Parkinson's disease starts in gut, moves to brain: study

Tue Jul 02, 2019 | Section: Neurologic Disorders

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It has long been known that alpha-synuclein pathology in Parkinson's disease is not limited to the brain, but is also observed in the enteric nervous system.

The German anatomist Heiko Braak hypothesized more than 15 years ago that misfolded alpha-synuclein pathology spreads from the gastrointestinal tract via the vagus nerve to the brain, where misfolded alpha-synuclein selectively kills dopamine neurons of the substantia nigra to cause Parkinson's disease with Lewy body dementia.

However, no one had been able to demonstrably prove the anatomist's hypothesis that Parkinson's disease can originate in gut until now.

Now, researchers from the Johns Hopkins University School of Medicine report in the latest issue of *Neuron* that injection of pre-formed fibrils (PFF) of alpha-synuclein into the stomach and duodenal myenteric plexus leads to transport through the vagus nerve to the brain to result in detectable Parkinson's-like pathology by 2-3 months, "when the pathology and the brain is there, but they don't yet have symptoms, which is kind of when you'd want to be treating human patients with Parkinson's disease and see if your interventions work," according to principal investigator Ted Dawson.

Injection of alpha-synuclein PFFs directly into the mouse brain were previously known to spread locally in a prion-like manner to cause a domino-like protein aggregation with cell death, but no one had been able to reproduce Parkinson's disease with Lewy body dementia after performing injections into the gastrointestinal tract until the release of this study.

It took great trial and error experimentation, but Kim and Johns Hopkins colleagues were able to identify highly innervated anatomic regions in the gastrointestinal tract that were responsive to this approach.

Dawson emphasized that the PFF stays in the stomach, where they cause the endogenous alpha-synuclein to misfold and transmit up the vagus nerve to the brain. Injecting PFF into alpha-synuclein knockouts did not lead to pathological aggregates, and surgically cutting the connection between gut and brain through vagotomy also prevented pathologic transmission.

More than motor symptoms

By 7-10 months after treatment, animals had a full range of non-motor symptoms, including depression and anxiety observed in Parkinson's disease. Another surprising result was that they observed abnormal gastrointestinal problems including reduced ghrelin levels and dysmotility.

Dawson and his team plan to work out the molecular mechanisms for these symptoms.

This was the first paper to develop an animal model based on the gut-brain hypothesis and to definitively connect the gut to brain pathogenesis that as originally proposed by Heiko Braak.

Dawson told *BioWorld Science*, "I think the most important point of the paper is that it supports the notion that Parkinson's disease can start in the gut. It can start in the stomach and pylorus and that once the endogenous alpha-synuclein becomes pathologic, it can transmit up the vagal nerve and spread throughout the brain to essentially caused all the features of Parkinson's disease in a mouse and so it really supports the Braak hypothesis."

The big outstanding elephant in a room question from this study is, what causes the endogenous alpha-synuclein in humans start to misfold? Scientists have data suggesting that it could be differences in the microbiome of Parkinson's disease patients involving bacterial lipids or metabolites that may be causing the alpha-synuclein to misfold.

Dawson highlighted data suggesting that a bacterial protein named curli, which has been shown to cause alpha-synuclein aggregation, may be involved. There is also data suggesting that misfolding could be caused by something as simple as the influenza virus in rats.

Next Dawson would like to use this model to continue work from their 2016 *Science* publication showing that lymphocyte-activation gene 3 (LAG3) can bind to alpha-synuclein PFFs to act as a receptor that enables transmission between neurons.

Ultimately, they hope to use their model for testing potential therapeutic interventions that may prevent or treat Parkinson's disease with Lewy body dementia.

(Kim, S. et al. Neuron 2019, Advanced publication).