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Comprehensive Parkinson's biomarker test has prognostic and diagnostic value

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Perelman School of Medicine researchers at the University of Pennsylvania report the first biomarker results reported from the Parkinson's Progression Markers Initiative (PPMI), showing that a comprehensive test of protein biomarkers in spinal fluid have prognostic and diagnostic value in early stages of Parkinson's disease. The study is reported in *JAMA Neurology*.

Compared to healthy adults, the study found that people with early Parkinson's had lower levels of amyloid beta, tau and alpha synuclein in their spinal fluid. In addition, those with lower concentrations of tau and alpha synuclein had greater motor dysfunction. And early Parkinson's patients with low levels of amyloid beta and tau were more likely to be classified as having the postural instability-gait disturbance- dominant (PIGD) motor type of disease, where falling, freezing, and walking difficulty are common.

"Biomarkers for Parkinson's disease such as these could help us diagnose patients earlier, and we've now shown that the simultaneous measurement of a variety of neurodegenerative disease proteins is valuable," said study senior author Leslie M. Shaw, PhD, professor of Pathology and Laboratory Medicine at Penn Medicine. Dr. Shaw and John Q. Trojanowski, MD, PhD, director of the Penn Udall Center for Parkinson's Research, are co-leaders of the Bioanalytics Core for the Parkinson's Progression Markers Initiative, an international observational clinical study sponsored by The Michael J. Fox Foundation for Parkinson's Research.

The team evaluated spinal fluid collected from baseline visits of the first 102 PPMI participants - 63 with early, untreated Parkinson's disease and 39 healthy controls. The spinal fluid was evaluated for levels of five biomarkers: amyloid beta, total tau, phosphorylated tau, alpha synuclein and the ratio of total tau to amyloid beta. Spinal fluid measures of amyloid and tau are currently used in research to distinguish Alzheimer's disease from other neurodegenerative diseases. In contrast to Alzheimer's, where tau levels are higher than healthy controls, the study found that early Parkinson's patients had lower levels of tau than healthy controls. One reason, researchers suggest, could be that interactions between tau and alpha synuclein may limit the release of tau into the cerebrospinal fluid of Parkinson's patients.

"Through PPMI, we are hoping to identify subgroups of Parkinson's patients whose disease is likely to progress at a different rate, as early as possible," said Dr. Trojanowski. "Early prediction is critical, for both motor and dementia symptoms."

The Parkinson's PIGD motor subtype has been associated with a more rapid cognitive decline as well as greater functional disability. Using the biomarker test, this initial study found that levels of all spinal fluid biomarkers were lower in the PIGD motor subtype than other types of PD as well as healthy controls. In addition, amyloid beta and phosphorylated tau were at lower levels in the PIGD motor subtype, but were no different in tremor or indeterminate subtypes compared to normal controls.

This spinal fluid testing procedure is only being used in research studies, and will be continued to be evaluated and validated in a larger study of the PPMI cohorts.

In addition to leading the Bioanalytics Core of PPMI, Penn's Parkinson's Disease and Movement Disorders Center is one of the two dozen trial

sites where volunteers are evaluated throughout the PPMI study. The Penn PDMDC has been part of the PPMI group studying people with early Parkinson's disease as well as healthy adults since 2010, and began enrollment for a new, pre-symptomatic arm of the study in the summer of 2013. The pre-motor arm of PPMI is enrolling participants who do not have Parkinson's disease and are living with one of three potential risk factors for PD: a reduced sense of smell (hyposmia); rapid eye movement sleep behavior disorder (RBD; a disorder in which the individual acts out his/her dreams); or a mutation in the LRRK2 gene (the single greatest genetic contributor to PD known to date).

"In addition to biomarker tests, validating risk factors could enable earlier detection of the disease and open new avenues in the quest for therapies that could slow or stop disease progression," said PPMI trial site study leader Matthew Stern, MD, professor of Neurology and director of Penn's Parkinson's Disease and Movement Disorders Center.

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