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Biomarkers for Neurodegenerative Diseases

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Abstract

Neurodegenerative disorders, especially Alzheimer's disease (AD) and Parkinson's disease (PD), are global challenges recently, with an increasing incidence and high expenses for treatment. The key pathophysiological characteristics are the accumulation of amyloid beta (Aß), tau protein in AD and ∂-synuclein (∂-syn) in PD. Pre-clinical stages of neurodegenerative diseases have been progressing for a long period prior to the appearance of specific symptoms. It is crucial to develop accurate and reliable biomarkers to improve early diagnosis and treatment that can extend the preclinical stage of patients. Because magnetic resonance imaging (MRI), positron emission tomography (PET) imaging, and cerebrospinal fluid (CSF) biomarkers are invasive or expensive, blood and salivary biomarkers that are widely available and reasonable in cost have been developed recently. This article advances our understanding of the current biomarkers for neurodegenerative disorders and their promising application in clinical practice and trials.

Introduction

Neurodegenerative diseases are a dominant etiology of cognitive decline in the elderly, and their prevalence is increasing in most countries. In 2015, around 50 million individuals globally reported having dementia, and this figure is predicted to increase to 131.5 million in 2050, which significantly raises the burden of disability, illness, and medical expenses[1]. AD is the most prevalent kind of dementia globally, around 60-80% of dementia patients[2]. People with AD often experience memory impairment, which is followed by additional cognitive symptoms such as language difficulties and executive and visuospatial function impairments. Although acetylcholinesterase inhibitor therapy can enhance cognitive function, it cannot stop the disease's progression.

Extracellular amyloid beta (Aß) plaque accumulation and intracellular Tau fibril-based neurofibrillary tangles are primarily pathophysiological characteristics of AD[3]. Aß plaques initially form in the basal isocortex (frontal, temporal, and occipital), then extend to the association cortices, subcortical regions (striatum, thalamus, and hypothalamus), and ultimately the primary sensorimotor areas. Tau fibrils are firstly found in the entorhinal cortex, then spread to the hippocampus and other paralimbic regions (amygdala, basal forebrain nuclei, anterodorsal thalamic nuclei) as well as mesial temporal and parietal/retrosplenial isocortex, eventually reaching the prefrontal areas[3]. In AD, medial temporal lobe pathologic alterations first appear, then extend to the neocortex[4,5], with the changes occurring decades prior to clinical symptom onset[6,7]. AD progression is classified into 3 stages: pre-clinical stage, prodromal stage or mild cognitive impairment (MCI stage), and clinical stage or dementia[8]. 10-20% of estimated patients with MCI develop AD each year[9]. In other neurodegenerative

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disorders, such as progressive supranuclear palsy (PSP), frontotemporal dementia (FTD) and corticobasal degeneration (CBD), Tau concentrates in different structures, and is not associated with Aß pathology[10].

With an annual incidence of 5-35/100,000 new cases, PD is the 2nd most prevalent neurodegenerative disorder following AD[11]. Bradykinesia, resting tremor, muscle rigidity, postural and gait abnormalities are main motor-symptoms of this movement disorder. Dopaminergic neuronal degeneration in the pars compacta of the substantia nigra is related to symptoms of PD. Non-motor symptoms are hyposmia, rapid eye movement sleep behavior disorder (RBD) and constipation, which generally occur 5-10 years before motor symptoms and are not related to dopamine loss[12]. The primary pathological characteristic of PD is the accumulation of ∂-syn in Lewy bodies and Lewy neuritis[13]. Similar to the classification of AD, there are three stages in the progression of PD: preclinical stage (from onset to appearance of nonmotor symptoms), prodromal stage (non-motor symptoms), and clinical stage (motor symptoms)[14]. Dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) are synucleinopathies similar to PD, while PSP and CBS are categorized as tauopathies[15].

The necessity of biomarkers for neurodegenerative diseases

Because most specific neurons have degraded and brain neuroplasticity has been diminished by the manifestation of specific symptoms, diagnosis of neurodegenerative disorders is carried out a long time after the onset[16, 17]. Early diagnosis (preclinical stage) and preventative therapy are able to extend the preclinical stage of patients[18]. The rate of misdiagnosed AD is high at specialized dementia clinics (25–30%), and this rate is higher for other dementias, such as vascular dementia, FTD, DLB[19-21]. In primary care, misdiagnosis occurs much more frequently[22]. In the case of PD, because of clinical overlap with other etiologies of parkinsonism, the rate of misdiagnosis in PD is also high, up to 20%[23]. Dopaminergic neuronal degeneration in the substantia nigra reaches nearly 50% before the first motor symptoms, so the preclinical and prodromal stages provide the best therapeutic window [24, 25]. The benefits of optimal therapeutic interventions are diminished by delayed diagnosis and misdiagnosis. As a result, it is crucial to find and recognize precise and valid biomarkers for the early diagnosis of neurodegenerative disorders.

A biomarker is defined as "a measurable indicator of some biological state or condition that is objectively measured and evaluated to examine normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"[26]. Based on their functional features, biomarkers are categorized into: pathophysiological biomarkers representing the correlation with the pathology of diseases; diagnostic biomarkers including clinical diagnosis and differential diagnosis; and prognostic biomarkers showing the prediction of development from preclinical or prodromal to clinical stage[27,28]. Overall, biomarkers are crucial for the diagnosis of neurodegenerative disorders, particularly during the early stages. Early and accurate diagnosis is important in supporting the optimization of therapeutictreatment. Biomarkers that are easily accessible, inexpensive, and precise

have the promise of being widely used in clinics, especially in primary care[29].

Imaging biomarkers

Structural MRI is an inexpensive and extensively utilized neuroimaging technique for supporting the diagnosis of AD[30]. MRI is thought to be a marker that can identify abnormalities in the later stages of neurodegenerative disorders[31]. Patients with AD mostly have hippocampal atrophy (sensitivity-Sn 95%; specificity-Sp 92%) as well as entorhinal cortex atrophy (Sn 90%; Sp 94%) compared to the normal cognitive elderly. When AD is distinguished from non-AD dementias, these figures reduce to 79 and 81 %, respectively[32].

FDG-PET (18F-fluorodeoxyglucose-PET) is a method of functional neuroimaging that measures the brain's glucose metabolism rate, which frequently decreases before structural brain alterations are visible[33]. Neurodegeneration can be observed as decreased glucose absorption in the temporoparietal and posterior cingulate cortex in AD or in amnestic MCI who later developed AD[34]. When distinguishing AD from healthy elderly people, FDG-PET has a high sensitivity and specificity (> 90%). When it is used for distinguishing between AD and non-AD dementias, specificity drops to 78%[32]. FDG-PET has also been shown to be superior than structural MRI in predicting the transformation to AD in people with MCI[35].

In PD, neurochemical alterations of the dopamine system are evaluated by dopamine transporter single-photon emission computed tomography (DAT-SPECT) and fluorodopa-PET (F-DOPA PET)[36]. Dopamine in the basal ganglia decreases in PET scans of patients with PD, MSA, PSP and CBD[37]. Many studies have reported that DAT-SPECT has good diagnosis accuracy for PD subjects (Sn 79-100% and Sp 80-100%)[36,38]. PET can be utilized to diagnose PD in the prodromal period by demonstrating the decrease of dopamine production, absorption, vesicular storage, and secretion in the nigrostriatal dopaminergic pathway[39-41].

CSF biomarkers

Because of its direct interaction and close relationship with the brain, CSF is thought to be a reliable biomarker for the evaluation of people with AD[42, 43]. Moreover, lumbar puncture is a common and well-tolerated technique with few complications[44]. Although CSF collection is an invasive procedure and can cause anxiety and fear in the patient, it can reveal crucial information reflecting the biochemical alterations in the preclinical stages of AD brain[45].

CSF amyloid

A major constituent of extracellular plaques is Aß peptides, formed by the sequential cutting of ß-amyloid precursor protein (APP) by ß-site amyloid precursor protein-cleaving enzyme 1 (BACE1) and y-secretase[46, 47]. Among the forms of Aß peptides released, Aß42 is a main element of the plaques found in the AD brain[48]. According to research, Aß42 levels in the CSF correlate inversely with plaque accumulation in autopsy or PET[49, 50].

The abnormality of Aß42 is first recognized in the CSF during the earliest stages of neurodegeneration, prior to the amyloid PET [51]. This implies that Aß42 in CSF is a more sensitive biomarker for AD detection at very early stages and that amyloid-PET could be utilized to grade early AD stages more accurately[28]. While cut-off values fluctuate among laboratories, a 50%

reduction in Aβ42 concentration in the CSF reveals its accumulation in the brain parenchyma of AD patients[42, 52]. Hulstaert et al. reported that using Aβ42 alone to distinguish AD patients from elderly controls had a Sn of 78% and a Sp of 81%[53, 54]. However, these figures decrease to Sn 73% and Sp 67% when distinguished from non-AD dementias[32]. In MCI patients, decreased CSF Aβ42 has a low predictive accuracy for AD progression (Sn 81% and Sp 64%). Therefore, it is not suggested to use CSF Aβ42 alone to diagnose AD pathology in MCI patients[55]. Additionally, in other neurodegenerative disorders, Aβ42 is also reduced in DLB and PD dementia but is normal in FTD patients[56].

In the case of differences between CSF biomarker characteristics, the CSF Aβ42/ Aβ40 ratio has been considered as a potential differentiating biomarker for AD. Lewczuk et al. reported that the CSF Aβ42/40 ratio had a stronger correlation with amyloid-PET than Aβ42, (area under the ROC curve - AUC 0.936 and 0.814, respectively)[50]. In addition, the CSF Aβ42/Aβ40 ratio was also found to distinguish AD from other types of dementias, with a Sn and Sp of 85% and 82%, respectively[57]. The effectiveness of the CSF Aβ42/Aβ40 ratio could be related to its ability to modulate differences among individuals in: total Aβ synthesis or release from neurons; CSF synthesis and clearance; and pre-analytical processing of CSF that influenced Aβ40, Aβ42[50].

CSF tau

Tau proteins are members of the microtubule-related molecule family, which can be detected in both neuronal and non-neuronal cells[58, 59]. Phosphorylation of tau can take place at more than 40 different sites[60]. Many studies have been conducted on CSF total tau (t-tau), tau phosphorylated at threonine 181 (p-tau181) and at threonine 217 (p-tau217)[60, 61]. According to a meta-analysis, all research demonstrated that CSF t-tau and p-tau elevated in AD[61], with cut-off values of 300% and 200% elevated levels of t-tau and p-tau respectively[42, 52]. Moreover, t-tau or p-tau increases are not only found in primary tauopathies[62] but also reflect tau metabolism changes induced or mediated by Aβ[63]. CSF p-tau concentrations associate with brain tau accumulation on tau-PET as well as with Aβ deposition measured on PET or CSF[60, 64]. CSF p-tau217 is reported to have a higher association with tau level and severity of disease than p-tau181[60].

CSF t-tau increases in AD but also in other disorders like stroke and Creutzfeldt–Jakob disease, so t-tau is non-specific for AD. In contrast, p-tau is demonstrated to be a more specific CSF biomarker than t-tau for the AD pathological process[65,66]. Bloudek et al. investigated using CSF to differentiate AD from healthy people and found results that sensitivity of 82% and specificity of 90% for t-tau, and sensitivity of 80% and specificity of 83% for p-tau. Nevertheless, when it comes to distinguish AD from non-AD dementias, these sensitivity and specificity reduce to 79% and 80% for p-tau, 78% and 75% for t-tau, respectively[32]. Many studies have revealed that CSF p-tau181 concentration is significantly higher in AD than in FTD, DLB, PD, or MSA patients, and can be a biomarker to discriminate AD from these diseases[67-69]. Additionally, CSF p-tau217may be used to differentiate AD from non-AD dementias with greater precision than p-tau181[60, 70].

Early diagnosis of AD in the prodromal stage (MCI stage) is crucial because novel disease

-modifying medications are most effective when started in the early stage. Buchhave carried out a study to assess the prediction of CSF p-tau in the progression of AD in MCI patients after 9-10 years. Patients who transformed to AD had lower CSF Aβ42 at baseline and higher p-tau concentrations than non-converters. In addition, early converters (0-5 years) had significantly higher CSF p-tau concentrations than late converters (5-10 years). The Aβ42/p-tau ratio at baseline predicted the conversion to AD in 9.2 years (Sn 88% and Sp 90%)[71]. Therefore, some authors suggest that using CSF p-tau combined with Aβ42 instead of CSF Aβ42 alone for predicting the conversion of AD in MCI patients[71, 72].

CSF ∂-synuclein

The pathological characteristics of PD are thought to include ∂-syn misfolding and accumulation in Lewy bodies, which are related to dopaminergic neuron loss[73]. Because of the prominent role of ∂-syn in PD pathology, CSF ∂-syn concentration has received the most concern as a potential biomarker. In comparison with healthy controls, many studies consistently reported decreased CSF total-∂-syn (t-∂-syn) concentrations in PD patients[74-76]. Other a-synuclein forms, including oligomeric a-synuclein (o-∂-syn) and phosphorylated a-synuclein (p-∂-syn), have been investigated as promising biomarkers for PD[77, 78]. CSF o-∂-syn and o-∂-syn/t-∂-syn ratio have been evaluated and revealed to be increased in PD subjects. Moreover, the increase in o-∂-syn/t-∂-syn was related to motor impairment, especially in PD with gait disorders and postural instability subgroups[79]. In the BioFIND cohort, Protein Misfolding Cyclic Amplification (PMCA) and the Real-Time Quaking-Induced Conversion (RT-QuIC) assay were utilized to evaluate o-∂-syn in discriminating PD from controls with AUC 0.93, Sn 95.2%, Sp 89.9% for PMCA and AUC 0.89, Sn 96.2%, Sp 82.3% for RT-QuIC[80]. Other research applied the RT-QuIC assay for detecting ∂-syn to discriminate Lewy body related disorders with a Sn of 95.3% and a Sp of 98%[81]. Singer et al. reported that applying PMCA to o-∂-syn had a high separation of MSA from PD/DLB patients[82]. However, neither PMCA nor RT-QuIC can discriminate between different synucleinopathies. Although ∂-syn biomarker is crucial in PD pathogenesis, it does not significantly influence in the early diagnosis of PD. The current methods for the improvement of early diagnosis are based on the identification of premotor symptoms and nigrostriatal dopaminergic system failure on PET during the prodromal phase, which corresponds to 10 years before motor symptom onset[83-85]. Non-motor symptoms of PD, which are constipation, hyposmia and REM sleep behavior disorder, are considered potential biomarkers in the identification of prodromal PD[86]. A study found that RBD is significantly related to PD, with a 45% risk of PD development after 5 years and a 76% risk after 10 years[87]. In the RBD cohort, the prodromal criteria had a Sn of 81.3% and a Sp of 67.9% for the development of PD after 4 years[88]. Because non-motor symptoms have insufficient specificity for early diagnosis, imaging biomarkers combined with non-motor symptoms might enhance the predictive value of biomarkers in PD. The combination of hyposmia and DAT-SPECT was demonstrated to detect the risk of PD development, with a 5% decrease in dopamine each year[89].

Blood biomarkers

Blood biomarkers are very popular biological technologies in research and clinical settings, especially in primary care. Blood biomarkers have several significant advantages over CSF procedures, including non-invasive, fast, convenient, inexpensive, easily repeatable and simple to measure. Thus, it can be carried out in a variety of places, like primary care, hospitals, and the patient's home, as well as through longitudinal research[90-92]. It is difficult to detect AD biomarkers in the blood because of the low concentrations of Tau proteins and Aß in peripheral blood, which requires the development of a highly sensitive technique for diagnostic biomarkers in AD[90]. As a result, some of the advanced technologies that enhance the transferation of blood biomarkers from CSF have emerged, including immunoprecipitation-mass spectrometry (IP-MS), electrochemiluminescence (ECL), Simoa (single molecule array), immunomagnetic reduction (IMR), and Meso Scale Discovery (MSD)[93].

Plasma amyloid

Most efforts failed until a 2016 research publication found that an ultra-sensitive technique for measuring plasma Aß42/40 could predict abnormal amyloid-PET with moderate accuracy[94]. Subsequently, the IP-MS method was established for detecting Aß in plasma and identifying cerebral Aß pathology with significantly better accuracy than most methods before[95-97]. Whereas the Aß42/40 ratio in the CSF is reduced to around 50% to reflect the Aß42 accumulation in the brain, it is reduced to 14.3% in the plasma of amyloid (+) people compared to amyloid (-) subjects[95]. The plasma Aß42/40 ratio has been demonstrated to detect Aß plaques in order to support the diagnosis of AD with high diagnostic accuracy (AUC 0.89)[95].

Plasma tau

While there are limitations to assessing the total tau and Aß42/40 ratio in plasma because of the minor changes in AD compared to in CSF, plasma p-tau has been proven to be a diagnostic, pathophysiological, and prognostic biomarker for AD[27]. According to neuropathology and PET studies, plasma p-tau181 and p-tau217 levels are related to both Aß plaques (early stages) and tau-tangles (later stages)[98]. In sporadic AD, p-tau217 and p-tau181 in CSF/plasma increase in the pre-clinical stage when Aß plaques appear and even before detection of tau-tangles by tau-PET[99-102]. Mielke reported that plasma p-tau181 was associated with tau/amyloid PET and CSF p-tau181, suggesting plasma p-tau181 can be utilized as a strong predictor of AD pathophysiology in the brain[103]. Plasma p-tau181 increases significantly after Aß42 in the CSF and plasma but before amyloid PET[100]. After that, Palmqvist demonstrated that plasma p-tau217 was mildly superior to p-tau181 for AD diagnosis and association with tau/amyloid-PET[104]. Therefore, plasma p-tau181 and p-tau217 may be effective biomarkers for diagnosing and determining the stage of AD in primary care, specialized centers, and clinical trials[105].

Plasma p-tau, similar to CSF p-tau, could distinguish AD from non-AD dementias and other neurodegenerative disorders[104]. In recent studies, plasma p-tau181 has the ability to differentiate AD from healthy people by Simoa[106], IMR[107], and MSD technologies[103]. Moreover, p-tau181 was

revealed to distinguish AD from non-AD dementias with high accuracy (AUC = 0.93)[99]. Plasma p-tau217 also had a high accuracy (AUC = 0.96) in distinguishing AD dementia from other neurodegenerative disorders, which was similar to p-tau181 and p-tau217 in the CSF, but better than plasma p-tau181[104]. Similar to plasma p-tau181, plasma p-tau231 can distinguish AD from other dementias with high accuracy (AUC = 0.93)[108]. In summary, p-tau217, p-tau181 and p-tau231 have high accuracy in differentiating AD patients from healthy people as well as from other dementias.

In MCI patients, plasma p-tau has prognostic value and its prediction of progression to AD has accuracy as well as CSF p-tau[109, 110]. Palmqvist et al. demonstrated the prediction of transformation to AD dementia at 4 years in MCI or cognitive impairment patients had a high AUC of 0.9 for p-tau181 (ADNI study) and 0.83 for p-tau217 (BioFINDER study)[109]. In addition, longitudinal research has demonstrated that p-tau in the plasma (especially p-tau217) rises over time in AD pre-clinical and prodromal stages, suggesting that it can be utilized to identify pharmacodynamic effects of medications[111].

It is still too early to widely utilize these plasma biomarkers to screen the general population without cognitive symptoms[112]. P-tau can be applied in clinical trials for patient recruitment, stratification, and monitoring therapeutic effectiveness[91]. Although plasma p-tau has a potential biomarker in clinical practice, p-tau181 or p-tau217 combined with Aβ42/Aβ40 ratio may provide a better evaluation of AD pathology in pre-clinical or prodromal stages, as well as diagnostic and prognostic value[113].

Blood ∂-synuclein

Because of its high degree of expression and synthesis by erythrocytes, ∂-syn could be identified in the blood[73]. Nevertheless, many studies have found inconsistent results when comparing the blood ∂-syn concentrations of PD patients to normal controls[114-116]. This could be related to the fact that red blood cells can be contaminated easily, as well as that different research utilizes different methods for sample collection and analysis[84].

Salivary biomarkers

Saliva is considered a promising biomarker because of several advantages including non-invasive, stress-free, easy and repeatable. Moreover, they do not require special storage conditions or clinician training[117]. Additionally, saliva has minimal to no danger of pathogen exposure or cross-contamination, is carried out easier than blood, does not coagulate, and is stable over time[118].

Most studies reveal higher levels of salivary Aβ42 in AD patients than in healthy controls, which is in contrast to CSF data, suggesting that salivary Aβ42 may be a specific and important biomarker for the diagnosis of AD[119, 120]. Nevertheless, other studies found a decrease in salivary concentrations[121, 122] or were unable to identify the presence of Aβ42 in saliva[123]. A variety of saliva sample collection, storage, processing, and analysis techniques, such as ELISA kit or an antibody-based magnetic nanoparticle immunoassay, as well as variations in the demographic and inclusion criteria, could all be contributing factors to the inconsistent results[119, 123].

The majority of research found that AD patients had higher salivary levels of p-tau as

well as p-tau/t-tau ratio[121, 124]. Whereas, salivary t-tau appears to decline or remain constant in patients when compared to healthy controls[121, 125]. However, salivary levels of t-tau and p-tau are broadly variable, and the p-tau/t-tau ratio did not significantly correlate with the CSF value in AD patients, which makes it difficult to consider salivary tau as a diagnostic biomarker[124].

Similar to CSF results, salivary t-∂-syn levels decreased in PD patients compared to healthy subjects. Additionally, salivary o-∂-syn and o-∂-syn/t-∂-syn ratio were demonstrated to be significantly higher in PD patients compared to healthy controls[126-128]. These results suggested that salivary t-∂-syn and o-∂-syn/t-∂-syn ratio might be used as a biomarker for PD diagnosis.

Novel candidate biomarkers for neurodegenerative diseases

A number of novel potential candidate biomarkers have been investigated, based on the corresponding pathophysiologic mechanisms, including synaptic dysfunction, neuronal injury, inflammation and glial activation. Nevertheless, the majority of these have yet to be validated and added to clinical guidelines.

Synaptic dysfunction

Synaptic dysfunction is defined as a disturbance in synaptic activity, and synapse loss is considered an early event in the pathophysiology of AD and other neurodegenerative disorders[129]. Neurogranin is a postsynaptic protein that is related to synaptic plasticity andlong-term potentiation[130]. CSF neurogranin has been proposed as a biomarker of early synapse loss and degeneration in AD and may predict progression of disease[131]. The study revealed that CSF neurogranin levels increase in the early clinical stages of AD and are specific to AD[132]. Other emerging biomarkers reflecting synaptic degeneration comprise of synaptosomal-associated protein 25 (SNAP-25)[133], synaptotagmin-1 (SYT-1)[134] and growth-associated protein 43 (GAP-43)[135], which increased in AD when comparing to healthy controls. CSF GAP-43 tends to be specific to AD and could help distinguish AD from other neurodegenerative diseases like PD and FTD[135].

Inflammation and glial activation

The majority of neurodegenerative disorders have primary characteristics of neuroinflammation, activation of microglial cells, and astrocytes[105]. YKL-40, also known as chitinase-3-like protein-1, is a glycoprotein that is produced in both astrocytes and microglia near Aß plaques and is related to t-tau and p-tau, revealing an involvement in the inflammatory conditions of AD[136]. Increased levels of CSF YKL-40 may be related to disease progression and may discriminate AD from DLB, PD, or vascular dementia[132]. Some findings reveal that plasma YKL-40 is elevated in people with early AD[137, 138], but additional research is required to confirm these results. Another marker expressed in microglial cells is soluble triggering receptor expressed on myeloid cells 2 (sTREM-2). CSF sTREM-2 was positively related to key neurodegenerative biomarkers including Aß42, p-tau, and t-tau[139]. Additionally, although CSF sTREM-2 levels were significantly higher in AD than controls, plasma sTREM-2 levels demonstrated no significant differences between groups[140]. Besides that, MCP-1 (monocyte chemotactic protein-1) is a proinflammatory signaling protein that regulates macrophage and monocyte recruitment, migration, and infiltration into inflammation locations[141]. CSF MCP-1

concentrations are detected in both the early and late stages of AD[132]. According to one study, increased plasma MCP-1 levels in AD patients are associated with the severity of disease and faster cognitive impairment[142].

Neuronal injury

Neurofilament light (NFL) is a significant biomarker for neuronal degeneration that is elevated in neurodegenerative, inflammatory, traumatic, and vascular disorders[143]. CSF NFL levels were highest in patients with AD, FTD, vascular dementia and could be used to evaluate disease progression in AD[144]. Concentrations of plasma NfL also increased in patients with AD[145] and FTD[146] when compared with controls. However, NFL's diagnosis potential in CSF is not better than other CSF markers and does not sufficiently distinguish between AD and other non-AD dementias[132]. Another potential biomarker reflecting neuronal injury is the neuronal calcium sensor protein visinin-like protein 1 (VLP-1). CSF VLP-1 levels were higher in AD patients compared to healthy controls[147]. VLP-1 is also used as a predictor for progression from MCI to AD[148]. Unlike NFL, VLP-1 can distinguish AD from non-AD dementias[149]. In conclusion, VLP-1 may be utilized together with NFL as a biomarker for neurodegeneration and disease progression in AD[105].

Conclusion

Because neuron degeneration and neuroplasticity depletion have already taken place in many brain regions by neurodegenerative disorders that are clinically diagnosed, it is crucial to have early and reliable diagnostic biomarkers for detection and preventive measures. Biomarkers for neurodegenerative disorders are necessary not only to improve clinical diagnosis but also to support the evaluation of therapeutic effec-tiveness. Aβ42, Aβ42/Aβ40 ratio, t-tau, p-tau181 or p-tau 217 biomarkers in CSF and PET can be utilized to better understand Aβ and tau pathology, increase clinical diagnostic accuracy of AD and predict the conversion of MCI to AD. CSF Aβ42 is the earliest biomarker to become abnormal in the preclinical stage of AD, whereas p-tau is considered a highly specific biomarker to discriminate AD from healthy controls as well as other dementias. However, because CSF is invasive and PET imaging is expensive, blood and saliva are promising biomarkers widely used in primary care. Blood biomarkers for AD have the crucial role of significantly transferring from CSF to the diagnosis of AD. Plasma p-tau181 or p-tau 217 has been demonstrated as a non-invasive and inexpensive biomarker in the diagnosis and prognosis of AD, especially when combining with plasma Aβ42/40 ratio in evaluating the progression in clinical trials. ∂-syn is a biomarker paid more attention to in the diagnosis of PD. Unfortunately, all attempts to develop an early diagnosis for PD were unsuccessful. The current methods to improve early diagnosis are premotor symptoms combined with nigrostriatal dopaminergic system failure on PET in the prodromal stage. Future studies will be needed to validate salivary biomarkers and novel potential biomarkers based on other pathophysiologic mechanisms.

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