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The second brain in Parkinson's disease: fact or fantasy?

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Parkinson's disease (PD) is a movement disorder characterized by reduced dopamine levels due to degeneration of the substantia nigra. The clinical presentation is underlined by bradykinesia, postural instability, and tremors. PD is the second most common neurodegenerative disease worldwide, with a huge monetary burden. In the United States alone, it is estimated that in 2017, the total economic cost was $51.9 billion, and projected to surpass $79 billion by 2037. Extensive research has been conducted into the pathophysiology and clinical implications of the disease. Within neurodegenerative disorder itself, the entity involving the brain-gut axis has been a fundamental model in understanding the disease process. More so than ever in PD, the association between gut health and neurological disease is gaining momentum, with the fascinating idea of influencing neurological health by treating the gut.

Second brain: The gut can be considered the second brain of the human body and may play a crucial role in the pathology of PD (Ochoa-Reparaz, 2016). A hypothesis first postulated by Heiko Braak in 2007 has gained a vast degree of interest in trying to improve our understanding of PD. Coined the "dual-hit" hypothesis, it explores the notion of gut involvement having a significant role to play in the pathogenesis of PD. This theory suggests that the development of alpha-synuclein enriched Lewy pathology, in response to a foreign pathogen, may first originate within the gut. It is proposed that through this enteric route, this protein travels along the path of the vagus nerve and accumulates in the central nervous system resulting in neurodegenerative disease. Supported by both clinical and histological evidence, no other theory has strongly delineated other possible mechanisms for the development of PD and its link with the gut (Hawkes, 2007). However, Braak's hypothesis is limited in that it advocates the notion of a unidirectional pathological process of "gut-to-brain". Given the bidirectional communication between the gut and the central nervous system, some studies have suggested an alternative "brain-to-gut" approach, whereby the neurodegenerative processes travel down the enteric nervous system affecting the gastrointestinal tract. Additionally, Braak's hypothesis also does not explain why not all patients with Parkinson's disease suffer gastrointestinal disorders. Despite its limitations, the theory provides an excellent framework for future research to widen our understanding of the pathogenesis of PD.

Gastrointestinal symptoms: Non-motor gastrointestinal tract symptoms, for example, constipation, tenesmus, defecation difficulties and gastroparesis, are rife in PD. Heavily associated with Braak's hypothesis, numerous research studies have investigated the prevalence of these symptoms in PD patients (Lubomski, 2020). The vagus nerve has also been found to be profoundly implicated in PD pathophysiology, with alterations of the vagal neurocircuitry manifesting in marked impairments of the upper gastrointestinal tract (Travagli, 2016). Patients with PD are therefore more likely to develop symptoms such as dysphagia and sialorrhea. Interestingly, a future intervention may involve non-invasive vagal nerve stimulation in reducing motor deficits. Non-invasive vagal nerve stimulation is already established in treating neurological diseases e.g., cluster headaches, and epilepsy. Multiple studies in rat models have noted vagal nerve stimulation increased locomotion and reduced neuroinflammation. A 2021 double-blinded sham-controlled crossover trial in PD patients recorded significant improvements in motor function, key gait parameters and reduced inflammatory markers such as tumor necrosis factor-alpha and glutathione levels. Furthermore, a randomized double-blinded pilot study showed non-invasive vagal nerve stimulation improved gastrointestinal complaints of patients with no side effects. These studies are the first of their kind and the promising findings could pave the way for more large-scale research into neuromodulation techniques in ameliorating PD symptoms.

Prodromal symptoms including constipation, delayed gastric emptying and dysphagia have been described in patients who are later diagnosed with PD. Complaints of constipation is the most associated symptom, and patients may report this up to 20 years before diagnosis. Similarly, Lewy pathology may be seen within the enteric nervous system, 20 years before diagnosis. Constipation itself is a non-specific symptom associated with a variety of gastrointestinal diseases. As a sole risk factor for prodromal PD, it is of low positive predictive value. However, in combination with other prodromal PD symptoms including psychiatric illnesses such as depression and REM sleep disorders, screening for these symptoms could prove valuable in identifying the early stages of PD (Heinzel, 2020). Current clinical guidelines do not recommend initiating treatment for patients without apparent motor symptoms that affect their quality of life, due to the efficacy and longevity of treatments. Early detection of PD through screening for gastrointestinal complaints may provide benefit to patients. Non-pharmacological interventions such as active exercise and speech therapy can be implemented early on to halt the progression of the disease. As described by Travagli et al. (2020), our current understanding of the mechanisms behind gastrointestinal dysfunction in PD is inadequate and therefore provides clinicians with the challenging task of diagnosing and initiating treatment. Consequently, there is scope for further evaluation into this field and forthcoming research may wish to investigate and validate the role of refined screening tools for prodromal PD.

Gut microbiome: The microbial colonization, along with gut dysbiosis, has been demonstrated to have functional implications in many neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis. Gut microbiota has several crucial roles within the human body including innate regulation through hormonal and gut peptides, regulation of intestinal epithelium and anti-inflammatory and immune properties. Multiple research papers have investigated the composition of gut microbiota and its role in the gut-brain axis. Significant differences have been identified in the composition of microbial communities between PD and healthy control groups (Romano, 2021). The complex interplay between gut dysbiosis and intestinal permeability noted in PD is a foundation for both bowel and neuro-inflammation. An association between PD and increased gut permeability has been described, likely associated with the reduced concentrations of short-chain fatty acids (Sampson, 2016). Short-chain fatty acids are important in intestinal mucus stimulation, tight junction protein regulation of colonic epithelium and in modulating activity of the enteric nervous system. Notably, short-chain fatty acids producers within the *Lachnospiraceae* family and *Faecalibacterium* genus were reduced in the gut. Furthermore, a strong association between small intestinal bacterial overgrowth and PD has been identified (Li, 2021). Whilst the causes of small intestinal bacterial overgrowth are still unclear, unusual small bowel motility and subsequent

breakdown in small bowel epithelium may provide a gateway for foreign pathogens and bacteria. The increased intestinal permeability and immunological response to bacteria may result in a further inflammatory reaction from alpha-synuclein enriched Lewy bodies within the gastrointestinal tract. Small intestinal bacterial overgrowth may contribute to the worsening of motor symptoms, with antibiotic and levodopa therapy seen to yield a positive response. In summary, there is evidence of a correlation between the alterations in gut microbiota and neuroinflammation.

Future therapeutics: The changes in the gut microbiota of patients with PD can have important implications for future therapies. In our opinion, personalized probiotics may be a step in the right direction to help influence the levels of "neurologically-healthy" bacteria and improve patient symptoms. A number of small studies have published some promising results. Two double-blinded randomized control trials have shown significant results in probiotic treatment in constipation (Barichella, 2016; Tan, 2021), whilst a further small study of 40 patients noted improvement in stool consistency, tenesmus and abdominal pain. However, the long-term implications and efficacy will need to be monitored, specifically in patients with diagnosed PD.

An alternative to probiotics may involve the use of faecal microbiota transplant. By altering the gut microbiota to favor a more beneficial profile, it has proven to be effective in conditions like Crohn's disease, *Clostridium difficile* infections and irritable bowel syndrome. Unfortunately, there has been very limited research in neurological disease, with only a few case reports depicting effectiveness in conditions like multiple sclerosis and autism. Mouse models have provided encouraging data involving increased dopamine and improved motor function, whilst one preliminary human study noted improvement in the UPDRS-III score. The concept may be promising with few side effects, in reality assessing the response of the intervention is difficult. In theory, whilst the treatment could be given years before diagnosis, measuring the effectiveness of the treatment will be challenging because of the nature of PD progression and the non-specificity of gastrointestinal symptoms. Granted, evaluating the efficacy is difficult, however, undeniably this may be a novel treatment and we encourage further trials in this area (Xue, 2020).

Lifestyle: Lifestyle may also be a key factor in PD. The role of lifestyle changes, in particular, nutritional and dietary habits may influence both the gut microbiota and clinical symptoms. Whilst there has yet been no proven diet or recommended guidelines, certain foods and compounds may be beneficial including tea, caffeine and fruits and vegetables. Whether regular vitamin supplementation (e.g., once daily supplementation) may be an appropriate synergistic therapy along with medical management is yet to be determined. Vitamin supplementation has been proven to reduce the incidence of conditions including cancer and cardiovascular disease. Vitamins such as B6, B12 and D have been identified as neuroprotective and reducing neuronal degeneration through minimizing oxidative stress and free radical formation. It is highlighted that this is an area for further examination as the benefits of supplementation far outweigh the risks due to its favorable side effect profile. In the not-so-distant future, it may become the norm for patients to have regular vitamins to complement existing therapies.

Conclusion: We have briefly expressed three components that are significant in promoting the complex involvement of the gut within PD. Thorough research has looked into the physiology and symptoms of PD, with further exploration into the gut microbiota a crucial step in truly understanding the disease process. Adopting strategies to ensure stable, healthy microbial consumption along with lifestyle modification may be the next step in targeting the disease process and the health-economic burden. We welcome further research into this field as only time will tell whether treating the second brain is a fact or fantasy.

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