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STUDY ON BLOOD PROTEIN MARKERS OF ALZHEIMER'S DISEASE

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Abstract: Alzheimer's disease (AD) is a common degenerative disease of the central nervous system, and early diagnosis is very important for its treatment. However, clinical diagnosis currently requires invasive lumbar puncture or expensive Aβ/Tau PET examination, resulting in a lag in early diagnosis. Peripheral blood has the advantages of being non-invasive, easy to obtain, and suitable for disease tracking and follow-up. Over the years, research has been striving to find early specific biomarkers of AD in peripheral blood. However, due to the low concentration of brain-derived proteins in blood and their vulnerability to interference from plasma matrix proteins, previous studies using traditional enzyme-linked immunosorbent assay (ELISA) to detect AD-related proteins in blood have been inconsistent. In recent years, some ultra-sensitive detection technologies have been gradually applied to the study of AD blood protein markers. The relevant results show that Aβ, p-Tau and exosomes in blood have potential application value in the early diagnosis, identification and prediction of AD. Therefore, this article reviews the research progress of AD protein markers in blood in the past five years to improve the understanding of blood biomarkers in the diagnosis and treatment of AD and provide guidance for their better early clinical application.
Keywords: Alzheimer's disease; Blood biomarkers; Ultra-sensitive detection technology

1 PLASMA Aβ DETECTION

Alzheimer's disease (AD) is In the form of amyloid-β (amyloid-β, Aβ) and tau protein A progressive central nervous system disorder in which neurofibrillary tangles are the main pathological feature Neurodegenerative diseases. The pathogenesis of the disease is currently unknown, and there is no clinically effective cure. In 2011, the National The National Institute on Aging-Alzheimer's Association (NIA-AA) points out in the AD diagnostic guidelines that AD is a progressive disease, and cognitive impairment Correlates are already present in the brains of AD patients at least 10 years before the damage appears. Pathological changes (called preclinical stage) [1]. This guide promotes early Research on biomarkers to identify AD pathology in the early stage and promote the research direction of early diagnosis and intervention of AD. Cerebrospinal fluid (CSF) and positron emission computed tomography (positron emission computed tomography, PET) inspection It can reflect the pathology of Aβ and Tau proteins in the brain and has been considered for many years. Recommended as a specific pathological biomarker of AD, it is the One of the indicators monitored in early diagnosis, clinical research and drug development one. In 2018, the NIA-AA recommendation was based on "A" (Aβ) "T" (Tau) "N" (neurodegeneration) pathological markers distinguish AD from nonAD spectrum diseases reaffirm the role of CSF and PET examination in AD diagnosis The meaning of breaking [2]. However, CSF and PET detection technologies are expensive, invasive, technically demanding, and have poor patient compliance. The method is popularized in clinical practice [3], so currently it is mainly combined with clinical Performance and cognitive scales are used to diagnose AD and have low specificity.

Because blood has the advantages of easy sampling, high safety, repeatability, and suitable for disease tracking and follow-up, researchers have been trying to find cost-effective early biomarkers for AD in order to break the current difficulties in diagnosis and treatment of AD. However, previous research results on the correlation between AD protein biomarkers in blood (mainly Aβ and Tau) and AD pathological markers (CSF and PET), and the diagnosis and prediction of AD by Aβ and Tau in blood have not been successful. Inconsistent[4-9]. The main reasons include [10] : ① The concentration of brain-derived Aβ or Tau in peripheral blood is low, and the detection range of traditional enzyme-linked immunosorbent assay (ELISA) is limited; ② Aβ and tau in blood It may also come from peripheral tissues; ③ Other abundant proteins in plasma such as albumin and immunoglobulin will affect the test results; (4) Aβ or Tau protein has a short half-life in the blood. In addition, ethnic differences, sample size, inclusion and exclusion criteria will also have an impact on the research results [11-12]. In recent years, ultra-sensitive detection technologies such as single-molecule immunoarray (Simoa), immunoprecipitation-mass spectrometry Combined (immunoprecipitation mass spectrometry, IP-MS), MSD (Meso Scale Discovery, MSD) electrochemical discovery Light, immunomagnetic reduction (IMR) The application has made great progress in the research of AD protein markers in blood. exhibition. Relevant research results show that some biomarkers in blood (such as Aβ, p-Tau, exosomes) can early reflect the pathological status of AD and provide early diagnosis and prediction of AD, which is expected to become an early stage of AD. Stage-specific humoral biomarkers. Therefore, this article summarizes the research progress of AD protein biomarkers in blood in the past 5 years.

1.1 Diagnosis of AD by Plasma Aβ

Compared with plasma Aβ42 alone, plasma assayed by Simoa Aβ42/Aβ40 is more reliable for the diagnosis of AD. Neurodegeneration in Sweden Biomarkers For Identifying Neurodegenerative Disorders Early and Reliably, a large retrospective study in the BioFINDER cohort Studies have shown [13] that compared with mild cognitive impairment (MCI) and control groups, plasma Aβ42, Aβ40, and Aβ42/Aβ40 detected by Simoa were significantly reduced in AD patients, but only plasma Aβ42/Aβ40 was significantly different between the control group and MCI group. Startin [14] applied Simoa to compare plasma Aβ in different patients and found that Plasma Aβ42 and Sporadic AD (sporadic AD, sAD) is significantly different from the control group There was no significant difference in plasma Aβ42 between sAD and the control group; however, the plasma Aβ42/Aβ40 in DS and sAD were significantly lower than those in the control group.

In the study of applying IMR to detect plasma Aβ and Tau proteins found [15 19] that compared with controls, the plasma of MCI and AD patients Aβ42 and Tau protein levels were significantly increased, and plasma Aβ40 levels were decreased. Receiver operating characteristic curve (ROC) analysis showed that plasma Aβ42 and Tau alone, or combined with biomarkers Aβ42/Aβ40 and Tau×Aβ42, were The area under the curve (AUC) that distinguishes the control group from AD is greater than 90%, but these indicators distinguish MCI from AD. AUC is only around 70%. A study including 83 patients with blood biomarkers A meta-analysis of clinical studies on drugs [20] showed that, with Simoa and Compared with ELISA, plasma Aβ42, Aβ40 and Aβ42/Aβ40 detected by IMR were significantly different between AD and control group. can watch It was found that compared with Simoa, plasma Aβ detected by IMR seems to be more accurate in diagnosing AD. However, in these studies, the diagnosis of AD Lack of Aβ or Tau pathology markers, so it is still necessary to identify AD pathology The diagnostic value of plasma Aβ for AD and preclinical AD was further studied in the marker cohort. It is worth noting that plasma Aβ42 levels detected by IMR tend to increase, which is consistent with the findings related to Simoa and IP-MS detection. On the contrary, the reason may lie in the different detection and analysis processes [16-17]. First, SIMOA uses magnetic beads to purify the target protein (this process usually involves resulting in the loss of the target protein), while IMR directly measures the target protein; Secondly, Simoa uses two monoclonal antibodies in the detection, while IMR only uses one specific antibody to capture the C-terminal in the detection, which makes IMR will detect Aβ42 monomers, oligomers, complexes, etc. in plasma.

1.2 Correlation Between Plasma Aβ and AD Pathological Markers

In patients with MCI and AD, there is a certain correlation between plasma Aβ detected by Smioa and IMR and AD pathological markers in CSF/PET, but their ability to distinguish abnormal AD pathological states in the brain needs further verification. Janelidze et al. [13] used Simoa to detect Aβ in the plasma of subjects. The results showed that plasma Aβ42 in MCI patients was slightly positively correlated with Aβ42 in CSF ($r=0.27$, $P<0.001$), and was slightly negatively correlated with Aβ PET ($r=0.27$, $P<0.001$). $r=-0.295$, $P=0.002$). Another study that applied Simoa to detect Aβ in plasma pointed out [21] that the positive correlation between plasma Aβ42/Aβ40 and CSF Aβ42/Tau in patients with amnestic MCI (aMCI) was higher than that in the control group (raMCI=0.51 > r control = 0.25); the AUC of plasma Aβ42/Aβ40 in predicting abnormal brain Aβ PET status in aMCI patients is 0.86. Teunissen et al [18] found a moderate negative correlation between plasma Aβ42 detected by IMR and CSF Aβ42 detected by ELISA in two cohorts of AD patients in the Netherlands and Sweden ($r=-0.352$). In a multi-center study of the AD Neuroimaging Project in Taiwan [22], plasma Aβ42 detected by IMR Taking 15.58 pg/mL as the cut-off value, combined with APOE ε4 status, the ability to distinguish abnormal Aβ deposition status in the brain of early AD patients was significantly improved (AUC alone = 0.611; AUC combined = 0.875).

Compared with Simoa and IMR, plasma Aβ detected by IP-MS can Can more accurately reflect cognitively normal persons, MCI and AD patients The level of Aβ deposition in the brain [23]. Application of IP-MS to Washington Medical 41 AD patients and cognitively normal subjects at the University AD Research Center Plasma Aβ was detected, and the results showed that plasma Aβ42/Aβ40 reflected The AUC of abnormal Aβ status in CSF and PET examinations was 89%; further correlation analysis between this ratio and CSF markers revealed that Now, Aβ42/Aβ40 in plasma and CSF are highly correlated ($r=0.7$, $P< 0.000\ 1$)[24]. Kaneko et al.[25] used IP-MS to detect 66 subjects. Amyloid precursor protein (amyloid precursor protein, APP) and Aβ in the plasma of the subjects, the results showed that the plasma APP669-711/Aβ42 distinction The ability of Aβ PET to detect abnormal states (AUC=0.969) is better than that of Aβ42/Aβ40 (AUC=0.798). Later, the research team worked at the National University of Japan National Center for Geriatrics and Gerontology (NCGG) and Australian Imaging on Aging, student Australian Imaging, Biomarker and Lifestyle Study of Ageing (AIBL) database The study in again confirmed that plasma Aβ42/Aβ40, APP669-711/Aβ42 and and their composite biomarkers can be used to detect Aβ PET-like An effective indicator of state (AUC>90%) [26].

1.3 Plasma Aβ Predicts Cognitive Progression

Some patients with SCD and aMCI may have early AD pathological changes in their brains and are more likely to experience cognitive function deterioration [27]. The presence of plasma Aβ and AD pathological markers detected by Simoa and IMR In correlation and thus able to predict cognitive level to a certain extent decline. Verberk et al. [3] followed 248 patients with subjective cognitive decline (SCD) for an average of 3 years and applied Simoa detected Aβ in his plasma and established the Cox proportional wind The hazard regression model found that after adjusting for age

and gender factors, blood Decreased plasma Aβ42/Aβ40 ratio in SCD progresses to MCI and dementia The risk increased 1.67-fold (95% CI: 1.15-2.44), whereas plasma Aβ42, Aβ40 and Tau do not predict the progression of MCI and dementia. Chen et al. [28] followed 22 aMCI patients for an average of 1.5 years. The results It shows that after adjusting for age, gender, education level, and APOE factors, the plasma Aβ42, Tau or Tau×Aβ42 detected by IMR increases by at least Increases the risk of cognitive decline by more than 5 times.

2 PLASMA TAU TEST

2.1 Diagnosis of AD by Plasma Tau

2.1.1 Diagnosis of plasma t-Tau in AD

The total plasma Tau protein (total-Tau, t-Tau; the plasma Tau mentioned above refers to t-Tau) in AD patients and normal people has a high degree of overlap., cannot be used as a specific biomarker for AD, but can reflect the progression of the disease. Although plasma t-Tau detected by Simoa is significantly elevated in AD patients, it cannot effectively distinguish AD from MCI and cognitively normal people [29 31]. Yang et al. [32] used IMR to detect plasma t-Tau in 215 recruits from National Taiwan University Hospital. The results showed that at a cut-off value of 17.43 pg/mL, plasma t-Tau could differentiate between dementia and normal cognitive subjects (AUC=90.8 %), but cannot effectively distinguish AD from non-AD dementia.

2.1.2 Diagnosis of plasma p-Tau in AD

Recently, in plasma Hyperphosphorylated Tau protein (phosphorylated tau, p-Tau) has gradually attracted attention as an AD blood biomarker. Current research The more phosphorylated sites include p-Tau181 and p-Tau217, as well as Research reports on plasma p-Tau231 in AD [33-34].

Plasma p-Tau181 and p-Tau217 increase in the MCI stage and even in the clinical stage. It is significantly elevated in the preclinical stage, which is important for the early diagnosis and differential diagnosis of AD. Both have good discrimination performance. 73 subjects were tested using IMR Plasma p-Tau181 was detected, and the results showed that in different At the cutoff level, plasma p-Tau181 can identify cognitively normal persons, MCI and mild AD patients [35]. Apply Simoa and MSD detection Research on plasma p-Tau181 found [36 39] that plasma p-Tau181 The MCI of Aβ+ was significantly higher than that in the control group, and it increased with the AD stage. Disease progression further increases, and the AUC for distinguishing clinically diagnosed or pathologically confirmed AD from non-AD degenerative diseases is around 90%. right. Palmqvist et al.[40] took the lead in applying MSD to different cohorts of people. The detection of plasma p-Tau217 in Distinguishing between the Arizona Neuropathology Cohort and the BioFINDER Cohort The AUC in AD and other neurodegenerative diseases exceeds 95%. Applying MSD to Aging in Washington Heights-Inwood Columbia Project (Washington Heights-Inwood Columbia Aging Project, WHICAP) tested plasma p-Tau from three ethnic groups and found that plasma p-Tau217 and p-Tau181 can Efficiently differentiate between ethnically diverse AD and AD in anatomical and clinical cohorts Photo group.

2.2 Correlation Between Plasma Tau and AD Pathology

2.2.1 Correlation between plasma t-Tau and AD pathological markers

Plasma t-Tau and AD markers in CSF detected by Simoa in AD patients The correlation between the two is weak and cannot become a specific pathological marker of AD. object, but can reflect the severity of nerve damage. Clinical at Mayo Studies in the Mayo Clinic Study of Aging (MCSA) showed that elevated plasma t-Tau was associated with decreased cognitive level and hippocampal volume shrinkage. small and cortical thickness reduction, but is related to Aβ deposition in the brain, neural Fibrous tangle pathology is not relevant [29]. A neuroimaging study on AD Return of plasma t-Tau changes in 189 cognitively normal, 195 MCI and 179 AD patients in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database within 2 years. Analysis of gender-based studies shows [30] that after adjusting diagnosis, age, gender, culture After APOE, the increase in plasma t-Tau is related to the rate of cognitive development. The researchers also found that the correlation between plasma t-Tau and CSF t-Tau in AD patients in the BioFINDER cohort was not strong (β =0.13, 95% CI: 0.039-0.22). at NYU School of Medicine (New York University School of Medicine, NYUSOM) A study in the cohort also showed that the plasma and There is no significant correlation between t-Tau in CSF (r=0.2, P=0.33) [31].

2.2.2 Correlation between plasma p-Tau and AD pathology

Before AD pathology appears in the brain, plasma levels of p-Tau181 and p-Tau217 have increased. Both are closely related to Aβ and Tau pathology and can accurately reflect AD pathology. Plasma p-Tau181 was tested with Simoa on 115 people from the Dementia Case Register (CDR) and Alzheimer's Research UK (ARUK) cohorts, and participants died After neuropathological evaluation, studies have shown that plasma p-Tau181 is elevated at least 8 years before the onset of AD pathology, and the AUC for distinguishing AD pathology from non-AD pathology reaches 97%. In a longitudinal study on the changes of plasma p-Tau181 (Simoa assay) in the course of AD in the ADNI database, the researchers used linear mixed effects model analysis to show that before Aβ PET and CSF Aβ42 reached abnormal levels, plasma p -Tau181 increases with the progression of Aβ pathology, and after adjusting for age, gender, and cognitive status, the longitudinal increase in plasma p-Tau181 in the Aβ+ group was associated with extensive aggregation of Tau protein 6 years later. In a cross-sectional study using Simoa and MSD to detect plasma p-Tau181, it

was found that plasma p-Tau181 was significantly different from CSF p-Tau and Tau only in the Aβ+ group (regardless of cognitive status).
PET has significant correlation [34, 36 38]. Palmqvist et al.[40] studied the correlation between plasma p-Tau217 detected by MSD and AD pathology. The study showed that plasma p-Tau217 was correlated with the density score of neural tangles in the Aβ + group confirmed by autopsy pathology (r=0.64, P< 0.001); the team's study in the BioFINDER cohort found that plasma p-Tau217 has a significant impact on the ability to identify abnormal states of Aβ/Tau PET Comparable to AD markers in CSF (AUC blood p-Tau217: 0.87-0.93; AUCCSF: 0.80-0.97). Recruiting from the University of Washington AD patients and healthy controls underwent Aβ PET and CSF examinations, and IP-MS was applied to detect p-Tau in the subjects' plasma, study table It was found that p-Tau217 in plasma and CSF was highly correlated (r>0.7, P<0.000 1), and the ROC analysis results showed that plasma p-Tau217 was correlated with The AUC of abnormal Aβ PET status exceeds 90%.

2.3 Plasma Tau Predicts Cognitive Progression

Janelidze et al studied 219 cognitively normal subjects and 125 Patients with MCI were followed up for 8 years, and whether they converted to AD was used as the outcome indicator. A Cox proportional hazards regression model was established, and the results showed that after adjusting for plasma After t-Tau, Aβ42/Aβ40, neurofilament light chain and other factors, high plasma p-Tau181 increases the risk of non-dementia patients converting to AD (HR: 3.59, 95% CI: 2.55-5.04). Palmqvist et al.[40] often The chromosomally dominant AD registry study cohort found that AD patients with PSEN1 mutations had blood glucose levels at least 20 years before the onset of cognitive impairment. Plasma p-Tau217 increased. The team then followed 250 subjects in the BioFINDER cohort for 6 years and used linear mixed effects. Model analysis showed that in Aβ+ cognitively normal subjects and MCI people Plasma p-Tau217 increases over time and is associated with cognitive performance Decreased strength is associated with brain atrophy. Brickman et al. 169 cognitively normal individuals in the WHICAP clinical cohort were followed interviews, research shows that adjusting for gender, age, race, and APOE factors Afterwards, elevated plasma p-Tau217 and p-Tau181 increased the risk of AD 4 years later (OR: 2.27, 95%CI: 1.31-3.93; OR: 2.74, 95%CI: 1.54 -4.86).

3 BLOOD EXOSOME TESTING

Exosomes are secreted by various cells including neurons It is a vesicle structure with a diameter of 30 to 150 nanometers, which can be separated and extracted from various body fluids such as blood, cerebrospinal fluid, and urine. within exosomes Contains a large amount of proteins, lipids, microRNA (miR-NA) and other contents from maternal cells, so it can be used as a reflection Biomarkers of central system disease. Current research on exosomes in AD mainly focuses on detecting AD-related proteins (Aβ, Tau, synaptophysin, etc.) and miRNA.
Existing research suggests that some proteins in blood exosomes can identify AD early and accurately reflect AD pathological changes. Exosomal Aβ, Tau, and p-Tau181 detected by ELISA were significantly increased in the preclinical stage of AD, and the combined biomarkers were better than single markers in distinguishing AD, aMCI, and controls. In a multi-center study in my country that explored the consistency of neurogenic exosomes in blood (ELISA detection) and AD markers in CSF, it was found that Aβ42, t-Tau, pin blood exosomes and CSF Tau181 are highly correlated with each other (R2=0.76-0.86, P<0.000 1). Recent studies have found that synaptic protein combinations in blood exosomes can predict the occurrence of AD 5 to 7 years before the onset of clinical symptoms (AUC=0.87-0.89).

4 BLOOD AND OTHER PROTEIN TESTS

In addition to the above-mentioned major AD-related protein markers in blood, there are also studies using high-throughput mass spectrometry analysis to detect proteins in blood. The results show that the combination of multiple blood protein indicators can often improve the accuracy of AD biomarkers. A mass spectrometry-based proteomic analysis in the Brain Aging Study Cohort for Early Diagnosis and Prediction of AD in Korea showed that multiple protein biomarker combinations can improve the sensitivity and specificity of AD diagnosis. Chinese scholars conducted proteomic analysis on the serum of AD patients and controls and selected 18 proteins that interact with APP as AD candidate biomarkers. It is speculated that changes in the expression levels or functions of these proteins may affect Aβ metabolism and thereby participate in the occurrence of AD.
In summary, there is a clear correlation between Aβ and p-Tau in plasma and blood exosomes detected by ultra-sensitive technology and AD pathological markers, which can identify AD pathology early; combined biomarker detection can increase the detection of AD. The accuracy of early diagnosis can predict the progression of dementia to a certain extent, and it is expected to become an early biomarker of AD. However, there are certain differences in the research results of different detection technologies on AD protein markers in blood. In addition to the different detection technology principles, the detection process, the cut-off values of different markers, as well as different races, sample sizes, and inclusion criteria will all have an impact on the results. Therefore, it is necessary to standardize the different detection methods and processes of AD protein markers as well as the criteria for the included populations. More meta-analyses and the establishment of "prospective, multi-ethnic, multi-center, large sample, real-world data" are

also needed. Cognition cohort of basic characteristics to clarify the application value of blood protein markers in AD, thereby promoting the early clinical application of AD blood protein markers.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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