UTJMS 2026 February 16, 15(S1):e1-e6 doi:10.46570/utjms-2026-1908

An Essay on Parkinson's Disease and the Gut-Brain Connection

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Received 12/3/2025

Accepted for publication 12/15/2025

Published 2/16/2026

1. Introduction

Parkinson's Disease (PD) is a neurodegenerative condition characterized by a wide range of motor and non-motor symptoms. According to Parkinson's Foundation, it is estimated that more than 10 million people are suffering from PD worldwide, and 90,000 individuals are diagnosed with PD in the U.S. per year, making it the second most common neurodegenerative disease following Alzheimer's disease (1). PD has also affected several prominent public figures, including Muhammad Ali, Neil Diamond, and Michael J. Fox, highlighting its broad clinical and societal impact. Although PD was depicted early on in ancient Chinese and Indian texts, it was only named in 1817 after James Parkinson, an English physician, who described it as "shaking palsy" and "paralysis agitans" (2). Parkinson later described the disease in his book, *An Essay on the Shaking Palsy,* as "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported" (3). After Parkinson's findings, French Neurologist Jean-Martin Charcot proceeded to characterize the clinical spectrum of the disease, noting the bradykinesia, which hinders the daily lives of those affected (3). In addition, he highlighted there are two models of the disease: the rigid and the tremorous form (3). This discovery led to the rejection of the portrayal of the disease as "paralysis agitans" or "shaking palsy," since those affected were not debilitated and did not always experience tremors. While it was suggested in the late 19th century that motor symptoms were due to the selective loss of dopamine neurons in the substantia nigra pars compacta, it was not until the 1960s that levodopa (dopamine replacement therapy) was developed as the mainstay clinical treatment for PD (4). This marks the "dopamine era," in which most efforts at treatment development were aimed at targeting the loss of dopamine neurons. This was later replaced by the "alpha synuclein era," at which efforts were aimed at targeting the other hallmark pathological finding of PD patients: Lewy bodies (2, 4). Lewy bodies are misfolded aggregates of the presynaptic neuronal protein alpha-synuclein (α-synuclein) found throughout the brains of PD patients (5). Despite these ongoing efforts to develop alternative disease-modifying treatments for PD, the lack of success over the years may be attributed to the fundamental question about PD that remains unsolved: What exactly causes the loss of these

dopamine neurons? There are numerous hypotheses to the etiology of PD, some of which include genetic predisposition, environmental toxicity, inflammation, and alterations in the gut-brain connection (6-9). In recent years, the involvement of the gut-brain connection in the pathogenesis of PD has gained considerable attention.

Recent work has found a link between the gut microbiome and the development of PD. Furthermore, emerging studies focusing on the gut-brain axis found that α-synuclein aggregates

(which form Lewy bodies) may stem from the gut and move to the brain via the vagus nerve (10). Understanding the mechanisms by which α-synuclein travels to the brain is significant to our understanding of how the gut may be involved in the pathogenesis of PD. The aim of this essay is to examine the role the gut-brain connection has in the pathogenesis of PD, apply this to the clinical presentation of a PD patient, and elucidate implications the gut-brain connection may have on the development of future PD treatments.

2. Background

Symptoms and Diagnosis

To contextualize the potential role of the gut in PD, it is necessary to first consider how the disease manifests clinically. PD is an age-related disease with the risk of the disease increasing with age. Only 25% of those afflicted are below the age of 65, and 5-10% of those afflicted are below the age of 50 years old (11). The incidence of PD is higher in men than women, however, women tend to experience greater "motor and non-motor response functions," which is said to be attributed to their lower body weight (11). The disease is characterized by two distinct features: motor and nonmotor symptoms. The cardinal motor symptoms include bradykinesia (slowness of movement), rigidity, resting tremor, and postural instability (12). PD symptoms, like many other diseases, vary in progression and severity for each patient. Motor symptoms typically begin as unilateral and progress to bilateral, followed by bulbar dysfunction in mature cases, (characterized by dysphagia (trouble swallowing) and dysarthria (trouble with speech)) (11, 12). Non-motor symptoms include cognitive deficits, sleep abnormalities, autonomic dysfunction, psychiatric disturbances, and sensory symptoms (12). Sleep abnormalities, specifically REM sleep behavioral disorder, typically occur early in the disease course, prior to motor deficits (13, 14). Psychiatric disturbances may include anxiety, depression, and hallucinations (14). Autonomic symptoms include drenching sweats, dyspnea, seborrhea, and gastrointestinal dysfunction (14). Sensory signs consist of tingling, akathisia, in addition to olfactory deficit (15). Cognitive deficits appear late in the disease course and consist of visuospatial or executive function deficits (14-16).

There are two theories as to how the gut is involved in the pathogenesis of PD, the brain-first and the gut-first hypotheses (17). The brain-first hypothesis states that the disease starts in the brain and spreads to the gut. Patients whose disease course is consistent with this hypothesis may have motor symptoms without early prodromal nonmotor symptoms such as REM Sleep Behavior Disorder or gastrointestinal dysfunction (17). On the other hand, the gut-first hypothesis states that the disease begins in the peripheral nervous system where misfolded α-synuclein proteins travel to the brain. Patients whose disease course is consistent with this hypothesis may have early autonomic dysfunction, gastrointestinal dysfunction, and REM Sleep Behavior Disorder prior to the onset of motor symptoms (17).

As a result of the clinical heterogeneity of PD, a wide range of diagnostic approaches is employed. In addition to a thorough physical exam and patient history, a variety of diagnostic tests may be run. Magnetic resonance imaging, dopaminergic imaging, transcranial ultrasound of the substantia nigra, genetic testing, autonomic function tests, olfactory tests, as well as tremor analysis, are examples of diagnostic methods (11).

Pathophysiology

Beyond its clinical presentation, PD reflects progressive dysfunction of the dopaminergic system and related neural circuits. Neuronal loss within the substantia nigra pars compacta disrupts basal ganglia signaling required for smooth, coordinated movement (18). In parallel, α-synuclein adopts misfolded conformations that aggregate into Lewy bodies across the central and enteric nervous systems, including the gastrointestinal (GI) tract (18-20). As a result of the diverse genetic, inflammatory, and environmental stressors that can damage dopaminergic neurons, multiple interacting risk factors have been implicated in the development of PD. Environmental risk factors including toxins, methanol exposure, aging, carbon monoxide poisoning, as well as trauma to the head, may result in neurodegeneration (7, 18). Genetic lesions, including mutations in synuclein alpha (SNCA), leucine-rich repeat kinase 2 (LRRK2), and glucosylceramidase beta (GBA), may predispose individuals to developing PD (15). Similarly, mitochondrial dysfunction and increased oxidative stress, which can be provoked by the environmental or genetic factors listed above, can lead to neuronal energy depletion in addition to loss of function (15).

3. The Gut-Brain Function

Overview

UTJMS 2026 February 16, 15(S1):e1-e6 doi:10.46570/utjms-2026-1908

The enteric nervous system (ENS) is a "nerve network composed of neurons and glial cells that regulates the motor and secretory functions of the GI tract" (19). The GI tract is a long structure between the mouth and the anus that houses all the organs essential for the breakdown and absorption of nutrients (22). In addition to these digestive functions, the GI tract contains a diverse community of microorganisms, collectively termed the gut microbiome. Deterioration of the gut microbiome can lead to harmful effects on the blood-brain barrier (19). The ENS and the nervous system are connected to the brain through the gut-brain axis (GBA), allowing the nervous system to send signals to the brain and vice versa. The vagus nerve plays an important role in the gut-brain axis, transmitting signals related to digestion and mood reciprocally between the central nervous system and the gut (20).

Recent Studies

Early researchers of PD found that GI symptoms manifested much earlier than other symptoms, leading to investigation of the gut in PD patients (13). Braak, a German anatomist and pathologist, conducted an autopsy-study in which tissue from the brain, distal esophagus, and the gastric wall of PD patients were investigated for Lewy body pathology (21). Braak found a buildup of Lewy body pathology in gastrointestinal structures as well as in the dorsal motor nucleus of the vagus nerve (DMV) in the brainstem, which connects the gut to the brain (21, 22). This work led to what is now referred to as the "Braak hypothesis" (21, 23), which states that PD pathology may originate in the GI tract, where an external agent triggers the misfolding and accumulation of α-synuclein aggregates (22, 24). In turn, the aggregates of α-synuclein travel retrogradely to the brain via the vagus nerve (22). This formation of Lewy bodies then leads to neurodegeneration of the vital dopaminergic structures in the basal ganglia.

On the contrary, not all neuropathological findings are consistent with Braak hypothesis. Several other autopsy studies conducted of patients with PD did not indicate any irregular buildup of Lewy bodies in relevant structures (25). This discrepancy raises an important question: Is vagotomy a viable treatment method for PD? A vagotomy is a surgical procedure involving the transection of the vagus nerve. There are two types of vagotomies, total and selective. A total vagotomy involves cutting the nerve before it branches, while selective vagotomy preserves some vagus nerve function in the intestines (26). A study conducted using nationwide Swedish registers of 9,430 vagotomized patients (3,455 truncal and 5,978 selective) showed that overall, vagotomy was not related to the risk of PD (27). Nevertheless, the evidence remains controversial as to how exactly the vagus nerve may be involved in the pathogenesis of PD.

An alternative method for targeting the gut in PD involves improving the gut microbiota as a method of reducing the risk of the disease as well associated symptoms. One study aimed at improving the imbalance of microorganisms in the gut (often referred to as gut dysbiosis) prescribed PD patients probiotics (living organisms that aid in our digestion) (21). The results indicated a reduction of non-motor symptoms associated with the disease compared to those given a placebo (21). Fecal microbiota transplantation (FMT) is another approach aimed at reducing symptoms in PD patients. FMT involves taking fecal matter from healthy donors and injecting it into PD patients to diversify the gut microbiota. One study found that after FMT, quality of sleep and life, anxiety and depression were improved (28). The study used PSQI (Pittsburgh Sleep Quality Index), HAMD (Hamilton Depression Rating Scale), HAMA (Hamilton Anxiety Rating Scale), PDQ-39 (Parkinson's Disease Questionnaire-39), NMSQ (Non-Motor Symptoms Questionnaire), and UPDRS-III (Unified Parkinson's Disease Rating Scale - Part III) in n=12 PD subjects (31). A statistically (p-value = 0.001 or < 0.001) significant improvement was reported compared to initial test scores (28). Specifically, changes in symptoms from baseline were observed as follows: PSQI decreased by 34%, HAMD and HAMA decreased by 55%, PDQ-39 decreased by 50%, NMSQ decreased by 35%, and UPDRS III decreased by 43% (28).

4. Patient Interview

In addition to reviewing experimental and clinical studies on PD, a real-world clinical case was examined through a live patient interview conducted as a part of Neuroscience 1000, a one-credit hour course focused on diagnosis, disease, and the pathophysiology of the nervous system. The course emphasizes live patient interviews, didactic question and answer sessions with patients, and the integration of disease pathophysiology with neuroanatomy. A summary of the patient's experience with PD is presented below.

The patient examined in class was a sixty-year-old Caucasian male diagnosed with PD in 2016. The patient experienced a prolonged diagnostic

UTJMS 2026 February 16, 15(S1):e1-e6 doi:10.46570/utjms-2026-1908

process. Since the patient was not exhibiting signs of tremor at the time of testing, establishing a diagnosis of PD was challenging. As a result, tests were done to rule out other diseases, and the diagnosis was ultimately determined to be PD. The patient displayed symptoms of rigidity in his left arm, difficulty moving, limping, as well as loss of mobility. He reports that his walking difficulties started in 2020, which were characterized by a shuffling gait. In addition, the patient experienced unsteadiness, lack of coordination, as well as difficulty with day-to-day tasks that required fine motor skills. The patient's wife also noted reduced olfactory function. Bradykinesia, a primary clinical feature of PD, was observed multiple times in this patient. Specifically, the patient had reduced facial expression, reduced blink rate, and bradykinesia in the jaw (slightly opened jaw). Two tests were conducted in class to highlight the patient's symptoms of bradykinesia. The first test performed was the finger tapping test, in which the patient tapped his index finger and thumb together repeatedly and as quickly as possible. Bradykinesia was noted as a reduced amplitude over time with finger tapping. The other test involved setting a 60-second timer to see how many times the patient blinks in that time. The patient blinked only once in those 60 seconds, compared to the average blink rate 15-20 times per minute, which is a drastic difference.

The patient was prescribed carbidopa-levodopa to treat his PD symptoms. He reported mobility improvement in his left arm weeks after starting levodopa treatment. Levodopa is the precursor to dopamine, which is converted to dopamine in the brain, allowing the body to replace the lost dopamine. Levodopa is administered in combination with carbidopa, which inhibits its peripheral conversion to dopamine, thereby increasing the amount of levodopa that reaches the brain. Given levodopa's relatively short half-life of about four hours, the patient's physicians shortened the dosing interval to every three hours to improve symptom control. Taking the drug consistently minimizes the fluctuations in dopamine levels and allows better control of PD symptoms. The patient reported being diligent with his medication, daily routine, and exercise, which has contributed to an improvement in his PD symptoms. Despite the adversity the patient has experienced, he sustained a highly positive mindset, which he linked to his strong support system.

5. Conclusion

PD may be difficult to diagnose due to the heterogeneous manifestation of symptoms amongst patients. PD may result from a genetic predisposition, exposure to environmental toxins, or a combination of both, a process known as the "double-strike theory." Considering recent work on the relationship between the gut-brain connection and PD pathophysiology, methods such as fecal microbiota transplant or probiotic prescription aimed at diversifying the gut microbiome may be useful treatments in the future. However, current evidence for these gut-targeted interventions remains preliminary.

More research regarding the use of vagotomy in treating PD patients should be performed to better understand the potential of this intervention for PD patients, as current evidence is not conclusive. Vagotomy is not currently an accepted treatment for PD due to the preliminary nature of current research regarding this as a potential treatment. In the future, several factors may be considered when evaluating the potential use of vagotomy for treatment in PD patients, including disease progression, severity of symptoms, prior treatments, and whether the patient's symptoms are consistent with the gut-first hypothesis.

Patients with symptoms that are consistent with the gut-first hypothesis may be more likely to benefit from vagotomy than patients with symptoms that are consistent with the brain-first hypothesis, but this possibility requires further investigation.

In summary, while dopaminergic replacement therapy, such as levodopa, is effective in alleviating and minimizing PD symptoms, the development of alternative treatments is needed. Increasing evidence in recent years has shed light on the connection between neurodegenerative diseases like PD and the gut. Nevertheless, more research is required to develop and validate gut-targeted therapeutic strategies as viable options for PD management.

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