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The Relationship Between Parkinson's Disease and the Microbiome

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Parkinson's Disease (PD) is a central nervous system movement disorder characterized by the formation of spherical protein deposits in the brain (Lewy bodies) and the development of spindle-like Lewy neurites in the body of the affected neuron. These start in the medulla oblongata and spread in a predictable pattern, resulting in a gradual drop in dopamine levels which causes tremors, rigidity and a progressive loss in mobility and body functions. In the later stages of the disease, behavioral and cognitive issues become prevalent.[1]

It has been known that in addition to prominent tremors and motor symptoms associated with Parkinson's disease, up to 75% of patients display gastrointestinal abnormalities as well.[2] These symptoms often precede the appearance of motor symptoms by many years, prompting speculation on the role of gut bacteria and the disease. While there are treatments for PD, no cure exists. Recent research examining the gut microbiota and its possible connection to PD offer potential new approaches to treatment. While this research is still in the early stages, it offers a glimmer of hope to Parkinson's patients.

A study by Sampson et al. investigated the alterations of bacteria in the gut, dysbiosis, and motor deficits in Parkinson's disease in mice. The team conducted three experiments to test this relationship, assessing bacterial microbiome and motor function in mice and how different microbiota affect symptoms. They first showed that gnotobiotic mice (mice lacking their natural gut microbiome) accumulated less alpha-synuclein in their brains, the primary protein component of Lewy bodies, and as such moved more freely. This provided a model for how the environment and gut flora may play a role in PD development as well as other neurodegenerative disorders. In the second experiment, Sampson's team examined whether imbalances in short-chain fatty acids (SCFAs) created in gut could be associated with activated immune responses in the brain. They discovered that germ-free mice treated with microbially produced SCFAs had higher levels of neuroinflammation, which is linked to the malfunction of neurons through the activation of microglia. The third experiment treated mice with fecal transplants using donor stool from human patients with and without Parkinson's disease. Mice

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that received stool from patients with Parkinson's developed deficits in motor function.[3] Future study by this team will focus on identification of specific organisms in the gut associated with the motor deficits. This could lead to alteration of the microbiome as a treatment for Parkinson's disease.

However, researchers in Finland have discovered decreased abundance of the Prevotellaceae family of bacteria in the gut microbiome of patients with PD compared to healthy controls. Prevotellaceae is normal in the human gut in varying amounts, however it was discovered that the mean abundance of Prevotellaceae in the feces of PD patients was reduced by 77.6% compared to healthy individuals.[4] Although PD patients display less Prevotellaceae, some controls had low levels as well, indicating that this cannot be the sole explanation of PD. This demonstration of how bacterial populations may influence disease has important implications for future research.

Another study by Tetz et al. demonstrated a significant correlation of gut bacteria with Parkinson's disease. The human GI tract is home to bacteria, archaea, fungi, and viruses, including bacteriophages, the last of which are a type of virus that infects, replicates within, and destroys bacteria. This study showed that drug-naïve patients with PD had a 10-fold decrease in *Lactococcus* species (lactic acid bacteria) compared with healthy controls. It was noted that an increase in lytic bacteriophages was accompanied by a decrease of *Lactococcus* bacteria, indicating that a depletion of *Lactococcus* in patients with PD could be caused by lytic phages.[4] A fourth way that gut bacteria could be implicated in Parkinson's disease is via the enteric nervous system (ENS). A study by Liu et al. demonstrated that a truncal vagotomy, in which the trunk of the vagus nerve is removed where it enters the stomach from the esophagus, was related to a reduced risk for PD.[5] Therefore, changes gut microbiota composition could cause alterations in the intestinal barrier function and permeability implicating both the immune system and the ENS, resulting in the development of PD symptoms.

A study by Hill-Burns et al. sought to find microbial causes of Parkinson's disease, partly by interrogating 39 potential confounders.[6] Of these 39, the test results of eight indicated potential involvement. Once these confounders were taken into consideration, the microbiome sequencing of 197 patients with Parkinson's disease and 130 controls were compared using three metrics. The team discovered several dysbiotic features of the PD microbiome, including elevated levels of *Akkermansia, Lactobacillus*, and *Bifidobacterium* and reduced levels of Lachnospiraceae. This study represents the largest to date of the microbiome in Parkinson's patients.

It is important to recognize the pivotal impact of microbiome research, since it shows that pathology in the gut can impact neurological diseases. Microbiome research and its relationship with Parkinson's disease is only in its infancy. Further research will hopefully identify new bacterial markers that contribute to the development of PD and guide new treatments. Although PD is likely a multicausal disease and the microbiome is not fully responsible, it is impossible to ignore the impact the gut microbiome could have on our future knowledge around Parkinson's Disease. ■

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