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REVIEW ARTICLE

Blood Biomarkers for Alzheimer's Dementia Diagnosis

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알츠하이머성 치매에서 혈액 진단을 위한 바이오마커

박창은

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ABSTRACT

Alzheimer's disease (AD) represents a major public health concern and has been identified as a research priority. Clinical research evidence supports that the core cerebrospinal fluid (CSF) biomarkers for AD, including amyloid-β (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau), reflect key elements of AD pathophysiology. Nevertheless, advances in the clinical identification of new indicators will be critical not only for the discovery of sensitive, specific, and reliable biomarkers of preclinical AD pathology, but also for the development of tests that facilitate the early detection and differential diagnosis of dementia and disease progression monitoring. The early detection of AD in its presymptomatic stages would represent a great opportunity for earlier therapeutic intervention. The chance of successful treatment would be increased since interventions would be performed before extensive synaptic damage and neuronal loss would have occurred. In this study, the importance of developing an early diagnostic method using cognitive decline biomarkers that can discriminate between normal, mild cognitive impairment (MCI), and AD preclinical stages has been emphasized.

INTRODUCTION

Cognitive dysfunction, the major clinical manifestation of Alzheimer's disease (AD), is caused by irreversible progressive neurological dysfunction. With the aging of the population, the incidence of AD is increasing year by year. Alzheimer's disease (AD) is a form of progressive dementia that includes cognitive impairment, learning and memory loss. A variety of proteins [such as amyloid precursor protein (APP) [1], β-amyloid (Aβ) [2], and tau protein [3] play important roles in the initiation and progression of Alzheimer's disease.

The role of the most important proteins and peptides in the pathogenesis of Alzheimer's disease. The structure, biosynthesis and physiological roles of APP are briefly demonstrated [4-6]. Details of the trafficking and processing of APP to Aβ, the cytoplasmic intracellular Aβ domain (AICD) [7] and small soluble proteins are shown along with other amyloidogenic proteins such as tau and α-synuclein (α-syn) [8]. Hypothetical physiological functions of Aβ are summarized. The mechanism of morphological change, formation and role of neurotoxic amyloid oligomers (oAβ) is indicated. The coexistence of different conformations (U-shaped and S-shaped) of Aβ monomers during fibril formation and in mature

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fibrils has been demonstrated [9, 10]. The demonstrate toxic interactions of Aβ species after binding to cellular receptors [11]. Tau phosphorylation, fibrillation, molecular structure of tau filaments and toxic effects on microtubules are shown [12].

The development of Aβ and tau imaging in AD brain and CSF as well as blood biomarkers is briefly summarized. Most likely pathological mechanisms of Alzheimer's disease, including toxic effects of oAβ and tau; The three (biochemical, cellular and clinical) stages of Alzheimer's disease are shown. Two characteristic features, tau and Aβ, are found in the brains of AD patients. Besides proteins, several other potential diagnostic markers have been linked to some. It has been suggested by older groups. GAP43 is associated with presynaptic terminals [13]. Much work remains to develop and validate blood-based biomarkersthat can reliably measure non-AD pathologies such as a synuclein [14] or TDP-43 [15].

As a neuromodulator present in the axon of cortical nerve cell, AD patient found in the dystrophic neurite around the senile plaques, and in the frontal lobe. It has been reported that expression levels are reduced in the hippocampus and MS-based studies suggest that a ratio of a certain APP fragment (APP669-711) to Aβ42 or Aβ 42/Aβ40 in plasma identifies Aβ-positive individuals with high sensitivity and specificity [16].

Alzheimer's disease (AD) is prevalent throughout the world and is the leading cause of dementia in older individuals (aged≥65 years). The worldwide toll of AD is evidenced by rising prevalence, incidence, and mortality due to AD-estimates which are low because of underdiagnosis of AD. Mild cognitive impairment (MCI) due to AD can ultimately progress to AD dementia [17].

Ubiquitin is naturally present in the human body. By covalently binding to the lysine of the protein to be degraded, proteolysis [18]. Alzheimer's disease extracellular vesicles (EVs) show higher transmissibility of tau via increased uptake by recipient neurons. At present, an increasing body of evidence suggests that EVs play a crucial role in the pathogenesis of AD, and it is of great significance to use them as specific biomarkers and novel therapeutic targets for cognitive impairment in AD [19].

MAIN BODY

The chronic neurodegenerative pathology known as Parkinson's disease (PD) can be described as an accumulation of a misfolded type of α-synuclein (the so-called Lewy bodies), an event occurring in dopaminergic neurons of the substantia nigra (SN) [20], other related neuronal pathway, which finally contribute both to non-motor and mainly to motor symptoms.

AD is a neurodegenerative disorder, often occurring in the elderly, which has a fundamental causative source in the impairments in the gut-microbiome-brain axis (GMBA). Recent data, which are to be further deepened and improved in any investigation planning, reported to date a close relationship between gut microbiota composition and AD onset, usually derived from neuroinflammation caused by bacteria products or bacterial brain migration, a circumstance that normally occurs to contribute to the regulation of brain synaptogenesis and development, besides mood and cognition evolution [21, 22].

Tau protein were detected to ultrasensitive immunoassay techniques also allow for measurement of tau protein in blood samples (plasma). Phosphorylated tau (p-tau) were measure of the amount of tau that is phosphorylated [23], the variant of tau found in tangles. Total tau gives a measure of neurodegeneration in AD, but is not a disease-specific marker [24]. Neurogranin is a synaptic protein in the dendritic spines, with CSF levels reflecting synaptic dysfunction and degeneration. High CSF neurorainin is semingly specific for AD. CSF Aβ42 is lowered in AD, reflecting the aggregation and deposition of the protein in the brain. Aβ40 is the most abundant variant of Aβ in CSF and thus the CSF Aβ 42/40 ratio compensates for between individual differences among Aβ isoforms [25].

Increased tau levels in plasma in AD found using both

the immunomagnetic reduction (IMR). The measurement of T-tau or P-tau in neuron-enriched exosome preparations may improve performance for tau as a blood biomarker, but further studies are needed to validate this finding.

Enzyme-responsive peptides: as the beta-secretase 1 (beta-site amyloid precursor protein cleaving enzyme 1; BACE1) enzyme also plays a vital role in AD pathology, peptides have been designed and synthesized as enzyme-responsive substrates to detect enzyme activity [26].

In this context, an important piece of knowledge is that high plasma (or CSF). Neurofilament (NFL) is not a feature that is specific for AD. Instead, increased levels are found in many neurodegenerative disorders, such as frontotemporal dementia, progressive supranuclear palsy and corticobasal syndrome. Thus, a possible future application for plasma NFL is as a screening test at the first clinical evaluation of patients with cognitive disturbances, for example at the primary care unit. Here, plasma NFL might serve as simple, non-invasive and cheap screening tool, primarily to rule out neurodegeneration [27].

YKL-40, recognized as chitinase 3-like protein 1 (CHI3L1) or human cartilage glycoprotein 39 (HC-gp39) is a chitin-binding lectin which belongs to the glycosyl hydrolase family 18. The name of YKL-40 was established based on its structure which consists of three N-terminal amino acids: tyrosine (Y), lysine (K) and leucine (L) and the molecular mass of the protein is 40 kDa [28]. The types and interpretations of biomarkers according to the progression of AD are shown in Table 1.

In gut microbiota (GM)-based AD biomarkers, gut-brain axis (GBA) consists of a signaling pathway between the gastrointestinal (GI) tract and the CNS, which allows a bidirectional communication between the two systems. Its primary role is to monitor and integrate intestinal functions as well as to link, through

Table 1. The list and interpretation of factors that can be used as biomarkers in the progression of Alzheimer's disease and MCI

Biomarkers	Characteristic
Amyloid-β 42/40, APP 669~711	Reduced Aβ42/Aβ40 ratio in AD High APP 669~711/Aβ42 ratio in AD Brain amyloid positive
ApoE	Directly interact with Aβ, tau, and α-synuclein
Apolipoprotein A1	Decreased in AD and MCI
BDNF	Decreased in AD but not in MCI
Clusterin/cyclin dependent kinase 5	Increased in AD and MCI
Cystatin C	Decreased in AD and MCI
Galectin-3	Microglial activity marker & AD biomarker
GAP-43	Lower in AD & prediction of AD 5~7 years before cognitive impairment
GSK-3β	Increased in AD and MCI
Homocysteine	Increased in AD
Neurofilament light	High plasma NFL in AD and MCI
Neurograinin	High CSF specific in AD
Protein kinase C	Formation of amyloid plaque in AD
SNAP25/synaptotagmin 1	Lower in AD & prediction of AD 5~7 years before cognitive impairment
TDP-43	Nervous system disorders, FTD
Total-tau and phosphorylated-tau	Increased in AD (MCI) and acute brain damage
YKL-40	Possible biomarker in the diagnosis and prognosis of AD
α-1-antitrypsin/α-2-macroglobulin	Increased in AD
α-synuclein	Aggregation of dementia with Lewy bodies (DLB)

Abbreviations: MCI, mild cognitive impairment; Aβ, amyloid-β; AD, Alzheimer's disease; APP, amyloid precursor protein; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; BDNF, brain-derived neurotrophic factor; NFL, neurofilament light; P-tau, phosphorylated tau; T-tau, total tau; Aβ1-42, 42-residue isoform of beta amyloid protein; GAP-43, growth associated protein; GSK-3β, glycogen synthase kinase 3β; BACE1, β-secretase 1; BDNF, brain-derived neurotrophic factor; SNAP25, synaptosome associated protein 25; Gal-3, galectin-3; ApoE, apolipoprotein E; TDP-43, transactive response DNA-binding protein 43 kDa; YKL-40, tyrosine (Y), lysine (K) and leucine (L) and the molecular mass of the protein is 40 kDa.

immune and neuro-endocrine mediators, the emotional and cognitive centers of the brain with peripheral intestinal mechanisms such as immune activation, intestinal permeability, enteric reflex, and entero-endocrine signaling [29]. As mentioned above, the gut microbiota has emerged as a key player in regulating both physiological and non-physiological conditions, thus gut microbiota-related biomarkers may represent a promising alternative/complementary tool to assess disease conditions.

CONCLUSION

Recently, biomarkers that can determine neuro-degeneration in spinal fluid include total tau (T-tau), neurofilament light protein (NFL) [30, 31], neuron-specific enolase (NSE) [32], visinin-like protein 1 (VLP-1) [33]. Amyloid β42 [34], amyloid β40 [35], and amyloid β38 [36] are known to affect APP metabolism. In addition, YKL-40, monocyte chemtactic protein-1 (MCP-1) [37], and glial fibrillary acidic protein (GFAP) [38] biomarkers associated with phosphorylated tau (P-tau) and glial cell activation associated with Tangle pathology that can show neuropathological changes etc. are also known. CSF consistently underline the relation of galectin-3 (Gal-3) with other key CSF biomarkers in AD progression. Higher Gal-3 levels correlated with tau and p-Tau181 levels, two indicators of pathology progression in AD [39].

In vitro diagnostic medical devices that help to check the accumulation of beta-amyloid in the brain are in the process of development, and amyloid beta [precise immunoassay], total tau protein [precise immuno-assay], phosphorylation tau protein [precise immuno-assay], oligomerized beta-amyloid [enzyme-linked immu-nosorbent method], etc. have been set and are being used for diagnosis [40-42].

A unified CSF handling protocol is recommended to reduce pre-analytical variability and facilitate comparison of CSF biomarkers across studies and laboratories. In future, experiments should use a gold standard with fresh CSF collected in low binding tubes [43].

Besides the two characteristic proteins, tau and Aβ, found in the brains of AD patients, several other potential diagnostic markers have been proposed by some research groups. growth associated protein 43 (GAP43) is a neuromodulator present in presynaptic terminals and axons of cortical neurons [44]. In AD patients, it is found in dystrophic neurons, and its expression level is reduced in the frontal lobe and hippocampus. Ubiquitin binds covalently to the lysine of proteins to be naturally degraded in the human body and triggers degradation by proteolytic enzymes.

The APOE gene (compared to the most common ε3 allele) continues to be the strongest genetic risk factor associated with sporadic Alzheimer's disease since its discovery in 1993. Moreover, the relatively rare APOE ε 2 allele remains by far the strongest genetic protective factor against sporadic Alzheimer's disease. ApoE has been shown to directly interact with Aβ, tau, and α -synuclein; likely directly contributing to the formation of protein aggregates or the response of the brain to these aggregates in various diseases [45, 46].

In recent years, GM-based Parkinson's disease (PD) biomarkers. Four different traits of the intestine have been proposed as PD biomarkers. Among GM-related molecules, low levels of urine urolithin, decreased plasma trimethylamine N-oxide (TMAO), reduced plasma acetic and propionic acids and low levels of circulating LPS binding protein (LBP) are associated with PD. The GMBA has been a focus of biomedical research and has been proposed as a potential therapeutic target for disorders affecting the central nervous system, including Alzheimer's disease [47]. In addition, the gut-brain axis (GBA) constitutes the signaling pathway between the GI and the CNS, enabling bi-directional communication between the two systems. In this communication network, the brain influences gut motor, sensory, and secretory functions, and signals from the gut in turn affect brain function. Thus, this relationship is of paramount importance in maintaining intestinal homeostasis and has been

reported to be involved in the pathogenesis of several metabolic and psychiatric and neurological dysfunctions and disorders. Various communication pathways between the gut microbiota and the brain have been proposed.

New diagnostic markers are based on knowledge accumulated through research so far [48-50]. Based on this, potential proteins identified as related to AD were identified. It will be discovered in the process of saving, and new protein that shows differences in expression by comparing and analyzing body fluids in large quantities. After discovering the quality, it is also possible to trace back the relationship with AD. The measurement of T-tau or P-tau in neuron-enriched exosome preparations may improve performance for tau as a blood biomarker, but further studies are needed to validate this finding.

요 약

알츠하이머병은 주요한 공중보건 문제로 나타나며 연구분야에서도 최우선적인 과제이다. 알츠하이머병(AD)에서 뇌척수액(CSF)을 활용한 바이오마커인 아밀로이드-β(Aβ42), 총 타우(T-tau) 및 인산화 타우(P-tau)가 알츠하이머병 병태생리학의 핵심 요소를 반영한다. 임상 연구 및 새로운 측정법을 통한 임상적으로 활용되는 진단은 전임상 알츠하이머병에 대해 민감적이고 특이적이며 신뢰할 수 있는 바이오마커의 발굴, 뿐만 아니라 치매의 조기 발견 및 감별 진단과 질병 진행 모니터링에 도움이 되는 검사법의 개발에도 중요할 것이다. 증상 전 단계에서 AD의 조기 발견은 시냅스 손상 및 신경 손실이 확장되기 전에 개입이 수행되기 때문에 치료 개입을 조기에 가능하게 하고 치료 성공을 위한 가능성이 더 큰 좋은 기회로 이어진다. 따라서 새롭고 접근하기 쉽고 비용이 적게 드는 바이오마커를 임상 진단에 활용하는 것이 매우 유익할 것이다. 치매의 초기단계에 일어나는 병리학적 변화나, 질병의 진행정도를 추적할 수 있는 다양한 바이오마커들의 진단방법을 찾는 일은 치료제 개발처럼 중요한 연구 분야이다. 조기진단을 위해 임상증상을 대변하거나(surrogate marker), 증상이 나타나기 이전 상태를 측정할 수 있는 새로운 진단마커가 필요한 상황이다. 이러한 이유로 인지기능 저하정도를 측정하여 정상, 경도인지장애(mild cognition impairment, MCI) 및 전임상(preclinical) 상태의 사람을 판별할 수 있는 바이오마커(biomarker)를 활용한 조기진단법 개발의 중요성이 강조되고 있다.

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