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Parkinson Disease and the Microbiome

Updates and clinical applications

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Abstract

Introduction

Parkinson disease (PD) is one of the fastest-growing neurodegenerative diseases, with gastrointestinal symptoms often preceding motor symptoms by several decades. As such, there has been an interest in understanding the potential role of the microbiome and how it relate to PD and what clinical implications this may have for patient management.

Objective

The aim of this review was to conceptualize current understandings of the crosstalk between neurological and gastrointestinal systems as they relate to PD pathogenesis.

Results

It is now understood that gut factors play a role in both initiating and promoting neurodegeneration in a subset of PD patients. Some of th major mechanisms underpinning these factors include intestinal dysbiosis, intestinal hyperpermeability, inflammation, and enteric alpha-synuclein aggregation. An integrative approach to the assessment of PD patients encompasses understanding such mechanisms and how they may be contributing to PD progression. Gut-specific treatments should focus on targeting pathogens that may enhance disease progression or interfere with medication efficacy, improving microbial diversity and gastrointestinal-related symptoms, targeting alpha-synuclein aggregation and neuronal inflammation, and promoting antioxidative function.

Conclusion

The gut microbiome offers potential opportunities to enhance care and promote patient outcomes for those with PD. While naturopathic and integrative medicine does not offer a cure, it may play a role in slowing disease progression and enhancing quality of life for these patients.

Introduction

Parkinson disease is a progressive neurodegenerative disorder affecting over 10 million individuals worldwide.[1] Second only to Alzheimer disease in prevalence, PD is the fastest-growing neurodegenerative disease, with rates of prevalence continuing to accelerate. [2] In those aged 45 years and more, the overall prevalence of PD has been reported as 572 per 100,000 people in North America.[3] Nearly 90,000 Americans are diagnosed with the condition each year, and some studies predict both prevalence and incidence will rise 30% by the year 2030.[4]

PD results from the loss and degeneration of dopaminergic neurons in the basal ganglia and an aggregation of Lewy bodies.[5] While motor features remain the hallmark of establishing a diagnosis, gastrointestinal symptoms can precede them by several decades and have led to an increased interest in the potential role of the microbiome in PD pathogenesis.[6] Novel strategies are needed to support clinical outcome as traditional approaches have thus far failed to encompass the entire spectrum of disease presentation.

Background

While the pathological signatures of PD have been well-documented, its pathomechanisms remain somewhat elusive.[7] A progressive loss dopaminergic neurons in both the substantia nigra (a component of the basal ganglia) and the locus coeruleus lead to dopamine deficienc in striatum receptors, causing interrupted transmission to the thalamus and motor cortex. This has consequences for motor functioning and results in the motor disturbances seen in individuals affected by the disease.[8]

Lewy bodies composed of alpha-synuclein aggregates and other proteins are another neuropathological hallmark of PD.[9] Alpha-synuclein proteins are abundant in dopamine-producing neuronal cells and are involved in the regulation of vesicular transport and neurotransmitt release; thus, they play an important role in the regulation of synaptic function.[10] In PD, there is a mismatch between the production and degradation of alpha-synuclein proteins, and this appears to play a central role in disease pathogenesis.[11] Under physiological circumstances, alpha-synuclein is produced and degraded in a balanced manner, but in PD there appears to be both increased productior of alpha-synuclein as well as decreased clearance rates, allowing for accumulation in the form of Lewy bodies.[12]

There are a few theories on why these processes may occur. A possible explanation includes disruptions to normal cellular mechanisms regulating alpha-synuclein turnover, including impaired lysosomal function, a process responsible for degrading and recycling cellular waste.[12] Genetic mutations are another potential mechanism in which several factors may increase the expression of alpha-synuclein or interfere with its degradation pathways.[12]

Additional external factors may also play a role in alpha-synuclein misfolding and the subsequent aggregation observed in PD. Oxidative stress, a process that occurs via an imbalance between the production of reactive oxygen species (ROS) and the host's antioxidant defense has been shown to promote alpha-synuclein misfolding and aggregation.[13–15] Via similar mechanisms, chronic inflammation,[16] environmental toxin exposure,[17,18] and traumatic brain injuries[19,20] are also thought to contribute to PD development due to associations between such factors and increased disease risk. Some evidence also suggests that certain microbial infections, which may promote inflammation and oxidative stress, contribute to Lewy-body formation as well and, thus, PD pathogenesis.[21]

Most alpha-synuclein aggregates are found in the brainstem, substantia nigra, and cortex. Interestingly, they have also been discovered in other areas, including the spinal cord, peripheral nervous system, cardiac plexus, and the enteric nervous system.[22] These aggregates found outside of the central nervous system have been identified as a potential marker, or even a contributing factor, in developing PD pathophysiology.

Both genetic and environmental factors are thought to play a role in PD pathogenesis. However, studies suggest that only 3% to 5% PD cases occur due to mutations in a single gene, while 16% to 36% of cases can be explained by influenced by variations in multiple genes.[23] Therefore, most PD cases remain idiopathic.[23]

The Critical Role of the Human Microbiome

The term "gut microbiome" refers to the trillions of microbes colonizing the gastrointestinal tract.[24] This system has now been recognized and implicated in various processes essential to human function. Research suggests that the microbiome plays an important role in neurological function, modulated through a bidirectional communication pathway known as the gut-brain axis.[25]

This connection is mediated by the vagus nerve, as well as various neurotransmitters and hormones, which allows neurological signals to influence the gut and vice versa.[26] Modulation of this axis by the microbiome is achieved through a variety of mechanisms. These include the modulation of host metabolic pathways, regulation of immune function, and the production of neurotransmitters and other signaling molecules.[24] For instance, specific microbial species have been found to aid in producing neurotransmitters, including serotonin and gamma-aminobutyric acid (GABA), key regulators of mood and behavior.[27]

A growing body of research supports the important role of the gut microbiome in overall health and as a potential therapeutic strategy in neurological disease. Microbiota diversity is not static, and many factors have been found to influence its composition, including mode of birth delivery, antibiotic usage, nutritional factors such as diet, stress levels, and genetics.[26] Recent studies have implicated the gut-brain axis in the pathogenesis of a variety of other neurological diseases, including multiple sclerosis, autism, schizophrenia, and Alzheimer disease.[26]

The gut microbiome has been found to influence immune functioning, which, in turn, can influence neurological functions.[28] Evidence suggests that disruptions in gut microbiota, such as increased intestinal permeability and dysbiosis, may trigger inflammatory cascades th cause immune activation, and such mechanisms have been implicated in the pathogenesis of various neurological disorders.[28] Such imbalances, including a reduction in beneficial strains and an increase in pathological strains, allow for the crossing of bacteria and other toxins into the bloodstream. When such processes occur, an inflammatory response is mounted, triggering immune activation throughout

toxins into the bloodstream. When such processes occur, an inflammatory response is mounted, triggering immune activation throughout the body, including within the central nervous system.[29]

Microbiome Alteration in Parkinson Disease

As indicated above, gastrointestinal symptoms can precede motor symptoms of PD by several decades. Specifically, constipation is 1 of the earliest nonmotor manifestations reported in the literature.[6] Such discoveries have sparked interest in gaining a better understanding of the relationship between PD and the gastrointestinal system as a strategy to identify prodromal patients and to better understand disease progression.

The discovery of alpha-synuclein aggregation in the enteric nervous system in the 1980s gave rise to the "ascending anatomic theory" hypothesis.[30] This theory postulates that insults to the gut microbiome may trigger misfolding and aggregation of alpha-synuclein within the enteric nervous system and propagation toward the brain via cell-to-cell transfer.[30]

More recent studies have produced evidence both for and against this hypothesis, with some findings suggesting potential "brain-first" and "gut-first" PD subtypes.[31] To date, there is an understanding that factors related to the gut may play a role in both initiation and promotion of neurodegeneration in a subset of PD patients.[11] Such factors include intestinal dysbiosis, hyperpermeability, inflammation, and enteric alpha-synuclein aggregation.[11] These factors appear to be closely related, each process influencing another. As such, a better understanding of the mechanisms behind these factors is needed, particularly in this "gut-first" subtype of PD patients.

Intestinal Dysbiosis

A symbiotic relationship exists between the gut microbiota and the human host. Dysbiosis is defined as a disruption of the normal balance between gastrointestinal microbiota and the human host.[32] The gut and brain communicate via various routes, including the vagus nerve, immune signaling, tryptophan metabolism, and various metabolites, including short-chain fatty acids, branched-chain amino acids, and peptidoglycans.[25]

Dysbiosis has been proposed as a trigger in the development of PD, with research implicating alterations in both the number and the composition of gut microbiota and their metabolites.[11] Variances in the abundance of specific taxa observed in PD patients compared to healthy controls share similarities with variances observed in other conditions, including multiple sclerosis and inflammatory bowel disorders.[33] Key taxa involved in short-chain fatty acid production are diminished in PD.[33] Some of the more commonly implicated alterations include decreased levels of butyrate-producing bacteria, including *Roseburia*, *Faecalibacterium*, and *Blautia*,[34] increased levels of *Akkermansia*,[34–36] *Bifidobacterium*,[35,37,38] *Enterobacteriaceae*,[37] and *Lactobacillus*,[39,40] and decreased *Prevotellaceae*[35] and *Bacteroides*.[41]

Other states of dysbiosis are also associated with PD, including elevated levels of *Helicobacter pylori* (*H pylori*) and small intestinal bacterial overgrowth (SIBO), both of which have been associated with greater motor-symptom severity in PD patients.[42]

Intestinal Hyperpermeability

The gastrointestinal system has a semipermeable gut barrier that regulates nutrient absorption while preventing harmful agents from crossing the intestinal epithelium.[41] It is thought that compromised intestinal barrier integrity can allow toxins and proinflammatory molecules to access neuronal tissue and promote oxidative stress.[43]

Lipopolysaccharide (LPS) is a bacterial toxin that can activate immune responses. LPS-expressing microbes seen in PD patients may activate toll-like receptors (TLRs).[44] TLRs are expressed on epithelial, immune, and enteric glial cells, and their activation can lead to dysbiosis, with downstream effects of intestinal and neural inflammation.[44–46]

Enteric Inflammation

Inflammation in the gut is a known risk factor for dysbiosis and hyperpermeability and has been documented in PD patients.[43] Enteric inflammation can drive PD pathogenesis via systemic effects, including increased cytokine production, blood-brain barrier disruption, microglial activation, and through migration of inflammatory cells to the brain.[11] Together, these processes may lead to neuronal dysfunction or loss.

Alpha-synuclein is thought to be involved in the body's immune responses and influenced by inflammation.[46] A vicious cycle exists in which inflammation can cause alpha-synuclein aggregation, which can trigger further inflammation.[43]

Colonic biopsies from PD patients show increased expression of proinflammatory cytokines and glial markers compared to healthy controls.[43] Such changes include an increased expression of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin 6 (IL-6), and IL-β.[43] There is reason to believe that enteric inflammation in PD is tightly associated with glial dysregulation and may affect disease

duration.[43]

Alpha-Synuclein Aggregation

Aberrant gut microbiota or their byproducts and resultant inflammation have been proposed to induce alpha-synuclein misfolding and result in its abnormal aggregation in the enteric nervous system.[37] Such fragments can then travel from the enteric nervous system to the central nervous system via the vagus nerve, where they can spread throughout various brain regions in a prion-like fashion.[11]

This has been demonstrated in multiple trials using animal models, in which injection of alpha-synuclein fibrils into gut mucosa converts endogenous alpha-synuclein into pathologic species that utilize the vagus nerve to spread from the ENS to the CNS.[47] Conversely, in subjects who underwent vagotomy, such neuropathology did not develop.[47] This highlights the role of the vagal nerve in propagating alph synuclein to the brain.

Assessment & Diagnostics

A naturopathic approach to assessing PD patients is multifactorial and encompasses the principles of understanding underlying mechanisms potentially contributing to PD progression. While not always the case, seeking out gut-related factors is important to treatme planning and may include:

A comprehensive neurological examination to obtain baseline data and monitor disease progression, which may include the use of the Unified Parkinson's Disease Rating Scale (UPDRS)[48]

Inquiry on dietary and bowel habits, including bowel regularity and frequency of constipation. A useful and validated tool that is specific tc PD patients, the Gastrointestinal Dysfunction Scale for Parkinson's Disease,[49] can be implemented into clinical practice.

Stool analysis

- Bacterial pathogens, such as *H pylori, Enterococcus faecalis, Desulfovibrio,* and *Proteus mirabilis*
- Reductions in commensal bacterial strains may also provide some insight, including strains such as *Roseburia*, *Faecalibacterium*, *Blauti Akkermansia*, *Bifidobacterium, Enterobacteriaceae, Lactobacillus, Prevotellaceae,* and *Bacteroides.*
- Zonulin, an important moderator of intracellular tight junctions, can be used to assess the integrity of the gastrointestinal wall and identify possible intestinal permeability.
- Calprotectin, an inflammatory marker, can be used to assess the level of neutrophil recruitment and intensity of inflammatory processes occurring in the intestinal wall.

Laboratory measurements

- Inflammatory markers (erythrocyte sedimentation rate [ESR] and high-sensitivity C-reactive protein [hs-CRP])
- Zinc and copper to determine balance between the 2, as higher levels of either are associated with neuronal degeneration[50]
- Ferritin, as higher levels are associated with deposition in the CNS and higher oxidative stress[51]
- Autoimmune panel to determine if there is an underlying autoimmune component
- Red blood cell (RBC) manganese, as higher levels are associated with worsening PD symptoms[50]

Food sensitivity testing may also be helpful to identify if there are any immune triggers that could heighten the patient's immune response

Clinical Considerations

The above information highlights the role of the microbiome in PD pathophysiology and provides opportunities in which naturopathic treatment can play a role in patient care. While naturopathic treatment will not cure PD, it may play a role in preventing disease progressic and in enhancing quality of life for these patients.

Gut-specific treatment goals may include eradicating specific pathogens that may contribute to disease progression or interfere with medication efficacy; improving microbial diversity and gastrointestinal symptoms; targeting alpha-synuclein aggregation and neuronal inflammation; and promoting antioxidative function.

Optimize Medication Efficacy

Levodopa, the most widely used medication in the treatment of PD, works by replacing dopamine in the brain. Levodopa efficacy decrease over time, necessitating frequent dose adjustments.

H pylori interferes with levodopa absorption by affecting gastric acid production, resulting in lower levels of the medication reaching the bloodstream.[52] *H pylori* infection is also associated with increased activity of catechol-O-methyltransferase (COMT), which is responsible fo breaking down levodopa in gut and peripheral tissues.[52] Higher COMT levels reduces levodopa bioavailability and effectiveness.[7] Eradicating *H pylori* infection may improve levodopa absorption, optimize efficacy, and reduce dose requirements.

Enterococcus faecalis converts levodopa into inactive compounds via decarboxylation reactions in the gastrointestinal tract.[52] This reduces the amount of active medication available for absorption into the bloodstream, leading to decreased efficacy.[52] Targeting and treating *Enterococcus faecalis* overgrowth may improve levodopa metabolism and efficacy in treating PD symptoms. Treatment may include increasing dietary prebiotics and reducing consumption of refined sugars thought to favor this bacteria's growth.

Desulfovibrio bacteria has recently emerged as another potential player in PD pathology, with studies revealing higher levels in PD patients compared to healthy controls as well as concentrations that correlate with disease severity.[53] *Desulfovibrio* produce hydrogen sulfide and LPS, which may induce oligomerization and aggregation of alpha-synuclein.[53] Reducing dietary sulfates may be beneficial, as this bacterium thrives in environments rich in sulfur-containing compounds. While nonspecific, low-FODMAP (fermentable oligosaccharides disaccharides monosaccharides, and polyols) dietary strategies may play a short-term role in helping to rebalance the microbiome, the diet lacks specific evidence supporting its use in PD.

Improve Gut-Related Factors & Immune Responses

Dysbiosis of the intestinal flora and conditions associated with increased intestinal permeability can cause an overstimulation of innate immune responses in the gut.[52] Gut inflammation and gut hyperpermeability may promote inflammation, toxin exposure, and oxidative stress, which may worsen PD symptoms.[52]

Targeting gastrointestinal inflammation may be achieved by supplementing with glutamine, an amino acid that supports the integrity of th gastrointestinal lining.[54] It has anti-inflammatory properties and the ability to act as an enterocyte fuel source, which supports tight-junction assembly and protective mucus production.[54]

Another important factor is increasing the rate of peristalsis to improve constipation symptoms and promote gastrointestinal detoxificatio in PD patients.[7] This may involve the use of gentle laxative agents to promote elimination pathways.

Tauroursodeoxycholic acid (TUDCA) is a hydrophilic bile acid that has shown important neuroprotective properties, including promotion o autophagy and neuronal self-repair.[55] TUDCA is thought to exert hormonal effects on gut microbiota composition.[56] Effects include reduction of protein aggregation and deposition, reduction of ROS and proinflammatory cytokine production, and modification of gene expression in cell-cycle regulation.[56]

Lactobacillus and *Bifidobacterium* probiotic species have demonstrated efficacy in some PD parameters.[57,58] Most consistently, effects include improvements in stool consistency, gastrointestinal transit time, and bowel-movement frequency.[57] There is also some evidence suggesting improvements in UPDRS scores as well as improvements in systemic inflammation.[57,58] While these results are promising, future research is warranted to understand these probiotics' disease-modifying effects.[58]

Dietary Adjustments & Adjunctive Therapies

Dietary strategies can play an important role in PD symptom management and may help in reducing disease progression. It is important t note that patients need to be aware that levodopa must be taken separately from food, as food intake delays and reduces medication absorption in the gastrointestinal tract.[11]

Foods to include in the diet include polyunsaturated fatty acids (PUFAs), antioxidant-rich foods, and prebiotics.[11] PUFAs inhibit TLR signalir and intestinal inflammation, which can improve gut immune responses and barrier integrity.[59] Fiber-rich foods, including prebiotics, promote bowel regularity and increase the rate of peristalsis, and nondigestive carbohydrate components produce short-chain fatty acids via bacterial fermentation.[60] Antioxidants may provide protection against neuronal death.[60] Additionally, supplementation with glutathion and ubiquinol for oxidation management may provide even more benefits in older patients.[61]

Another important consideration is docosahexaenoic (DHA), which has unique roles in neuronal membranes and phospholipid productior (both phosphatidylcholine and phosphatidylserine)[62] and is thought to promote neuronal survival.[59] DHA has antioxidant properties and

plays a role in mitochondrial function and energy production.[59] Of all neurodegenerative conditions, PD is associated with the highest oxidative stress due to the pro-oxidant qualities of dopamine degradation.[61] Hence, there is likely an increased demand for antioxidants, DHA specifically.

Conclusions

Microbiome research in PD is still in its infancy and will likely change rapidly. While early research suggests the microbiome may play a contributing role in the disease, much remains unknown. Our current understanding may not translate to improving specific patient outcomes or disease parameters. However, naturopathic medicine involves treating the whole person, and this remains a cornerstone in helping PD patients and providing appropriate and competent collaborative care.

Conflict of Interest

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