Multicenter Study

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Development of a Biochemical Diagnosis of Parkinson Disease by Detection of α-Synuclein Misfolded Aggregates in Cerebrospinal Fluid

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Abstract

Importance: Parkinson disease (PD) is a highly prevalent and incurable neurodegenerative disease associated with the accumulation of misfolded α-synuclein (αSyn) aggregates. An important problem in this disease is the lack of a sensitive, specific, and noninvasive biochemical diagnosis to help in clinical evaluation, monitoring of disease progression, and early differential diagnosis from related neurodegenerative diseases.

Objective: To develop a novel assay with high sensitivity and specificity to detect small quantities of αSyn aggregates circulating in cerebrospinal fluid (CSF) of patients affected by PD and related synucleinopathies.

Design, setting, and participants: The strategy evaluated in this proof-of-concept study uses the protein misfolding cyclic amplification (PMCA) technology that detects minute amounts of misfolded oligomers by taking advantage of their ability to nucleate

further aggregation, enabling a very high amplification of the signal. The technology was first adapted with synthetic αSyn oligomers prepared in vitro and used to screen in 2 blinded cohorts of CSF samples from German and Japanese patients with PD (n = 76) and individuals serving as controls affected by other neurologic disorders (n = 65), neurodegenerative diseases (n = 18), and Alzheimer disease (n = 14). The kinetics of αSyn aggregation were measured by αSyn-PMCA in the presence of CSF samples from the participants to detect αSyn oligomeric seeds present in this biological fluid. The assays were conducted from November 15, 2013, to August 28, 2015.

Main outcomes and measures: Kinetic parameters correlated with disease severity at the time of sample collection, measured by the Hoehn and Yahr scale, with the lowest grade indicating unilateral involvement with minimal or no functional impairment, and the highest grade defining patients with complete confinement to wheelchair or bed.

Results: Studies with synthetic αSyn aggregates showed that αSyn-PMCA enabled to detect as little as 0.1 pg/mL of αSyn oligomers. The αSyn-PMCA signal was directly proportional to the amount of αSyn oligomers added to the reaction. A blinded study of CSF samples correctly identified patients affected by PD with an overall sensitivity of 88.5% (95% CI, 79.2%-94.6%) and specificity of 96.9% (95% CI, 89.3%-99.6%). The αSyn-PMCA results for different patients correlated with the severity of the clinical symptoms of PD (Japanese cohort: rs = -0.54, P = .006; German cohort: rs = -0.36, P = .02).

Conclusions and relevance: The findings suggest that detection of αSyn oligomers by αSyn-PMCA in the CSF of patients affected by PD may offer a good opportunity for a sensitive and specific biochemical diagnosis of the disease. Further studies are needed to investigate the usefulness of αSyn-PMCA to monitor disease progression and for preclinical identification of patients who may develop PD.