α-Syn-PMCA in cerebrospinal fluid has diagnostic potential in Parkinson's disease

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Parkinson's disease (PD) is the second most common neurodegenerative disease, with the prevalence of approximately 1% at age >60 years and 4% at age >80 years worldwide (1,2). The major pathological findings in PD are the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of intraneuronal inclusions, Lewy bodies (3). Clinically, PD is characterized by motor symptoms, including bradykinesia, rigidity, resting tremor, and postural instability (4). PD is also associated with a high incidence of various non-motor symptoms, such as hyposmia, constipation, sleep problems, dysautonomia and psychological symptoms (4,5).

Being a complex disease, PD has three stages, gradually progressing from preclinical stage, prodromal stage to the clinical stage. Preclinical stage refers to the initiation of neurodegenerative processes without obvious symptoms and signs (6). Prodromal stage is a transition period during which symptoms and signs are noticeable but not enough to confirm the diagnosis. Clinical stage is defined by the presence of typical PD symptoms and signs (7). Diagnosis of PD in living patients is largely based on clinical symptoms. These clinical features have been outlined in the United Kingdom Brain Bank Criteria (8) and MDS Clinical Diagnostic Criteria (9). However, PD shares some clinical profiles with several other neurodegenerative diseases, such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), complicating its diagnosis. The diagnostic error rate can be as high as 25% in early stage of the

disease (10). The molecular imaging technologies such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) have been increasingly used to support the clinical diagnosis of PD, but these technologies often cannot differentiate PD from related neurodegenerative diseases (11). In another common neurodegenerative disease—Alzheimer's disease (AD), the quantification of cerebrospinal fluid (CSF) proteins including tau protein, phosphorylated tau protein and amyloid-β (Aβ) has been introduced to complement the clinical criteria (12). In parallel, the quantification of α-synuclein (α-Syn) in CSF has been proposed as a diagnostic biomarker for PD.

Abnormal filamentous aggregates of misfolded a-Syn are the major components of Lewy bodies in the brains of patients with PD, MSA and DLB, which are termed as synucleinopathies (13). Both mutations in the gene *SNCA* in familial PD and the risk factors of common genetic variabilities in *SNCA* for sporadic PD suggest the critical role for α-Syn in the etiology of the disease (14). Misfolded α-Syn might be the triggering event leading to the subsequent pathologic abnormalities (15,16). Therefore, detection of soluble misfolded α-Syn oligomers in biological fluids including plasma, conditioned cell media, and CSF might represent a good strategy for biochemical diagnosis of PD. In a study recently published in *JAMA Neurology*, a team led by Claudio Soto at the University of Texas Houston Medical School, adapted protein misfolding cyclic amplification (PMCA) for highly sensitive detection of

α-Syn aggregates (α-Syn-PMCA) and used it to distinguish CSF samples obtained from patients affected by PD from those of individuals affected by other neurologic diseases (17).

The PMCA is a technology first described in 2001 that enables ultrasensitive detection of misfolded aggregates through amplification of the misfolding and aggregation process *in vitro* (18). The PMCA technique was well known to neuroscientists for its high sensitivity to detect misfolded prion protein in the blood and urine of Creutzfeldt-Jakob disease's patients (19). This technique was also adapted to detect Aβ oligomers circulating in the CSF of patients with AD to distinguish AD from those with other forms of dementia or neurodegenerative diseases in 2014 (20).

In a cohort study done in German and Japanese patients, the level of α-Syn was screened and compared between PD patients (n=76) and controls with related neurological diseases (n=97) via the PMCA technique. Claudio Soto and colleagues used oligomeric seeds prepared *in vitro* from purified recombinant human α-Syn to optimize and implement the conditions for α-Syn-PMCA. Fortunately, this novel α-Syn-PMCA assay was shown to have 88% sensitivity and 97% specificity for correctly identifying PD from other neurologic disorders. "*The major advantage of α-Syn-PMCA assay is all-or-none, which could offer a much easier interpretation of the results and no overlapping with control samples*," concludes Claudio Soto. "*Considering that collection of human CSF is a moderately invasive procedure, we are currently attempting to optimize a blood-based α-Syn-PMCA assay*." The research group also found that α-Syn-PMCA values were significantly correlated with the scores on the Hoehn and Yahr scale in both PD cohorts. These data indicated the kinetic factors of α-Syn aggregation were positively correlated with disease severity in PD. Thus α-Syn-PMCA was assumed to be useful in monitoring disease progression and studying the efficacy of therapeutic interventions.

There are also some limitations for the report. Firstly, samples used for the study were defined by clinical diagnosis and were not pathologically confirmed. Future studies containing pathologically confirmed PD and other neurologic disorders samples should be needed to estimate the true sensitivity and specificity of α-Syn-PMCA. In addition, α-Syn-PMCA of the current format cannot differentiate PD from other synucleinopathies, such as MSA and DLB. In Claudio Soto's report, all 10 of the DLB samples and 8 of the MSA samples were positive in α-Syn-PMCA testing, which was similar to that in PD. In summary, Claudio Soto and colleagues' study indicates that α-Syn-PMCA may be helpful in early diagnosis and preclinical identification of prodromal PD patients. Further studies are needed to explore the utility of α-Syn-PMCA to monitor disease progression and for preclinical identification of patients who are at risk of developing PD in later lives.

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Footnote

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