

Higher levels of CSF alpha-synuclein predict faster cognitive loss in Parkinson disease

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The course of Parkinson disease (PD) can vary from gradual deterioration to precipitous decline in motor or cognitive function. Therefore identifying predictors of progression can benefit understanding of PD disease progression and impact management. Data from 304 PD patients followed for up to 8 years indicate that patients with higher cerebrospinal fluid (CSF) alpha-synuclein levels experienced faster cognitive decline in the following months, although no associations were found between alpha-synuclein levels and motor changes. The results are published in *The American Journal of Pathology*.

A characteristic pathological feature of PD is the presence of Lewy bodies, which are formed by intracellular deposits of the protein alpha-synuclein in neurons. Although several large studies have shown that alpha-synuclein levels are lower in the CSF of PD patients and those with related synucleinopathies compared to controls, its role in [cognitive decline](#) and dementia had been unexplored.

Researchers were able to access CSF samples from the deprenyl and tocopherol antioxidative therapy of Parkinsonism (DATATOP) study, which is the largest cohort assembled to date with longitudinal collection of biological fluids and clinical data from PD patients. "DATATOP subjects were recruited at early disease stages, without apparent signs of dementia and prior to needing dopamine-supplementing drugs, making this cohort ideal for studying PD progression," explains Jing Zhang, MD, PhD, Department of Pathology at the University of Washington School

of Medicine (Seattle).

Cognitive performance and other clinical measures, including the United Parkinson Disease Rating Scale (UPDRS), Mini-Mental State Exam (MMSE), and Hoehn and Yahr scales, were assessed at the beginning of the study and subsequently every 6 months, with an average follow-up time of 1.8 years and maximum of 8 years. Data were separated into Phase I (the time between study entry and a clinician's determination that levodopa therapy was required) and Phase II (the time between initiation of levodopa therapy and the conclusion of follow-up). CSF samples were collected at the beginning of Phases I and II. Although the study began as a randomized trial that divided subjects into four treatment groups (placebo, deprenyl, alpha-tocopherol, and deprenyl/alpha-tocopherol), this was terminated early because positive effects of deprenyl were observed and all subjects then received deprenyl for approximately 18 months.

The investigators found that although alpha-synuclein levels decreased significantly over the course of the study, in agreement with previous studies lacking the longitudinal component, its values did not predict the worsening of motor symptoms (as measured by UPDRS) over Phase I or Phase II. "One possible explanation is that UPDRS reflects primarily deficits arising from nigrostriatal degeneration, whereas CSF alpha-synuclein levels are influenced by the whole brain and may serve as a proxy for total brain pathology," says Dr. Zhang.

The findings for cognition were quite different: Higher CSF alpha-synuclein levels predicted faster cognitive decline. The results were significant during Phase II. Analyses were controlled for age, sex, education, exposure to study drug, and prescribed dose of levodopa. The tests evaluated multiple modes of cognition, including verbal learning and memory and visuospatial working memory/processing speed. Similar trends were found for all tests.

"The finding that alpha-synuclein levels decrease as PD progresses, yet those with higher alpha-synuclein levels experience faster cognitive decline, is somewhat counterintuitive," comments Dr. Zhang. He and his colleagues, including first author, Tessandra Stewart, PhD, suggest that the decrease in CSF alpha-synuclein may be the result of a compensatory process, reflecting greater retention of the protein in the brain. This may allow damaged or degenerating neurons to maintain their function for longer than those who are less efficient at retaining alpha-synuclein.

Dr. Zhang points out that the unique value of this study derives from the ability to perform longitudinal assessments of cognition in PD patients over a long time period and access to data from a large cohort that began when patients were in the earliest stage of disease.

More information: "Cerebrospinal fluid alpha-synuclein predicts cognitive decline in Parkinson disease progression in the DATATOP cohort," by Tessandra Stewart, Changqin Liu, Carmen Gingham, Kevin C. Cain, Peggy Auinger, Brenna Cholerton, Min Shi, Jing Zhang, and the Parkinson Study Group DATATOP investigators (DOI: [dx.doi.org/10.1016/j.ajpath.2013.12.007](https://doi.org/10.1016/j.ajpath.2013.12.007)), *The American Journal of Pathology*, Volume 184, Issue 4 (April 2014)

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