Protein levels in spinal fluid correlate to posture and gait difficulty in Parkinson's

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Dr. Jennifer Goldman, lead author of the study and movement disorders neurologist at Rush University Medical Center. Credit: Rush University Medical Center

Levels of a protein found in the brain called alpha-synuclein (α-syn) are significantly lower than normal in cerebrospinal fluid collected in Parkinson's disease patients suffering from postural instability and gait difficulty, a study led by movement disorders experts at Rush University Medical Center has found. The results recently were published online in the journal *Movement Disorders*.

"This report is an important contribution in our efforts to understand and quantify Parkinson's biology to accelerate drug development," said Mark Frasier, PhD, an author on the study and the senior vice president of

research programs at the Michael J. Fox Foundation, which provided funding for the study.

A mysteriously harmful presence

Alpha-synuclein's function in the brain is currently unknown but of great interest to Parkinson's researchers because it is a major constituent of Lewy bodies - the protein clumps that are the pathological hallmark of Parkinson's disease.

The illness gradually destroys neurons that produce the chemical dopamine, which conveys nerve signals, in turn causing the tremors and difficulty moving that are a common symptom of Parkinson's disease. The prevailing wisdom has been that these neurons may die from a toxic reaction to alpha-synuclein deposits.

However, Parkinson's disease has been linked to some gene variants that affect how the immune system works, leading to an alternative theory that alpha-synuclein causes Parkinson's disease by triggering the immune system to attack the brain.

In addition to its presence in the brain, alpha-synuclein can be found in peripheral tissues and body fluids. The *Movement Disorders* study, called BioFIND, is the first to try to differentiate the biomarkers of neurodegeneration in Parkinson's disease patients based on fluids collected from spinal fluid, blood and saliva.

The cross-sectional, observational study collected data and body fluid samples from 120 people with moderately advanced Parkinson's disease and 100 control volunteers across eight academic sites in the U.S. at two points over two weeks.

Dr. Jennifer G. Goldman, a movement disorders neurologist at Rush

University Medical Center and the study lead author, has profiled the Parkinson's-associated protein levels in these biofluids and their relationships to clinical features of the disease. The study found that levels of alpha-synuclein were lower in cerebrospinal fluid from Parkinson's patients with certain motor function impairments - specifically in those who had more problems with balance and walking compared to those with more tremor.

In addition, levels of beta-amyloid, known for its association with Alzheimer's disease, were lower in those with Parkinson's and related to worse scores on a memory recall in Parkinson's as measured on a rest of thinking and memory given to study participants.

The study also showed that alpha-synuclein levels in plasma and saliva did not differ between people with Parkinson's and control volunteers, and alpha-synuclein did not significantly correlate among other biological fluids.

Findings can help guide selection for clinical trials

"These are important insights for the ongoing pursuit of accessible biomarker tests to diagnose and track the disease," said Goldman. "For example, people with Parkinson's and lower beta-amyloid may be more likely to develop memory problems and therefore would benefit more from a cognitive therapy," said Goldman. "Enrolling this population in trials can help us see a treatment effect more clearly than testing the therapy on people who will not have this symptom."

Future studies may further explore biomarkers

Next steps include validation of these findings in the Parkinson's Progression Markers Initiative (PPMI), a biomarkers study sponsored by

the Michael J. Fox Foundation that is following more than 1,500 people with Parkinson's or risk factors and control volunteers over at least five years. Additionally, trials ongoing or launching in the near future could use alpha-synuclein or beta-amyloid levels as exploratory biomarkers in motor symptom or cognition drug trials, respectively.

Parkinson's disease is the second most common age-related neurodegenerative disorder after Alzheimer's disease, affecting an estimated 7 million to 10 million people worldwide.

Many of the affected neurons signal via the neurotransmitter dopamine; therefore, traditional therapy continues to rely on dopamine replacement therapy. This approach alleviates symptoms, but does not halt disease progression. Currently, there is no cure for Parkinson's disease.

Provided by Rush University Medical Center