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IMPORTANCE OF THE GUT–BRAIN AXIS AS A NOVEL THERAPEUTIC TARGET IN THE MANAGEMENT AND TREATMENT OF PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder, recognized as the second most common neurodegenerative disease globally, primarily impacting older adults. Neuropathologically, it is defined by the selective degeneration of dopaminergic neurons located in the substantia nigra pars compacta, alongside the intracellular buildup of misfolded α-synuclein protein, which forms Lewy bodies and Lewy neurites. Lewy pathology is identified in up to 90% of clinically diagnosed PD cases and extends beyond the nigrostriatal system, affecting brainstem nuclei, peripheral autonomic regions, the limbic system, and neocortical areas. There is growing evidence indicating that α-synuclein pathology may initiate years prior to the emergence of classical motor symptoms, impacting areas such as the gastrointestinal tract, olfactory structures, and the autonomic nervous system. The incidence and prevalence of PD rise with age, exhibiting a male predominance of approximately 2:1. While PD has been reported more frequently in White populations, postmortem studies reveal a similar prevalence of Lewy bodies across different racial groups. Mortality rates for PD are significantly elevated compared to the general population, and the socioeconomic impact of PD is considerable, with healthcare expenses expected to increase dramatically in the forthcoming decades. The etiology of PD is complex, involving a combination of genetic and environmental factors. Monogenic forms represent about 20% of cases and include autosomal dominant variants such as LRRK2, GBA1, and SNCA, as well as autosomal recessive

variants like PRKN, PINK1, and DJ-1. Environmental factors, particularly exposure to pesticides and industrial solvents, have been strongly linked to an increased risk of developing PD, likely through mechanisms related to mitochondrial dysfunction and oxidative stress. Additionally, epigenetic regulation, including histone modifications that influence SNCA expression, plays a significant role in disease susceptibility. Recent research underscores the essential role of the brain–gut–microbiota axis in the pathophysiology of PD.

KEYWORDS: Parkinson's disease (PD), Pathophysiology, Drug use in Parkinson, Brain–gut microbiota axis, Importance of gut brain axis in treating Parkinson.

INTRODUCTION

Parkinson's disease (PD) is a long-term, progressive neurodegenerative condition marked by the early and significant loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), along with a widespread accumulation of alpha synuclein (alphaSyn), which is an intracellular protein.[1] During autopsy, there is an observed accumulation of misfolded α-synuclein protein within neurons (referred to as Lewy bodies and Lewy neurites, collectively known as "Lewy pathology"), which is found in up to 90% of clinically diagnosed Parkinson's disease cases. This pathology selectively impacts brain-stem nuclei (including the dorsal motor nucleus of the vagus, locus coeruleus, and substantia nigra), the peripheral autonomic region (such as the myenteric plexus, sympathetic ganglia, and skin autonomic nervous system), as well as the limbic and neocortical areas.[2] The degeneration of pigmented neurons, especially those in the substantia nigra that produce dopamine, is regarded as another distinctly characteristic aspect of the disease. While the clinical diagnostic criteria are still valuable, they do possess certain limitations.[3]

The occurrence and frequency of Parkinson's disease rise with advancing age, exhibiting a male to female ratio of about 2:1. Various studies indicate that incidence rates vary from 47 to 77 cases per 100,000 individuals aged 45 years or older, and from 108 to 212 cases per 100,000 individuals aged 65 years or older. Generally, the incidence of Parkinson's disease has been more prevalent among White individuals compared to Black or Asian individuals; however, the detection of Lewy bodies at autopsy—a defining characteristic of Parkinson's disease, as elaborated below—has shown similar frequencies among Black and White individuals. The prevalence of this condition is estimated to be around 572 cases per 100,000 individuals aged 45 years or older. Age and sex-adjusted mortality rates are estimated to be approximately 60%, which surpasses the mortality rates found in the general population.

Furthermore, the economic impact of Parkinson's disease in the United States is projected to rise from $52 billion in 2017 to $79 billion by 2037.[4]

Pharmacologic approaches at this stage concentrate on enhancing the response to levodopa while postponing the emergence of debilitating motor complications. Levodopa administration may require division into smaller, more frequent doses (for instance, every 3 hours instead of every 4–6 hours) or an adjustment in the total daily dosage to maintain "on" time without triggering dyskinesias. Immediate-release (IR) formulations are still favored for their flexibility in titration.Dopamine agonists (such as pramipexole, ropinirole, and rotigotine) can help to smooth motor responses and prolong the benefits of levodopa when incorporated into the treatment plan, although tolerability concerns may restrict their use in older individuals.[5] Catechol-O-methyltransferase (COMT) inhibitors (including entacapone and opicapone) work by inhibiting the breakdown of levodopa in the periphery, thereby extending its plasma half-life and decreasing "off" time.[6] MAO-B inhibitors like rasagiline or safinamide can offer modest additional symptomatic relief and may help to diminish motor fluctuations when used alongside levodopa. Adenosine A2A antagonists (such as istradefylline) can decrease "off" time by modulating the output of the basal ganglia and may be beneficial for patients who continue to experience fluctuations despite conventional adjunct therapies.[7]

The parasympathetic nerves and enteric nervous systems are among the earliest structures impacted by aSyn pathology. The dysfunction of the brain-gut-microbiota axis in Parkinson's Disease (PD) may correlate with non-motor symptoms that manifest prior to the classical motor symptoms, thereby supporting the hypothesis that the pathological process propagates from the gut to the brain. Gut microbiomes are crucial in regulating movement disorders, and changes in the microbiota could serve as a risk factor for PD. Sampson et al. reported that in mice overexpressing alphaSyn, alterations in the gut microbiota were necessary for the development of motor deficits, microglial activation, and alphaSyn pathology. Antibiotic treatment improved conditions, while microbial re-colonization exacerbated the pathophysiology in adult animals, indicating that postnatal signaling between the gut and the brain influences the onset and progression of the disease. The oral administration of specific microbial metabolites, such as short-chain fatty acids (SCFA), to germ-free mice facilitated the emergence of neuroinflammation and motor symptoms. Research has demonstrated that changes in the gut microbiome are linked to various clinical features. A recent study

conducted in Finland revealed that changes in microbiota composition, particularly the abundance of Enterobacteriaceae, are positively correlated with the severity of postural instabi lity and gait difficulties in PD patients. PD patients contained lower levels of short-chain fatty acids (SCFA), including butyrate, which are produced by bacteria that may have anti-inflammatory effects. Additionally, an increase in intestinal permeability and dysfunction in intestinal symbiosis have been suggested as mechanisms responsible for the development and progression of PD.[1]

PARKINSON

Parkinson's disease (PD), often referred to as idiopathic or primary parkinsonism, hypokinetic rigid syndrome, or paralysis agitans, ranks as the second most prevalent progressive neurodegenerative disorder, impacting 2% to 3% of individuals over the age of 65. The disease is characterized by the degeneration of dopaminergic neurons in the substantia nigra, along with the intracellular buildup of alpha-synuclein (α-synuclein) in the form of Lewy bodies, which serves as the neuropathological signature of the condition.[12] PD typically manifests later in life. There is an increasing acknowledgment that the pathology of Parkinson's Disease (PD) starts at least ten years prior to clinical diagnosis, characterized by the deposition of α-synuclein in various neurons, such as those found in the gastrointestinal tract, olfactory regions, hypothalamus, and autonomic nervous system.[4][13]

Pathophysiology of Parkinson

Parkinson’s disease is believed to have various causes, stemming from both genetic and non-genetic factors. Genetic variants with significant effect sizes have been discovered in around 20% of individuals with Parkinson’s disease (monogenic Parkinson’s disease). Autosomal dominant Parkinson’s disease with incomplete penetrance encompasses variants in LRRK2(Leucine-Rich Repeat Kinase 2) (found in about 1 to 2% of all cases and up to 40% of familial cases); GBA1(Glucosylceramidase Beta 1), which encodes glucocerebrosidase (present in 5 to 15% of cases and most prevalent in populations of Ashkenazi Jewish or North African descent); and VPS35(Vacuolar Protein Sorting 35) and SNCA(Synuclein Alpha), which are even rarer (occurring in less than 1% of cases). Recessively inherited variants of Parkinson’s disease include PRKN(Parkin RBR E3 ubiquitin protein ligase), PINK1(PTEN induced putative kinase 1), and DJ1(Protein deglycase DJ-1), which are responsible for the majority of cases that manifest at a young age. While all these variants are uncommon, they represent the most frequent genetic causes in certain populations. Abnormal α-synuclein is

observed in Parkinson's disease linked to SNCA or GBA1 and in approximately half of the cases associated with LRRK2, but it is infrequent in cases related to recessive variants; recessively inherited Parkinson's disease tends to exhibit fewer non-motor symptoms and more pronounced dystonia compared to the typical form of the disorder.[8][9] The majority of genetic research has concentrated on individuals of White European descent. As global initiatives progress, it is possible that new genetic associations will be discovered. A notable example is the finding of a novel variant in GBA1, which is responsible for 39% of Parkinson's disease cases among individuals of African ancestry.[10] In individuals lacking a significant genetic risk factor for Parkinson's disease, heritability is estimated to range from 20 to 30%, indicating a role for nongenetic factors. The identification of risk factors has been restricted to observations within specific populations, which are susceptible to various biases. Unlike genetic risk studies, most epidemiological research has examined only a limited number of risk factors, despite the fact that individuals typically encounter numerous potential exposures throughout their lives. Exposure to pesticides, whether residential or occupational (such as paraquat, rotenone, 2,4-dichlorophenoxyacetic acid, along with various organochlorines and organophosphates), or to chlorinated solvents (including trichloroethylene and perchloroethylene), has been linked to a dose-dependent risk of Parkinson's disease, exceeding 40% in the majority of studies. Laboratory investigations indicate that these toxic substances can induce experimental models of Parkinson's disease by disrupting mitochondrial function, leading to the selective loss of dopaminergic neurons, motor dysfunction, and other related alterations. Furthermore, a prospective cohort study revealed that a high intake of dairy products correlates with an elevated risk of receiving a clinical or pathological diagnosis of Parkinson's disease, as well as increased brain levels of heptachlor, an organochlorine pesticide, which may arise from the bioconcentration of this substance in milk.[4] The histone modification plays a critical role in the expression of the PD-associated α-synuclein coding gene SNCA, indicating that histone methylation may also be essential in regulating the SNCA gene.[11]

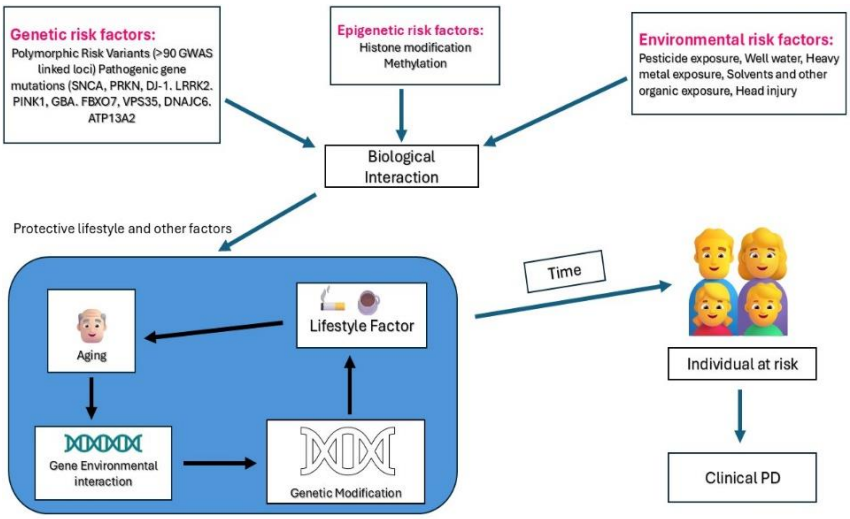

Figure 1: Pathophysiology of Parkinson.

GUT BRAIN AXIS IN PARKINSON

The parasympathetic nerves and enteric nervous systems represent some of the earliest structures affected by aSyn pathology. The dysfunction of the brain-gut-microbiota axis in Parkinson's Disease (PD) may be associated with non-motor symptoms that appear before the classical motor symptoms, thereby reinforcing the hypothesis that the pathological process spreads from the gut to the brain.[14] Gut microbiomes play a vital role in regulating movement disorders, and alterations in the microbiota could act as a risk factor for PD. Antibiotic treatment has shown to improve conditions, whereas microbial re-colonization has worsened the pathophysiology in adult animals, suggesting that postnatal signaling between the gut and the brain affects the onset and progression of the disease.[15] The oral administration of specific microbial metabolites, such as short-chain fatty acids (SCFA), to germ-free mice has promoted the development of neuroinflammation and motor symptoms. Research has indicated that alterations in the gut microbiome are associated with various clinical features. A recent study conducted in Finland found that changes in microbiota composition, particularly the prevalence of Enterobacteriaceae, are positively correlated with the severity of postural instability and gait difficulties in PD patients.[16] It has been observed that feces from PD patients contained reduced levels of short-chain fatty acids (SCFA), including butyrate, which are produced by bacteria that may possess anti-inflammatory properties.[17][18] Furthermore, an increase in intestinal permeability and dysfunction in intestinal symbiosis have been proposed as mechanisms responsible for the onset and progression of PD[19] Bidirectional communication between the central nervous system (CNS) and the gastrointestinal (GI) tract, known as the brain-gut axis, takes place in both

healthy and diseased states. The neural network responsible for regulating GI functions comprises both intrinsic and extrinsic nervous systems, forming a hierarchical four-level integrative structure.[20][21] The first level is the enteric nervous system (ENS), which includes neurons from the myenteric (Auerbach's) and submucosal (Meissner's) plexuses, as well as enteric glial cells (EGCs).[22] Local reflexes, such as the migrating motor complex and peristaltic reflex, are governed by the ENS through intrinsic primary afferent neurons (IPANs). These IPANs, found in the myenteric and submucosal plexuses, extend dendritic processes that form synapses with motor neurons and interneurons. The primary excitatory enteric motor neurons and interneurons are cholinergic in nature. Neurons that express vasoactive intestinal peptide (VIP) and/or nitric oxide (NO) induce relaxation of smooth muscle, while submucosal VIP neurons also promote intestinal secretion. Additionally, enteric dopaminergic neurons, which may inhibit intestinal motility, are distributed along an oral-aboral gradient within the GI tract. Dopaminergic neurons constitute 14%-20% of the enteric neurons in the upper GI tract, but their proportion diminishes to 1%-6% in the lower small intestine and large bowel.[23] The second level consists of the prevertebral ganglia, which modulate numerous peripheral visceral reflex responses.[24] The third level encompasses the autonomic nervous system (ANS) within the spinal cord, which is the origin of the sympathetic (T5-L2) and sacral (S2-S4) parasympathetic nervous systems, as well as the brainstem, which includes the nucleus tractus solitarius (NTS) and the dorsal motor nucleus of the vagus nerve (DMVN). The NTS and DMVN are responsible for receiving and originating the afferent and efferent fibers of the vagus nerve (VN), respectively. The influence of the DMVN is particularly significant in the upper GI tract, where cholinergic myenteric neurons facilitate vagal excitatory effects, while VIP/NO neurons mediate inhibitory reflexes.[25] The fourth level encompasses higher brain centers. Information from both cortical and subcortical centers, including the basal ganglia, is directed towards specific nuclei in the brainstem, which regulate numerous gastrointestinal (GI) functions. Disruptions at any level of this neural control can influence the modulation of GI functions, including mechanisms related to local enteric reflexes and extrinsic neural control. Recently, the significance of the enteric microbiota, which includes both commensal and pathogenic organisms, in the interactions of the brain-gut axis has been increasingly acknowledged. This recognition has led to a revised terminology that incorporates the broader concept of the brain-gut-enteric microbiota axis. The influence of gut microflora on the regulation of the brain-gut axis involves immunological, neuroendocrine, and direct neural mechanisms. It is known that gut microbiota can enhance local and systemic inflammation due to

lipopolysaccharides (LPS) produced by pathogenic bacteria and the generation of pro-inflammatory cytokines. Overstimulation of the innate immune system, resulting from gut dysbiosis, small intestinal bacterial overgrowth, and increased intestinal permeability, may lead to systemic and/or central nervous system (CNS) inflammation. Furthermore, the adaptive immune system may be affected by bacterial proteins that cross-react with human antigens. Gut bacteria are capable of synthesizing a variety of neurotransmitters and neuromodulators, including γ-aminobutyric acid, serotonin, dopamine, and short-chain fatty acids. The production of these neurochemicals also facilitates intracellular communication among microbiota members. Consequently, the concept of a "microbial organ-specific nervous system" can be speculated upon. Additionally, bacterial enzymes may generate neurotoxic metabolites such as D-lactic acid and ammonia. Direct neural communication between the gut and the brain occurs through the vagus nerve (VN), as bacteria can activate afferent neurons of the enteric nervous system (ENS). Vagal signals originating from the gut can trigger an anti-inflammatory response that safeguards against microbial-induced sepsis in a manner dependent on the nicotinic acetylcholine receptor α7 subunit. Numerous effects of the gut microbiota or potential probiotics on brain function have been demonstrated to rely on vagal activation.[26][27][28] Additionally, the colonization of the gut by bacteria significantly influences the postnatal development and maturation of the immune, endocrine, and even neural systems.[29] These processes are crucial elements that support CNS signaling. Dysfunction within the brain-gut-microbiota axis has been associated with stress-related disorders such as depression, anxiety, irritable bowel syndrome, and inflammatory bowel disease, as well as neurodevelopmental disorders like autism.[14]

IMPORTANCE OF GUT BRAIN AXIS IN TREATING PARKINSON

Neurological, immunological, and endocrine processes are all impacted by the gut microbiome. Therefore, through processes including the hypothalamic-pituitary-adrenal axis, lipopolysaccharides, neurotransmitters, and short-chain fatty acids, gut dysbiosis can impact behaviour, mood, and neuroinflammatory responses.[30,31]

Table 1: Association Between Gut Microbiota Composition and Clinical Features of Parkinson's Disease.

Microbiota Changes	Impact on Parkinson Disease	Correlation
Enterobacteriaceae ↑	Postural instability and gait disturbances	Positive

Enterococcus, Proteus, Escherichia–Shigella ↑	Severity of disease and duration	Positive
Lachnospiraceae ↓	Disease severity and cognitive impairment	Positive
Lactobacillaceae ↑, Christensenellaceae ↑	Disease severity and cognitive impairment	Positive
Bacteroides	Motor symptoms	Positive
Roseburia (Firmicutes phylum) at baseline ↓	Disease severity	Positive
Ruminococcaceae and Actinobacteria at baseline ↓	Faster cognitive impairment	Positive
SCFA-producing genera (*Blautia, Fusicatenibacter, Faecalibacterium*) ↓	Accelerated disease progression	Positive

TREATMENT OF PARKINSON

Levodopa-The cornerstone of contemporary Parkinson's disease (PD) treatment consists of levodopa based medications, which are formulated to replenish the dopamine levels in the depleted striatum. As previously mentioned, dopamine itself cannot penetrate the blood-brain barrier (BBB) and is therefore ineffective for treating PD. Conversely, the dopamine precursor levodopa can cross the BBB and is utilized as a therapeutic option. Once absorbed and transported across the BBB, levodopa is converted into the neurotransmitter dopamine by the enzyme DOPA decarboxylase. It is common practice for patients to start with a low dose of levodopa, with adjustments made based on the patient's response to the treatment, while also considering any adverse effects that may arise. Most patients typically require a daily dosage ranging from 150 to 1000 mg, administered in multiple doses throughout the day. Generally, the therapeutic effects of levodopa are observed relatively quickly and can last for several hours, especially in the initial stages of the disease. However, as the disease progresses, the effects of the medication tend to diminish more rapidly, often necessitating an increase in the frequency of dosing.[32]

Dopamine agonist-Dopamine receptor agonists were introduced in 1978 for the treatment of Parkinson's disease (PD). The commonly prescribed agonists include an ethanolamine moiety and can be classified into ergot and non-ergot types, depending on their receptor specificities. These medications enhance the dopamine system's activity by attaching to dopaminergic receptors and, unlike levodopa, do not require conversion into dopamine. Dopamine agonists are frequently recommended as a first-line treatment for PD, especially in younger patients. This strategy helps postpone the initiation of levodopa therapy, potentially minimizing the adverse motor complications mentioned earlier.[33]

Monoamine Oxidase B (MAO-B) inhibitors-One notable class of these medications is the MAO-B inhibitors. MAO-B is a key enzyme responsible for the breakdown of dopamine, and by decreasing the activity of this enzyme, there is an increase in dopaminergic activity within the striatum, facilitated by endogenous dopamine. The use of these inhibitors alleviates motor symptoms in PD patients, and similar to dopamine agonists, they can serve as an initial treatment option to postpone the necessity for levodopa therapy and to minimize the risk of motor complications induced by levodopa. Although they may be adequate for managing symptoms in the early stages of the disease, the majority of patients will eventually need treatment based on levodopa. Additionally, MAO-B inhibitors can be utilized alongside levodopa-based therapies to enable a reduction in the dosage of levodopa.[34]

Catechol-O-methyl transferase inhibitors-COMT inhibitors provide a therapeutic approach to maintaining endogenous dopamine levels by minimizing its breakdown. These inhibitors are primarily utilized as adjunctive therapy alongside levodopa, extending its duration of action by enhancing its half-life and facilitating its delivery to the brain. For some patients, this results in better control of motor symptoms, leading to a decrease in off time compared to standard combinations of levodopa and DOPA decarboxylase inhibitors. They are frequently prescribed to patients experiencing end-of-dose 'wearing-off' issues specifically with levodopa therapy alone.[35]

Anticholinergics-The medications discussed thus far are all intended to enhance dopaminergic activity within the striatum. A limited number of drugs utilized in the treatment of Parkinson's Disease (PD) operate through non-dopaminergic mechanisms. One such category of medications is anticholinergics. These drugs diminish the activity of the neurotransmitter acetylcholine by functioning as antagonists at cholinergic receptors. Although their use is restricted and they are now rarely prescribed, they may provide some advantages in alleviating rigidity and tremors associated with PD. The loss of dopaminergic neurons disrupts the typical equilibrium between dopamine and acetylcholine in the brain, and anticholinergic medications may help restore and maintain this normal balance between the two neurotransmitters.[36]

Amantadine-Originally, amantadine (Symmetrel) was created as an antiviral medication for flu treatment, but it has since been utilized for managing Parkinson's disease (PD). It can be employed to address rigidity, resting tremor, and occasionally fatigue, potentially providing a temporary enhancement in symptoms. Additionally, it may enable a reduced dosage of

levodopa, thereby lowering the risk of dyskinesia. Nevertheless, its most significant advantage is likely its ability to mitigate the severity of dyskinesias induced by levodopa.[37]

CONCLUSION

A deeper comprehension of the interactions between the brain-gut-microbiota axis iexpected to provide new insights into the pathophysiology of Parkinson's Disease (PD), facilitate earlier diagnosis focusing on peripheral biomarkers within the enteric nervous system (ENS), and lead to innovative therapeutic options for PD. Interventions, whether dietary or pharmacological, should aim to alter the composition of gut microbiota and improve the integrity of the intestinal epithelial barrier in patients with PD or those at increased risk for the disease. This could potentially impact the initial phase of the subsequent neurodegeneration cascade in PD. Understanding the temporal and causal relationship between changes in gut microbiota and the development of PD will hold significant clinical importance. Additional research into novel therapeutic strategies for PD that involve modifying gut microbiota through probiotics, prebiotics, or even fecal microbiota transplantation is eagerly anticipated.[14]

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