of total tau (t-tau) and p-tau181. Due to the limitations of PET and CSF, a blood test for AD screening would be a significant step toward earlier intervention and less society burden. Although blood-based biomarkers (ie, Aβ, p-tau) are still not recommended in clinical practice which need to be further standardized and validated.[7] The recommendations for use of blood biomarkers in AD proposed by the Alzheimer's Association suggest that blood-based biomarkers can be used in specialized memory clinics for cognitively impaired individuals but the results still need to be confirmed by CSF or PET.[8]

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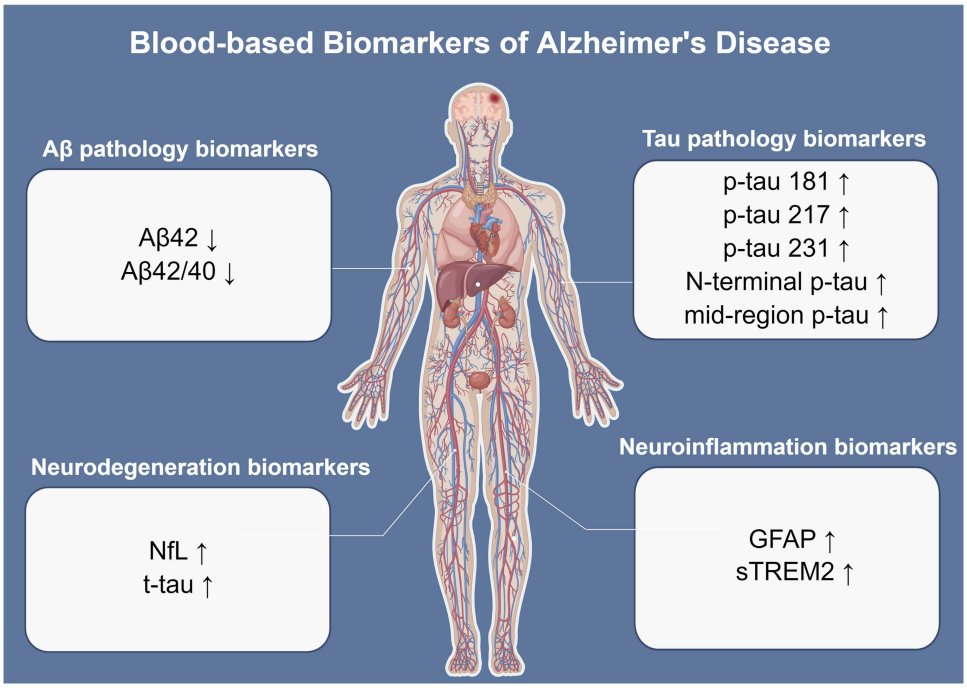

Figure 1 Overview of the most promising blood-based biomarkers of AD. The biomarkers can be divided into four aspects: Aβ pathology (Aβ42 and Aβ42/40 ratio), tau pathology (p-tau181, p-tau217, p-tau231, N-terminal p-tau, and mid-region p-tau), neurodegeneration (NfL and t-tau), and neuroinflammation (GFAP and sTREM2). The figure was made by Figdraw (ID: RAWSR4a31d).

Blood-Based Biomarkers of AD

Several blood biomarkers include the plasma Aβ42, Aβ42/40 ratio, p-tau, t-tau, neurofilament light polypeptide (NfL), glial fibrillary acidic protein (GFAP), and soluble triggering receptor expressed on myeloid cells 2 (sTREM2) have been considered as the promising biomarkers of AD (Figure 1). Their roles in diagnostic, progress monitoring, and prognosis have been intensively discussed in recent years.

Blood-Based Aβ Pathology Biomarkers

Initial studies used enzyme linked immunosorbent assays (ELISA) immunoassays to assess plasma levels of Aβ42 which showed negative association with AD.[9] Subsequently, one study using single-molecule array (Simoa) reported that reduced concentration of plasma Aβ42 was observed in AD compared to controls, but plasma Aβ42 showed negative correlation with brain amyloid deposition which measured by PET.[10] Later, several studies using sensitive assays such as Simoa, electrochemiluminescence immunoassays (Elecsys) and Immunoprecipitation-Mass Spectrometry (IP/MS) assays further confirmed that the decreased plasma Aβ42 and Aβ42/Aβ40 ratios in AD and subjective cognitive decline (SCD).[11,12] More recently, a head-to-head comparison study evaluated the performance of eight plasma Aβ42/40 IP/MS based assays to identify abnormal CSF Aβ42/40 and Aβ-PET status. The results showed that certain MS-based methods had best performance for brain Aβ pathology detection.[13] Plasma Aβ42/Aβ40 has been considered as a promising blood-based biomarker for AD screening. However, there is lack of evidence that the plasma Aβ42/40 can differentiate AD from non-AD dementias currently. Considering the availability and relative high cost, both Simoa and IP/MS based assays still need to be optimized in several aspects before they can be used in screening for AD in large populations.

Blood Based Tau Pathology Biomarkers

P-tau is a key component of neurofibrillary tangles in AD brain. CSF p-tau181 is the most commonly studied soluble p-tau.[14] Similar to Aβ, various new developed sensitive assays (ie, Simoa) were used to assay p-tau181 in recent years. Many researchers found plasma p-tau181 was significantly elevated in AD, compared with cognitively normal controls,

and other non-AD dementia patients. Furthermore, plasma p-tau181 has a positive association with tau-PET and longitudinal cognitive decline in AD patients.[15] It also showed that p-tau181 could predict AD pathology 8 years prior to post-mortem,[16] indicating that p-tau 181 is a practicable blood-based biomarker of AD. However, a recent study reported plasma p-tau181 was also elevated in patients with amyotrophic lateral sclerosis (ALS).[17] More recently, several studies reported that other forms of p-tau such as tau phosphorylated at threonine 217 (p-tau217) and tau phosphorylated at threonine 231 (p-tau231) had better diagnostic performances than p-tau181 as a diagnostic biomarker of AD.[18,19] Then, a following study compared the diagnostic performance of three types of CSF p-tau biomarkers, N-terminal-directed p-tau217 (N-p-tau217), N-terminal-directed p-tau181 (N-p-tau181) and standard mid-region p-tau181 (Mid-p-tau181), found that N-p-tau217 and N-p-tau181 had a better diagnostic accuracy than Mid-p-tau181.[13] Furthermore, plasma p-tau217 could accurately determine AD, and discriminated non-AD dementia.[20,21] Plasma p-tau217 is also correlated with Aβ and p-tau pathology in the brain and a good predicter of AD and cognitive decline in MCI, making it become one of the most promising blood-based AD biomarkers.[22]

Blood Based Neurodegeneration Biomarkers (NfL, t-tau)

The concentration of plasma t-tau was elevated in patients with AD compared with cognitively normal controls, but t-tau measured in plasma do not correspond to CSF measures.[23] Furthermore, plasma t-tau elevation is not specific in AD, and is also found in several other neurodegenerative diseases.[24] CSF NfL is one of the most promising neurodegenerative biomarkers. Notably, plasma NfL corresponds well to CSF measures, making it a good blood-based biomarker.[25] Considering NfL being increased in multiple neurological disorders such as ALS, frontotemporal lobar degeneration (FTLD) and multiple system atrophy (MSA), it is considered to be a non-specific marker of neuronal neurodegeneration or injury and it has poor diagnostic performance for the separation of AD dementia and non-AD dementia. Recently, several studies found that NfL could serve as a biomarker for disease severity evaluation, and treatment effects monitoring.[5] Furthermore, patients with neurodegenerative diseases who have higher levels of NfL are associated with faster disease progression.[26]

Blood Based Neuroinflammation Biomarkers (GFAP, and sTREM2)

Multiple lines of evidence indicate that neuroinflammation plays an important role in AD. Several necroinflammation related biomarkers such as GFAP, sTREM2, YKL-40, and S100 calcium-binding protein B (S100B) have been assessed in AD.

Previous studies have revealed that YKL-40 is also a biomarker linked to cardiovascular disease and diabetes, and its levels in serum can be altered by many other conditions.[27,28] S100B is expressed in astrocytes and oligodendrocytes. Studies conducted at single-centers have not demonstrated any consistent evidence that S100B in plasma or serum can be used to specifically diagnose AD.[29] In recent years, the importance of blood GFAP and sTREM2 in the early identification of Alzheimer's Disease has been increasingly recognized. GFAP is a well-known marker of astroglia activation. It has been reported that both CSF and serum GFAP concentrations were significantly increased in AD compared to cognitively unimpaired (CU) participants and correlates with cognitive impairment.[30,31] Furthermore, plasma GFAP levels were significantly elevated in Aβ+ CU participants compared to Aβ- CU participants,[32] and it could predict clinical AD risk.[33] In addition, one study with small sample scale reported that serum GFAP could discriminate AD from FTLD patients (with 89% sensitivity and a specificity of 79%).[30] However, in another study, higher serum GFAP level is also found in FTLD and can serve as a disease severity biomarker for FTLD.[34] A recent study reported that plasma GFAP was correlated with both longitudinal Aβ-PET and cognitive decline, suggesting that the elevation of GFAP was a response to Aβ aggregation.[35] From this perspective, plasma GFAP is also considered an Aβ related biomarker. Another biomarker related to neuroinflammation is sTREM2, which regulates microglial function. It was found that plasma sTREM2 was significantly correlated with CSF sTREM2.[36] It indicates periphery could reflect the central system. A study reported the level of sTREM2 in plasma was highest in MCI.[37] However, the plasma sTREM2 concentrations between AD patients and controls are still ambiguous.[38] Several researches focused on the relationship between the plasma sTREM2 and other AD biomarkers. It was reported that plasma sTREM2 was significantly associated with CSF Aβ42, but not t-tau and p-tau in AD participants.[36] And another study investigated that plasma sTREM2 was independently related to tau-positive scan and white matter hyperintensity volume in AD and cerebral amyloid angiopathy.[39]

Furthermore, plasma sTREM2 is also considered a potential biomarker in FTLD,[40] Parkinson's disease,[41] and cerebrovascular injury.[42]

Blood-Based Biomarkers' Panel

Many studies reported that some other neurodegenerative diseases also showed positive Aβ or p-tau pathological changes pattern which emerges as comorbidities. More and more researchers realized that Aβ and p-tau represent only a fraction of the complicated pathophysiology underlying AD. In this context, systemic and comprehensive workflows were explored by several large MS-based proteomic analysis studies and revealed a number of combined blood-based potential early diagnostic biomarkers which were more specific as compared with single protein.[43] However, the inaccessibility of blood-based biomarkers panel detection impedes its use as the screening test for AD.

Conclusions and Future Prospects

It has been over a hundred years since the first AD patient was reported. However, immense challenges still exist in the early diagnosis, pathogenesis, and treatment of the disease. Owing to the development of sensitive and precise assays, the field of blood-based biomarkers advanced rapidly in recent years. As the discovery of effective disease-modifying therapies remains a critical need for patients with this devastating disease, blood-based biomarkers will be crucial for optimizing clinical trial strategies by facilitating early diagnosis and precise management. The usage of specific and sensitive blood-based biomarkers will help us move to a new era that AD could be better intervened in an early stage. However, tremendous efforts were needed to further validate blood-based biomarkers in unselected large-scale ethnically diverse populations. In addition, future efforts are also needed to develop and validate blood-based biomarkers for non-AD dementias in order to better discriminate the different types of dementia. If the blood-based biomarkers can achieve comparable high performance like CSF or PET testing, suspected AD patients will be easily determined at primary care settings at an early stage, which will greatly improve the situation of early diagnosis of AD.

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Disclosure

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