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Review Article

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What is the Clinical Significance of Cerebrospinal Fluid Biomarkers in Parkinson's disease? Is the Significance Diagnostic or Prognostic?

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The clinical diagnostic criteria of Parkinson's disease (PD) have limitations in detecting the disease at early stage and in differentiating heterogeneous clinical progression. The lack of reliable biomarker(s) for early diagnosis and prediction of prognosis is a major hurdle to achieve optimal clinical care of patients and efficient design of clinical trials for disease-modifying therapeutics. Numerous efforts to discover PD biomarkers in CSF were conducted. In this review, we describe the molecular pathogenesis of PD and discuss its implication to develop PD biomarkers in CSF. Next, we summarize the clinical utility of CSF biomarkers including alpha-synuclein for early and differential diagnosis, and prediction of PD progression. Given the heterogeneity in the clinical features of PD and none of the CSF biomarkers for an early diagnosis have been developed, research efforts to develop biomarkers to predict heterogeneous disease progression is on-going. Notably, a rapid cognitive decline followed by the development of dementia is a risk factor of poor prognosis in PD. In connection to this, CSF levels of Alzheimer's disease (AD) biomarkers have received considerable attention. However, we still need long-term longitudinal observational studies employing large cohorts to evaluate the clinical utility of CSF biomarkers reflecting Lewy body pathology and AD pathology in the brain. We believe that current research efforts including the Parkinson's Progression Markers Initiative will resolve the current needs of early diagnosis and/or prediction of disease progression using CSF biomarkers, and which will further accelerate the development of disease-modifying therapeutics and optimize the clinical management of PD patients.

Key words: Parkinson's disease, Biomarker, Cerebrospinal fluid, alpha-synuclein, Progression markers

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease (AD). PD is a progressive and complex disease with heterogeneous clinical features including motor and non-motor symptoms. Although PD

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itself is not a direct cause of death, the broad spectrum of motor and non-motor symptoms causes a decrease in the quality of life and the life span of afflicted persons [1]. PD slowly progresses, and clinical manifestations of the disease are observed only after degeneration of over 50% of dopaminergic neurons in the basal ganglia, particularly in the substantia nigra (SN).

Parkinson's disease is typically diagnosed by clinical criteria, such as United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank Clinical Criteria or the National Institute of Neurological Disorders and Stroke (NINDS) Criteria. According to UKPDS criteria, the diagnosis of probable PD requires the presence of bradykinesia and at least one of the following clinical features: muscular rigidity, 4~6 Hz resting tremors, or postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction. In addition, three of the following supportive features are required: unilateral onset, resting tremors, progressive disorder, persistent asymmetry primarily affecting the side of onset, excellent response (70~100%) to levodopa, severe levodopa induced chorea (dyskinesia), levodopa response for 5 years or more, and a clinical course of 10 years or more [2]. In the NINDS criteria for PD diagnosis, clinical features are divided into group A and B and are composed of relevant criteria. There are three levels of diagnostic confidence differentiated by "possible", "probable" and a "definite" diagnosis of PD in the NINDS criteria [3].

The cardinal motor signs of PD are tremors, rigidity, bradykinesia and postural instability. The progression of PD pathology initiates from the brain stem and distributes caudo-rostrally to the neocortex through the mid-brain and basal ganglia (Fig. 1). The pre-motor symptoms of PD are largely associated with the distribution of pathology throughout the brain. Nevertheless, the procedures of clinical diagnosis seems to be straightforward when patients have a typical presentation, yet, only about 75% of the clinical diagnoses of PD are confirmed at autopsy ("definite" PD) [2]. In addition, other movement disorders with overlapping clinical symptoms (e.g., multiple system atrophy, corticobasal degeneration and progressive supranuclear palsy) decrease the accuracy of the clinical diagnosis of PD. There are several issues to concern the current clinical diagnostic tools; the relative low accuracy of clinical diagnoses at early stage, the progressive nature of the disease, and the difficulty in early diagnosis and in prediction of disease progression. In addition, clinical diagnosis does not reflect the etiology and pathophysiology of sporadic PD, which might limit the development of novel disease-modifying therapeutics. As the tool(s) to overcome the limitations of the clinical approaches, biochemical, imaging, and/or genetic biomarker(s) will play a role in the improvement of early diagnostic accuracy and predictive performance.

Biomarkers, defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" [4], have clinical significance of, but not limited to the following: 1) early diagnostic potential, 2) predictive performance of disease progression, 3) a bridge between biochemical and molecular pathogenesis and clinical manifestations, 4) tools for differential diagnosis from other movement disorders, and 5) tools for therapeutic optimization and monitoring in PD. In addition, the biomarkers will provide the insight on the pathogenesis of PD. In particular, given the heterogeneous clinical features and progression in PD, the biomarkers may have fingerprints of the heterogeneity of the disease. PD is a disease of the central nervous system, and therefore, cerebrospinal fluid (CSF) is the most reliable source of

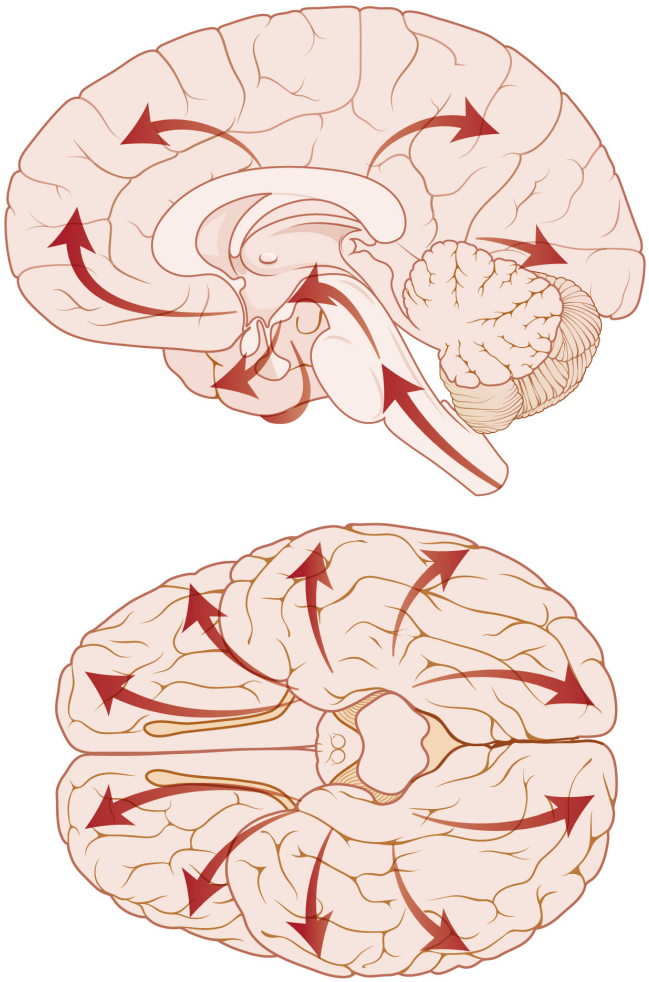

Fig. 1. Evolution of PD pathology from caudal area (medulla oblongata and pontine tegmentum) to the neocortex. Initially, pathologic legion (usually Lewy neurite) occurs in the dorsal IX/X motor nucleus and anterior olfactory nucleus without typical motor symptoms. The pathology expands to the brain stem with upward course through the basal ganglia, and finally involves neocortical areas.

biofluid, since CSF is in direct contact with the extracellular space of the brain.

In this paper, we discuss the clinical significance of CSF PD biomarkers. On the one hand, CSF PD biomarkers may have diagnostic utility, but on the other, we should consider the utility for the prediction of PD progression. First, we describe several pathogenic mechanisms, including protein misfolding, defective protein degradation, mitochondrial dysfunction and neuroinflamamtion. We then summarize CSF biomarker candidates based on the molecular aspects of proposed PD pathogenesis, and clinical utility of these CSF biomarkers for diagnostic and prognostic performance. In addition, we introduce a large-scale longitudinal, observational, and multinational prospective clinical study for the prediction of heterogeneous disease progression using CSF biomarkers, i.e., a Parkinson's Progression Markers Initiative (PPMI) study.

PROTEINOPATHY IN PD PATHOGENESIS

The most well-known pathologic hallmark of PD is the Lewy body (LB) in the SN. The LB is a circular, eosinophilic inclusion, and protein aggregates including alpha-synuclein (α-syn), neurofilaments and ubiquitin are present in this intraneuronal inclusion body. The major proposed hypotheses of PD pathogenesis are related to the LB-related proteinopathy (Fig. 2), yet, the mechanisms of the pathogenesis of PD are largely unknown. In addition, much evidence suggests that LB may be not specific to PD since LBs are found not only in PD patients but also in normal, elderly subjects and in patients with other neurodegenerative diseases.

A key protein in the LB is α-syn, a protein that is 140 amino acids long and approximately 16 kDa in size. α-Syn has been intensely researched due to the fact that mutation or multiplication of the

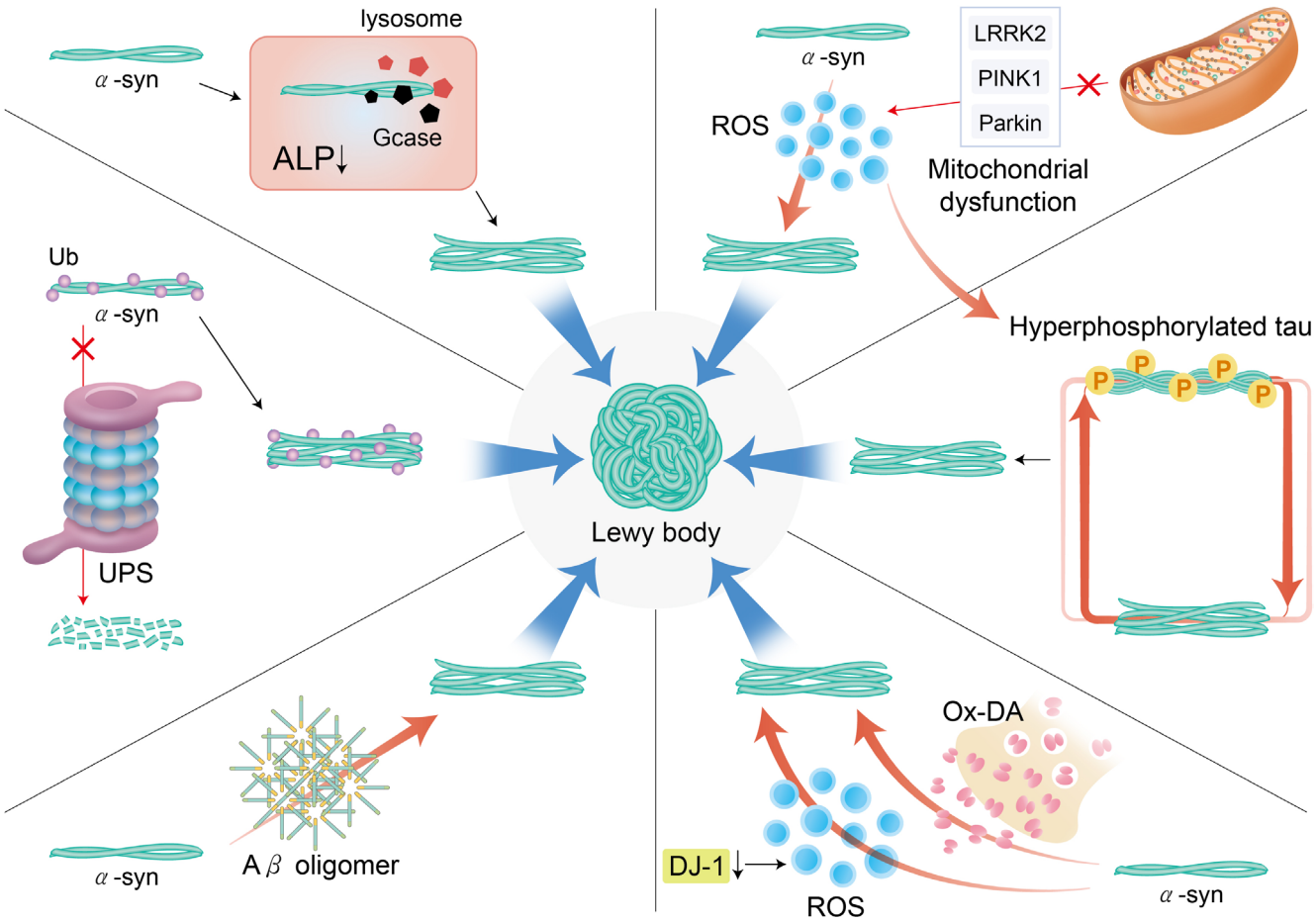

Fig. 2. Proposed pathogenic mechanisms of α-syn-related Lewy body formation in PD. The failure of clearance of α-syn and/or acceleration of α-syn aggregation is associated with failure of protein quality control systems, such as ubiquitin-proteasome system (UPS) or lysosomal degradation (e.g., autophagy-lysosomal pathway; ALP). The mitochondrial dysfunction caused by genetic and environmental factors, auto-oxidation of dopamine (Ox-DA) or decreased antioxidant molecules (e.g., DJ-1) produces unfavorable reactive oxygen species (ROS). Overproduction of ROS accelerates α-syn aggregation, and which is accelerated by interaction with Aβ and tau oligomers and vice versa.

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α-syn-encoding *SNCA* gene is known to cause familial PD [5, 6]. The physiological function of α-syn requires further elucidation, although much evidence suggests that the synaptic unfolded monomeric α-syn may play roles in neurotransmission and synaptic vesicle release [7-9]. Against the normal function of monomeric α-syn, the formation of aggregated α-syn, particulary of oligomeric α-syn, gains toxic properties rather than a loss of functions. Several reasons including genetic factors induce the formation of aggregated α-syn, and this step would be a critical step toward the formation of LB pathology. Besides mutant α-syn, the increased "normal" α-syn is itself a cause of toxicity via an enhanced tendency of the production of misfolded proteins followed by oligomer, pre-fibrillar and fibrillar structure formations. The acceleration of α-syn aggregate, particularly of α-syn toxic oligomers could be mediated by diverse events, including point mutations in the *SNCA* gene, lipid peroxidation [10], phosphorylation of α-syn at Ser219, a decrease in pH, the presence of metal ions, tissue transglutaminase activation, perturbation of dopamine homeostasis, or endoplasmic reticulum (ER) stress [11, 12, and reviewed in reference 13]. These toxic species of α-syn further produce insoluble amyloid-like fibrils and mediate mitochondrial dysfunction, and perturbatioin of lysosomal function and calcium homeostasis [14-16].

A misfolded protein is normally refolded by a molecular chaperone or removed via the ubiquitin-proteasome system (UPS) and the authophagy-lysosomal pathway (ALP). The failure of these protein quality control systems contribute to ER stress and the production of toxic proteins, like α-syn oligomers, and may lead to pathological cascades [17]. In fact, it was found that the proteasome activity in the SN of PD patients is lower than that of a matched control [18], coupled with the presence of ubiquitinated proteins in the LB [19]. The lysosomal degradation pathway is attenuated by the alteration in the function of glucocerebrosidase, a lysosomal enzyme. The glucocerebrosidase-mediated attenuation of lysosomal activity induces accumulation of abnormal α-syn and toxic aggregates, and increases the amount of glucosylceremide followed by a stabilization of soluble oligomeric intermediates, and vice versa (Fig. 2). In addition to α-syn, a proteomic analysis found that many other proteins are present in LBs, including kinases, ubiquitin ligases, chaperones, and proteins involved in protein folding, membrane trafficking and oxidative stress [20].

MITOCHONDRIAL DYSFUNCTION AND INFLAMMATION IN PD PATHOGENESIS

Since Langston and colleagues reported that several illicit drug users, aged from 26 to 42 years, have developed acutely a severe form of Parkinsonian syndrome [21]. The mitochondrial dysfunction through the inhibition of complex I of the electron-transport chain by a contaminant, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) has been extensively investigated. Rotenone is another complex I inhibitor. These neurotoxins are widely used as agents to promote PD in animal models. The mitochondrial complex I inhibition by MPTP or rotenone causes ATP depletion, excitotoxicity, increased mitochondrial free-radical generation and, consequently, oxidative stress. In addition, mitochondrial dysfunction is likely to induce apoptosis-mediated cell death. Indeed, increased levels of oxidatively modified proteins and nitrated proteins have been identified in the SN of PD patients compared to controls [22-24], while a reduction of mitochondrial complex I activity, glutathione content [25] and ATP synthase expression [26] in the post-mortem brain of PD patients was observed. The increased oxidative stress in the SN induces α-syn misfolding and aggregation, selective dopaminergic neuronal injury and cell death, and consequently development of motor symptoms in PD patients. However, it is largely unknown what causes the increase of oxidative stress in the SN of sporadic PD patients.

In the SN of PD patients, microglial activation, astrogliosis and lymphocytic infiltration were observed [27], and an increase of the proinflammatory cytokines including tumor necrosis factor-α, interferon γ and interleukins, and of the enzymes involved in inflammatory process, such as inducible nitric oxide synthase and cyclooxygenase 2, were observed [28]. Studies using CSF or serum of PD patients also showed an increased expression of inflammatory cytokines or increased markers of microglial activation, indicating that the inflammatory processes might be involved in the pathogenesis of PD.

GENETICS

The monogenetic causes of autosomal dominant PD are mutations in *LRRK2* (leucine-rich repeat kinase 2; PARK8), *SNCA* (α-syn; PARK1/4), *VPS35* (vacuolar protein sorting 35 homolog), or the *EIF4G1* (eukaryotic translocation initiation factor-4-gamma 1) gene. Mutations in *PRKN* (Parkin, E3 protein ligase, PARK2), *PINK1* (PTEN-induced kinase 1, PARK6), *DJ-1* (daisuke-junko-1, PARK7), *ATP13A2* (lysosomal P-type ATPase, PARK9), *PLA2G6* (calcium independent phospholipase A2, PARK14), *FBXO7* (F-box only protein 7, PARK15), or *DNAJC6* (neuronal-specific clathrin-uncoating co-chaperone auxilin) are responsible to autosomal recessive forms of PD [reviewed in reference 29]. These familial forms of PD (fPD) caused by a specific mutation only account for approximately 10% of total PD

cases. However, the discovery of genes causing fPD has provided new insights into the molecular pathogenesis of PD. For example, fPD caused by mutations in *LRRK2* encoding dardarin is the most common fPD, and LRRK2 involves the phosphorylation of α-syn or the tau protein and the autophagy-lysosomal pathway. The multiplication of *SNCA* gene causes overproduction of α-syn followed by aggregation in connection with an *LRRK2* mutation, and is related to atypical clinical features. Moreover, a genome-wide association study revealed that the variants of these genes were genetic risk factors of sporadic PD. Therefore, clinical studies providing genetic implication in PD could open the discovery of novel biochemical biomarkers in the field of PD.

ALZHEIMER PATHOLOGY IN PD

AD, the most common neurodegenerative disease, is pathologically characterized by amyloid plaque and neurofibrillary tangles in the cerebral cortex. In PD patients, the prevalence of cognitive dysfunction is higher than that in the normal population, and the risk of developing dementia is six-fold compared to subjects without PD [reviewed in reference 30]. In addition, post-mortem studies provide evidence that AD pathology is common (32~44%) in the PD brain, particularly in patients with PD dementia [31-33]. In connection with the mixed pathology of LBs with AD pathology, it has been suggested that the heterogeneous clinical features and progression of the disease may be associated with AD pathology. The cognitive impairment, a common non-motor co-morbidity of PD, progresses to overt dementia in approximately 80% of PD patients with wide variations in duration from onset of PD to the onset of dementia [30, 34]. Given the fact of increased cost of care and the higher mortality in PD dementia patients, the development of dementia in PD is critical to the clinical management of PD patients. In regards to the molecular aspects, there are interactions between α-syn and AD biomarkers (amyloid beta (Aβ) and tau proteins). In fact, several in vitro and in vivo studies provided evidences that Aβ induces α-syn aggregation [35], α-syn enhances $A\beta_{1-42}$ aggregation [36], and α-syn increases tau hyperphosphorylation [37] and tau inclusions in neurons [38]. Therefore, the biomarkers predicting the progression of PD are very important in clinical settings as well as for understanding the progression of the disease.

CSF BIOMARKERS RELATED TO PATHOGENESIS

Based on the proposed mechanisms of PD pathogenesis, numerous clinical studies evaluated the diagnostic or prognostic potential of CSF biomarkers in their cohorts. In this review, we searched previous literature using the keywords "CSF biomarker" and "Parkinson's disease" in a PUBMED search. We included cross-sectional and longitudinal studies that enrolled at least 100 subjects of PD patients and controls to diagnose PD or compare the levels of biomarker between PD and controls or other neurodegenerative disease, and summarized in Table 1 and 2, respectively, according to the pathogenic mechanism. However, small studies that provided novel biomarkers and new analytical technology or studies with long-term follow-up in a limited number of subjects were also included. Most previous clinical studies suggested that the CSF biomarkers related to the pathogenesis, as described above, have a limited diagnostic utility.

CSF Biomarkers related to proteinopathy

α-Syn is the most extensively studied CSF biomarker, but results have not been consistent. The level of CSF α-syn in PD was lower than in the control group in numerous studies, while there have been no significant differences in other studies. The higher levels of α-syn oligomer or phosphorylated α-syn in PD, as compared to the controls, have also not been consistent. The attempts to measure the diagnostic sensitivity (sens.) and specificity (spec.) using the optimal cut-off values of α-syn have failed to get the high sens. and spec. that are clinically applicable (> 85% of sens. and spec.). A recent clinical study reported that the activities of endolysosomal enzymes (β-galatosidase and cathepsin E) in CSF of PD were significantly different from those in healthy controls; however, the levels were significantly overlapped between the groups. Another study measuring the level of CSF ubiquitin C-terminal hydrolase (UCH-1) in PD, other atypical Parkinsonism, tauopathy and control subjects reported a significant difference of the UCH-1 levels among groups with a relatively high sens. but limited spec. to diagnose PD vs healthy controls (87% of sens. and 79% of spec.). A chaperone glycoprotein, clusterin is associated with Aβ clearance and cell viability, and therefore, it was reported as one of the AD biomarkers for early detection [39]. The increased level of clusterin in the brain implicates the regenerative response process and may inhibit the aggregation of α-syn [40]. However, the results for the level of CSF clusterin level in PD as compared to the controls were not consistent [40, 41].

Biomarkers related to oxidative stress

As described above, oxidative stress is one of the pathogenic mechanisms of PD. DJ-1 is related to oxidative stress, and has been linked to both familial and sporadic PD [42]. Waragai et al reported that the level of CSF DJ-1 in PD was higher than the non-PD control using western blotting [43]. However, using bead-based Luminex analysis, recent studies reported that the level of CSF

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Table 1. Diagnostic sensitivity and specificity of various CSF biomarkers reported in previous clinical studies for early diagnosis of PD from controls, and their related pathogenesis

Subjects (N)	Major findings related to PD pathogenesis in PD group vs. control group					Diagnostic performance* (Sens., Spec.; %)	References
	Protein aggregation	Protein degradation	Oxidative stress	AD pathology	Combination		
PD (71), OND (45)	↓ α-syn ↔ o-syn ↑ o-syn/α-syn	↓ β GCase ↑ β HAase		↔ t-tau ↔ p-tau	o-syn/α-syn + βGCase + age[a]	82, 72[a]	Parnetti et al. [53]
PD (53), HC (50)	↓ α-syn[b] ↓ α-syn/t-protein[c]					56, 74[b] 70, 74[c]	Van Dijk et al. [65]
PD (58), HC (52)		↑ α FUCase ↑ β Gal ↓ Cathepsin E			↔ α-FUCase + β-Gal[d]	63, 63%[d]	Van Dijk et al. [68]
Discovery[†] PD (83), HC (51) Others (69)	↓ α-syn[e] ↑ p-syn[f] ↑ p-syn/α-syn[g] p-syn+α-syn[h]					63, 82 / 83, 59[e] 30, 86 / 82, 41[f] 54, 87 / 81, 64[g] 61, 86 / 81, 64[h]	Wang et al. [54]
Validation[†] PD (109), HC (71) AD (50), Others (44)	↓ α-syn ↔ p-syn ↑ p-syn/α-syn p-syn+ α-syn[i]					57, 56 / 79, 36[i]	
PD (126), NC (137) MSA (32), AD (50)	↓ α-syn[j]		↓ DJ-1[k]	↓ $A\beta_{42}$ ↓ t-tau[l] ↓ p-tau[m] ↓ p-tau/ t-tau	↔ Flt3L ↔ Fractalkine DJ-1+Flt3L[n]	92, 38[j] 94, 50[k] 91, 25[l] 90, 33[m] 94, 60[n]	Shi et al. [45]
PD (117), HC (132) AD (50)	↓ α-syn[o]		↓ DJ-1[p]		α-syn + DJ-1[q]	94, 50[o] 93, 39[p] 95, 42[q]	Hong et al. [44]

*The values with superscripts indicated the diagnostic performance of the alphabetically matched individual biomarker or combination. †Discovery and validation indicate the cohort to discover biomarkers and independently validate these, respectively. Two different pairs of sensitivity and specificity indicate the values when specificity (left) or sensitivity (right) is anchoring >80%, respectively.
Abbreviations: Sens., Sensitivity; Spec., Specificity; OND, other neurologic disease control; HC, healthy controls; MSA, multiple system atrophy; t-protein, total protein in CSF; o-syn; oligomeric α-syn; p-syn, phosphorylated α-syn; βGCase, β-glucocerebrosidase; βHAase, β-hexoaminidase; αFUCase, α-fucosidase; βGal, β-galactosidase.

DJ-1 in PD was lower than healthy controls with a high sens. (94% and 93%) but limited spec. (50% and 39%) [44, 45]. Interestingly, the specificity of CSF DJ-1 for PD diagnosis was slightly improved when subjects aged greater than 65 years only were included. Uric acid, a highly abundant antioxidant in body fluid, could serve as an endogenous protector against oxidative stress in PD. Despite the tenfold gradient of urate concentration from blood to CSF, there is a consistently tight correlation between serum and CSF urate concentration with limited passive diffusion. Available data on CSF urate for PD diagnosis are very limited [46, 47]. However, the DATATOP study, one of the largest longitudinal cohort studies to date, reported an inverse relationship between CSF urate concentrations at baseline and the rate of PD progression [48]. The level of 8-hydroxydeoxyguanosine (8-OHdG), a product of DNA oxidation in PD, was higher than other neurologic disease controls [49]. However, the indicators related to oxidative stress are not specific to PD but are related to wide variety of the diseases or environmental factors. Therefore, there are no useful biomarkers related to the oxidative stress for PD diagnosis and the prediction of the disease.

Biomarkers related to AD

The level of CSF $A\beta_{1-42}$, total tau (t-tau) and phosphorylated tau at position of Thr181 (p-tau) are well-known AD biomarkers. In AD patients, the level of CSF $A\beta_{1-42}$ is lower, while t-tau and p-tau levels are higher than the CSF levels of matched healthy controls. Although these AD biomarkers could differentiate AD patients from PD patients, when the levels of AD CSF biomarkers in PD were compared with those in controls, the results were not consistent. However, the level of CSF $A\beta_{1-42}$ could be a biomarker

Table 2. Comparison of CSF biomarker levels related to pathogenesis between PD patients and controls or other neurodegenerative diseases

Subjects (N)	Major findings related to PD pathogenesis in PD group vs. control group				References
	Protein aggregation	Oxidative stress	AD pathology	Combination	
Initial PPMI cohort; PD (63), HC (39)	↓ α-syn		↓ $A\beta_{42}$, ↓ p-tau ↓ t-tau/ $A\beta_{42}$		Kang et al. [64]
PD (78), HC (48)	↓ α-syn				Mollenhauer et al. [66]
PD (99), HC (46)			↓ $A\beta_{42}$, ↓ $A\beta_{38}$ in PD, ↓ $A\beta_{42/40}$, ↓ $A\beta_{38/40}$ in PIGD		Alves G et al. [67]
PD+PDD (123),HC (107), AD (48), Others (78)	↓ α-syn		↔ $A\beta_{42}$ ↓ t-tau		Hall et al. [69]
PD (58), HC (57)	↔ α-syn				Aerts et al.[70]
PD (55), HC (76) PDD (20) DLB (20)		↔ UA		↔ UA + t tau ↔ UA + $A\beta_{42}$	Maetzler et al.[46]
Training† PD (51), HC (76) AD (62), Others (84)	↓ α-syn ↓ α-syn/t-protein		↔ t-tau		Mollenhauer et al. [71]
Validation† PD (273), NC (23), Others (111)	↓ α-syn ↓ α-syn/t-protein		↔ $A\beta_{42}$, ↔ t-tau		
PD (217), HC (26)				↑ [XAN]/ [HVA]	LeWitt et al. [72]
PD (41), HC (150) PD-CI (69), AD (49), MCI (24)			↔ $A\beta_{42}$, ↔ t-tau, ↓ p-tau		Montine et al. [73]
PD (109), HC (36) AD (20)			↓ $A\beta_{42}$, ↓ $A\beta_{38}$, ↓ $A\beta_{40}$ ↔ t-tau, ↔ p-tau		Alves et al. [74]

†Training and validation set indicate the cohort to discover biomarkers and independently validate these, respectively.
Abbreviations: HC, healthy controls; PDD, PD dementia; DLB, dementia with Lewy bodies, PD-CI, PD with cognitive impairment; MCI, mild cognitive impairment; t-protein, total protein in CSF; UA, uric acid; XAN, xanthine; HVA, homovallinic acid.

to predict the progression of cognitive decline in PD patients. In fact, PD patients with low (pathologic) CSF $A\beta_{1-42}$ levels exhibited a more rapid cognitive decline as compared to the patients with normal CSF $A\beta_{1-42}$ levels [50, 51]. For tau species, the results also were not consistent. These results may have resulted from the different disease stages of PD (e.g., PD without cognitive decline vs. PD dementia), different control groups and different methodology to measure AD biomarkers among the studies. Therefore, studies in a large cohort of early stages of PD and matched healthy controls should be conducted to evaluate the diagnostic and prognostic potential of AD biomarkers in PD. In connection with this, the Parkinson's Progression Markers Initiative (PPMI) study, a large (over 600 subjects including over 400 early drug-naïve PD patients and 200 matched healthy controls), multinational, 5-year longitudinal study is on-going to discover and validate CSF biomarkers of PD.

CLINICAL UTILITY OF CSF BIOMARKERS

Diagnostic CSF biomarkers, single vs combination

The level of α-syn in CSF is the most studied biomarker candidate for PD diagnosis. However, as demonstrated in the clinical utility of CSF biomarkers (i.e., $A\beta_{1-42}$, t-tau and p-tau) in AD, the combination of two or more biomarkers may increase the diagnostic performance as compared to the performance of a single biomarker [52]. Based on the in vitro evidence for possible interactions between α-syn and AD biomarkers, several studies reported the diagnostic performance of a single (α-syn) or of multiple CSF biomarkers [45,46]. However, none of the single or multiple CSF biomarkers showed clinically reliable diagnostic sens. and spec., although individual CSF biomarkers in PD were significantly different from those in the matched control groups. It should be noted that α-syn is abundantly expressed not only in the brain but also in peripheral blood cells. Therefore, the contamination of blood cells during the CSF collection procedure (traumatic lumbar puncture) will largely increase the

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Table 3. Clinical performance of various CSF biomarkers reported in previous clinical studies for differential diagnosis of PD from other neurodegenerative diseases

PD vs PSP	Sens., Spec. (%)	PD vs MSA	Sens., Spec. (%)	PD vs aPS	Sens., Spec. (%)	PD vs AD	Sens., Spec. (%)
p-syn	63, 83 [54] 84, 58 [54]	α-syn	91, 25 [45]	UCH-1	77, 58 [75]	α-syn	93, 63 [44] 92, 62 [45]
p-syn/α-syn	61, 83 [54] 84, 58 [54]	p-syn	64, 86 [54] 82, 50 [54]	NF-L	86, 81 [77]	DJ-1	93, 63 [44] 94, 55 [45]
p-syn+α-syn	72, 83 [54] 86, 63 [54]	DJ-1	78, 78 [76] 94, 55 [45]			$A\beta_{42}$	91, 40 [45]
		Flt3L	99, 95 [45]			t-tau	92, 68 [45]
		p-tau/t-tau	90, 96 [45]			p-tau	93, 87 [45]
		p-tau/$A\beta_{42}$	80, 20 [45]			α-syn+DJ-1	95, 50 [44] 92, 63 [45]
		α-syn, p-tau, t-tau	90, 65 [45]			α-syn+$A\beta_{42}$	93, 84 [45]
		DJ-1+t-tau+p-tau	82, 81 [76]			t-tau/$A\beta_{42}$	92, 84 [45]
		DJ-1+Flt3L	91, 60 [45]			p-tau/$A\beta_{42}$	93, 90 [45]

Abbreviations: PSP, Progressive supranuclear palsy; aPS, Atypical parkinsonism; Flt3L, Flt3 ligand; NF-L, Neurofilament Light protein, p-syn, phosphorylated α-syn.
Numbers in parenthesis indicate reference numbers.

measured level (pre-analytical bias) of CSF α-syn [45]. However, there was little information for the blood contamination effect on the level of CSF α-syn and its diagnostic performance for PD diagnosis in several of the previous reports. The level of another PD pathogenesis-related CSF biomarker, DJ-1, is also influenced by blood contamination. Recent clinical studies with a large cohort reported that CSF DJ-1 and α-syn levels in PD were lower than those in matched controls [45, 46]. However, the diagnostic performance of DJ-1 is disappointing as described above. The low specificity of these proteins is still observed after exclusion of subjects with high CSF hemoglobin levels. When the levels of DJ-1 and the Flt3 ligand in CSF were combined, the sens. and specificity for diagnosis of PD against healthy controls were 94% and 60%, respectively [46]. A recent study also reported the moderate diagnostic sens. (82%) and spec. (71%) even when α-syn (total and oligomeric), glucocerebrosidase and age were combined to differentiate PD patients from neurologic control subjects [53]. There are several issues in previous studies need to be addressed. For example, the diagnostic performance of single or multiple CSF biomarker(s) that were evaluated in previous studies were evaluated in different stages of PD patients and different sets of matched controls (e.g., healthy controls vs. neurologic controls). In addition, the methodologies to measure CSF biomarkers were different among clinical studies, and many studies reported the diagnostic performance in a cohort with a relatively small number of subjects. Therefore, more studies should be conducted in a large cohort with early-stage PD patients and matched healthy controls recruited from multiple qualified centers to test the diagnostic performance of CSF biomarkers.

To differentiate PD patients from other neurodegenerative diseases, CSF α-syn, Flt3 ligand, or α-syn plus AD biomarkers seems to be good biomarkers (Table 3). For example, the level of CSF Flt3 ligand in PD was significantly higher than that in patients with multiple system atrophy with excellent sens. (99%) and spec. (95%) [46]. The combination of total and phosphorylated α-syn level in the CSF showed moderate sens. (82%) and spec. (63%) to differentiate PD from PSP [54].

CSF biomarkers for disease heterogeneity and disease severity

It is well known that the clinical heterogeneity of PD is remarkable. For example, the motor phenotypes of PD and age of onset are a way to classify PD patients [55, 56, and reviewed in reference 57]. Longitudinal follow-up studies revealed that PD patients with tremor-dominant (TD) motor phenotypes followed a benign clinical progression (e.g. slow progression of cognitive decline and lower mortality rate) as compared to patients with postural instability and gait disturbance (PIGD) phenotypes [55, 58, 59]. The heterogeneity of PD was not only observed in clinical characteristics, but also in the pathology [60, 61]. Although it should be further clarified, the concurrence of amyloid pathology in a PD brain that is frequently observed, might be a factor to determine the clinical heterogeneity of PD. In connection with the malignant progression of a PIGD phenotype as compared to a TD phenotype,

recent studies reported that PD patients with low CSF $A\beta_{1-42}$ levels showed a rapid progression of cognitive decline as compared to patients with normal CSF $A\beta_{1-42}$ [51,52]. The development of dementia in PD patients is associated with a higher mortality rate and poorer activity of daily living, as compared to non-demented patients. Therefore, the convergence of synucleinopathy, tau and amyloid pathology may act synergistically to confer a worse prognosis of PD [reviewed in reference 62].

The disease severity of PD can be determined by the Unified Parkinson's Disease Rating Scale (UPDRS) scores or Hoehn and Yahr staging (H&Y). There are several studies showing that glucocerebrosidase activity and t-tau levels in CSF [53], phosphorylated α-syn, or the fractalkine/$A\beta_{1-42}$ ratio, were significantly associated with UPDRS scores or H&Y.

Prognostic CSF biomarkers and the Parkinson's Progression Markers Initiative (PPMI) study

As described above, the motor phenotype in PD may be a good clinical marker to predict disease progression. However, there are inevitable limitations to use this for early-stage PD patients as a prognostic marker. Indeed, the motor phenotype at early stages of the disease is not stable, and many patients with a TD phenotype can change to a PIGD phenotype as the disease progresses [63]. In addition, a significant proportion of early-stage PD patients showed mixed or intermediate motor phenotypes. Furthermore, the motor phenotype is easily influenced by pharmacotherapy. Therefore, the prediction of disease progression by biochemical, imaging and/or genetic biomarkers contributes more. Recent evidence that the level of CSF $A\beta_{1-42}$ or the amyloid plaque burden is a prognostic biomarker to predict the cognitive decline in PD patients has been reported. However, biomarkers related to the progression of other symptoms including motor symptoms have been limited.

Recently, the Parkinson's Progression Markers Initiative (PPMI), a five-year international multicenter, prospective, longitudinal observational study, was designed to discover and validate biomarker(s) that predict the progression of PD in a large cohort of drug naïve early-stage PD patients and matched healthy controls (HC). A preliminary study to characterize the CSF biomarkers (α-syn and AD biomarkers) and clinical features at baseline in an initial 102 subjects reported that levels of α-syn, t-tau, p-tau and $A\beta_{1-42}$ in the CSF of PD patients were lower than those of HC, and the lower levels of CSF biomarkers may be associated with PIGD phenotypes rather than the TD phenotype [64]. However, results from other previous studies do not agree with this result, particularly regarding the levels of t-tau and p-tau. Currently, the measurement of α-syn and AD biomarkers in baseline samples from whole PPMI subjects recruited from 24 qualified centers was completed, and therefore the prognostic performance of baseline CSF biomarkers levels through the longitudinal follow-up of disease progression will be determined. The PPMI study has several significant implications in the field of PD biomarkers. First, the PPMI is a collaborative effort of PD researchers with expertise in biomarker development, clinical study design and implementation, bioinformatics, statistics, and data management. Secondly, the PPMI study has a large cohort including drug-naïve early-stage PD, HC and even subjects without evidence of dopamine deficits. Thirdly, the PPMI would allow us to better define subgroups to more effectively assess potential disease modifying therapies. Finally, the longitudinal design and regular measurement of CSF biomarkers levels will further allow us to assess the temporal patterns of biomarker changes.

CONCLUSION

The major clinical symptoms which are involved in the clinical diagnostic criteria are developed when most dopaminergic neurons have undergone degeneration. Although other non-motor symptoms such as autonomic symptoms or sleep disturbances are likely developed before the motor symptoms, these are non-specific. Therefore, we need reliable biomarker(s) underlying fundamental molecular features of pathogenesis and neuropathology to detect PD at an early stage, e.g., at the prodromal stage. However, the reliable diagnostic biomarkers in the most brain-specific body fluid, CSF, are currently lacking. Besides early diagnostic biomarkers, the prediction of the heterogeneous progression of PD is another clinical unmet need. Several studies have provided evidence that concurrent AD pathology in the PD brain plays a role in cognitive decline in PD, and therefore, CSF AD biomarkers may represent reliable predictive biomarkers. To develop the predictive biomarkers in the PD field, the longitudinal study with a large qualified cohort is currently limited. The PPMI study, the largest multicenter longitudinal observational study in early-stage PD and HC will lead to breakthroughs in predictive biomarker development. Of course, in combination with CSF biomarkers, imaging and genetic biomarkers will play roles in the understanding the underlying pathogenesis of heterogeneous clinical features and the progression of the disease. These efforts will give us an answer(s) to the question, "what is the clinical significance of CSF biomarkers, diagnostic, prognostic or both?".

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