Inflammatory Bowel Diseases and Parkinson’s Disease

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Abstract. The etiology of Parkinson’s disease (PD) is multifactorial, with genetics, aging, and environmental agents all part of the PD pathogenesis. Widespread aggregation of the α-synuclein protein in the form of Lewy bodies and Lewy neurites, and degeneration of substantia nigra dopamine neurons are the pathological hallmarks of PD. Inflammatory responses manifested by glial reactions, T cell infiltration, and increased expression of inflammatory cytokines, as well as other toxic mediators derived from activated glial cells, are currently recognized as prominent features of PD. Experimental, clinical and epidemiological data suggest that intestinal inflammation contributes to the pathogenesis of PD, and the increasing number of studies suggests that the condition may start in the gastrointestinal system years before any motor symptoms develop. Patients with inflammatory bowel disease (IBD) have a higher risk of developing PD compared with non-IBD individuals. Gene association study has found a genetic link between IBD and PD, and an evidence from animal studies suggests that gut inflammation, similar to that observed in IBD, may induce loss of dopaminergic neurons. Based on preclinical models of PD, it is suggested that the enteric microbiome changes early in PD, and gut infections trigger α-synuclein release and aggregation. In this paper, the possible link between IBD and PD is reviewed based on the available literature. Given the potentially critical role of gastrointestinal pathology in PD pathogenesis, there is reason to suspect that IBD or its treatments may impact PD risk. Thus, clinicians should be aware of PD symptoms in IBD patients.

Keywords: Parkinson’s disease, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, enteric nervous system, brain-gut axis, gastrointestinal track inflammation, inflammation

INTRODUCTION

The majority of Parkinson’s disease (PD) patients experience non-motor-symptoms such as chronic constipation and/or impairment of gastrointestinal (GI) transit many years prior to disease onset [1–4]. The work by Braak and his colleagues suggested that the pathological process in PD originates in the GI tract [5] and spreads from the enteric nervous system (ENS) via the vagus nerve to the central nervous system (CNS) in predictable stages [6], thereby affecting the brain and consequently resulting in neurodegeneration. Lewy pathology has been detected in the gut of PD patients and, thus, GI inclusions of α-synuclein (α-syn) have been investigated as a potential biomarker for prodromal PD [7]. Accordingly, α-syn immunostaining has been showed in distal colon tissue samples removed 2 to 5 years before the first reported symptom of PD in patients experiencing constipation prior to PD onset [8]. Subsequently, two multi-investigator blinded-panel...
evaluations of α-syn pathology clearly established its selective, however inconsistent, presence in the PD colon and exclusion from controls [9, 10]. However, no single staining method or staining pattern had a sensitivity and specificity of more than 80% [10].

This review will focus mainly on chronic inflammatory process in the GI tract, which makes up a connection between the surrounding environment and the CNS and thus function as an entry point for pathogens and other environmental factors that might predispose certain individuals to develop PD [6, 11]. Recent studies have investigated the GI microbiome to elucidate whether the composition of the microbiome or eventually dysbiosis might play a role in intestinal inflammation and GI barrier-function in PD [12–15]. The inflammatory processes that have been found to occur in some patients with PD have naturally led to discussion of an association between inflammatory bowel disease (IBD) and PD since the two share some basic characteristics. IBD is characterized by chronic pro-inflammatory immune activity, a trait which is now suggested also to be a fundamental element of neurodegenerative disorders [16–18]. Therefore, intestinal inflammation may be of particular relevance in the pathogenesis of PD.

INFLAMMATORY BOWEL DISEASE

In IBD, the tridirectional relationship between the commensal flora (microbiota), genetic susceptibility to disease development, and mucosal immune system is dysregulated, leading to chronic inflammation. Each of these three aspects is affected by genetic and environmental factors that determine the risk for the disease [19, 20]. IBD is currently considered as an inappropriate immune response to the endogenous commensal microbiota within the intestines, with or without some components of autoimmunity [21, 22]. IBD includes Crohn’s disease (CD) and ulcerative colitis (UC). CD can affect any part of the GI tract in a discontinuous transmural pattern. Active CD is characterized by focal inflammation and formation of fistula tracts, which resolve by fibrosis and structuring of the bowel. The bowel wall thickens, becomes narrowed and fibrotic, leading to chronic, recurrent bowel obstructions. UC typically involves the large intestine in an uninterrupted pattern with typical confinement to the mucosa leaving the deeper layers unaffected except in fulminant disease. The major symptoms of UC are diarrhea, rectal bleeding, tenesmus, passage of mucus, and crampy abdominal pain [20].

In a PD rat model, bowel inflammation can exacerbate neuroinflammation and disrupt the blood–brain barrier (BBB), leading to dopaminergic neuronal loss in the substantia nigra [18]. Further, several studies have shown clinical evidence of bowel inflammation in PD patients [13, 16, 23]. However, the possible connection between inflammatory processes in the GI tract and PD questions whether IBD could constitute a risk factor for developing PD or eventually exacerbate disease progression.

PD AND IBD: GENETIC BACKGROUND

The association between PD and CD has been a focus point since it was discovered in genome-wide association studies that the leucine rich repeat kinase 2 (LRRK2) gene is a common susceptibility factor in both diseases [24–32]. LRRK2 mutations are now known to be the most common genetic cause of PD, accounting for 10%–40% of familial cases depending on the population studied [33]. Polymorphisms in the gene have also been linked to an increased risk of CD [34, 35]. Unlike other PD-associated genes, LRRK2 associated parkinsonism manifests similar clinical phenotypes to idiopathic PD, displaying strong age-dependent development of PD symptoms [29]. LRRK2 is probably involved in the pathological interplay between peripheral and CNS innate immunity which contributes to the progression of PD. The expression of LRRK2 is tightly regulated in both systems [36]. Hui and colleagues identified recently a novel coding variant in the LRRK2 gene, N2081D, to be associated with increased risk for CD (OR, 1.73; P = 2.56 × 10−9), after exome sequencing followed by array-based genotyping of 2066 cases and 3633 controls in the Ashkenazi Jewish population [32]. In addition, they identified a protective haplotype, which has previously also been shown to reduce risk in PD [37].

Despite these results, the following important question remains: how do these variants influence the disease mechanism? An obvious explanation could be that the gene-alterations predisposing to the two diseases are located at different positions on the gene or/and possibly also flanking regions that regulate gene expression (e.g. SNPs in promoter or non-coding regions) or in genes coregulated with LRRK2 [38]. The LRRK2 protein is a large protein with different domains providing several different cellular
functions [39]. Since the alterations are located in different positions of the protein, they may affect different domains and thereby different pathways, different cellular processes and distinct pathological mechanisms. LRRK2-dysfunction in PD is associated with aberrant kinase or GTPase-activity which is not the case for IBD [40, 41]. The most prevalent LRRK2 mutations in PD have been shown to affect macroautophagy in various cellular models while a role in autophagy signaling has been recapitulated in vivo. Dysregulation of autophagy has been implicated in PD pathology, and this raises the possibility that differential autophagic activity is relevant to disease progression in PD patients carrying LRRK2 mutations. Indeed, recent data support a distinct molecular signature for LRRK2 PD compared to idiopathic PD, where dysregulation of vesicular trafficking and sequestration of lysosomal components underpins alterations in macroautophagy and protein clearance [42].

Another important factor is the cell type affected by LRRK2 mutations. LRRK2 is expressed not only by the neurons and immune cells in human brain, but also peripheral myeloid cells express LRRK2 at high levels, and the expression of LRRK2 is upregulated by inflammatory signals [43–46]. It has been shown that a common risk variant at the LRRK2 locus is associated with higher LRRK2 expression in microglia-like cells derived from human monocytes [47]. This suggests that the role of LRRK2 risk variants may be more prominent under situations where microglia are stimulated. LRRK2 expression enhances transcriptional activation of inflammatory responses [44] and PD-linked mutations induce cytokine production in activated microglia [48]. Inhibition of LRRK2, either by small-molecule kinase inhibitors or RNAi knockdown, attenuates microglial inflammatory responses [49] and LRRK2 deficiency impairs immune clearance in vivo [50].

In the gastrointestinal tract of CD patients, LRRK2 expression is restricted to lamina propria macrophages, dendritic cells and B-lymphocytes, and is induced by interferon-γ, which is consistent with its role in IBD [44]. A recent study has found high expression of LRRK2 in Paneth cells in the ileum, demonstrating that both NOD2 and LRRK2 are required for proper lysosomal sorting within Paneth cells [51]. Thus, in relation to genetic factors it is worth mentioning that polymorphisms in the CARD15/NOD2 gene are associated with CD [28, 52–54]. This gene has been found to be overexpressed in PD patients [55]. CARD15/NOD2 protein represents a pattern recognition receptor that plays a role in the initiation of inflammatory host immune responses [56] and CARD15/NOD2 mutations have been associated with the development of chronic IBD. Further, monocytes/macrophages derived from humans or mice with such mutations demonstrate altered NF-κB activity and inflammatory cytokine production [57, 58]. NOD2 receptors function as intracellular sensors to bacterial infections generating damaging CNS inflammation and they have been shown to be constitutively expressed in microglia and astrocytes [59].

Highlighting the relevance of the immune system, large genome-wide association studies (GWAS) and pathway analyses based on 138,511 individuals of European ancestry identified 17 shared loci between PD and seven autoimmune diseases including celiac disease, rheumatoid arthritis, type 1 diabetes, multiple sclerosis, psoriasis, ulcerative colitis and Crohn’s disease [38]. Among these autoimmune diseases, the strongest pleiotropic enrichment was observed between PD and Crohn’s disease including both LRRK2 and MAPT genes. The findings further indicate that defects in cargo transport mechanism might underlie the disease pathogenesis in both phenotypes. Another shared gene HLA-DQB1 involved in immune response and antigen presentation implicates overlapping factors related to the immune system. In agreement with the epidemiological findings (discussed in the next section), the GWAS found only moderate polygenic pleiotropic enrichment between PD and UC, whereas genetic enrichment with type 1 diabetes, celiac disease, psoriasis, and multiple sclerosis was very weak [38].

EPIDEMILOGICAL EVIDENCE FOR A LINK BETWEEN IBD AND PD

With consistent genetic and functional evidence established between PD and IBD, epidemiological studies have emerged investigating IBD as a risk factor for PD. In 2016, Lin et al. were first to investigate associations between PD and IBD in a Taiwanese nationwide retrospective cohort study. The study concluded that IBD was associated with a 35% increased risk of PD which was most pronounced in CD patients [60]. Another retrospective study by Fujioka et al. investigated the occurrence of CD with PD by searching the medical records of 876 PD patients and subsequently looked for incidences of prior or current CD. The study found that the co-occurrence of
CD with PD was consistent with the number of cases expected in the general population [61]. However, limitations to this study was the relatively small number of subjects. Furthermore, the study was based on medical records and the research team did not perform any confirmatory tests to detect the presence of CD in the patients.

One year later, three large cohort studies from Denmark, Sweden and USA were published [62–65]. In the Danish study, we have shown that IBD patients have a 22% increased risk of PD as compared with non-IBD individuals (HR = 1.22; 95% CI 1.09 to 1.35). When stratifying, the increased risk of Parkinsonism was significantly higher among patients with UC but not with CD [62]. In the Swedish and American studies, the increased PD hazard ratio was observed for both UC and CD [64, 65]. In a recent, Korean nationwide population-based study of approximately 160,000 individuals, including 39,000 IBD patients and a mean follow-up of 5 years, CD and UC patients were at 2.2- and 1.9-times higher risk for PD than controls, respectively [66]. Furthermore, American patients with IBD who were prescribed anti-TNF therapy had a lower risk of developing PD than those patients with IBD who were not treated with anti-TNF [65]. In the Korean study none of the IBD patients receiving TNF anti-TNF agents developed PD and steroid therapy reduced the risk of developing PD by 92% among CD patients [66]. This further supports a causal role of inflammation in PD and a potential benefit of targeting peripheral TNF. Interestingly, a lower risk of PD was observed in individuals with IBD aged ≤65 years and treated with mesalazine (5-aminosalicylic acid (5-ASA)) or its derivative sulfasalazine, the first-line anti-inflammatory treatment in UC [67, 68].

It is important to underline at this point that only a very small fraction of IBD patients develops PD. In yet another case–control study enrolling patients aged 65 years or older with newly diagnosed PD (n = 89,790) and controls (n = 118,095), an inverse correlation between PD and IBD has been shown, suggesting that patients with IBD are less likely to develop PD [69]. All population studies were summarized in an elegant meta-analysis by Zhu et al., demonstrating 46% increased risk of PD in IBD patients compared to controls. The increased risk remained significant when separately analyzing CD and UC groups [70].

Cigarette smoking habit is yet another epidemiological evidence for a connection between PD and IBD, which, however, should be taken with a grain of salt. A meta-analysis from 1989 has shown that tobacco smoking is associated with a reduced risk of developing UC (in contrast to CD) [71]. UC appears to be predominantly a disease of ex-smokers and nonsmokers as reviewed by [72]. Similar to UC, long-term smoking also reduces the risk of PD [73]. Compared with never-smokers, the risk of PD was shown to be 58% lower in current smokers and 41% lower in ever-smokers. The biological mechanism behind the protective effects of smoking in UC and PD remains to be clarified, but it is known that both smoking and nicotine affect the composition of the microbiota and reduce the production of proinflammatory cytokines [74]. Nicotine also stimulates dopaminergic neurons, relieves PD symptoms, and possesses a neuroprotective effect [75]. Interestingly, a cohort study by Ritz et al. based on Danish registries showed that PD patients quit smoking more easily than unaffected controls [76]. This may suggest a decreased responsiveness to nicotine as an event prodromal to PD. Further, this may indicate a reverse causation as the primary explanation for this apparent association between PD risk and tobacco use [76].

EVIDENCE FROM ANIMAL MODELS OF GI INFLAMMATION

Prior to the onset of motor features, many PD patients exhibit a variety of non-motor symptoms including constipation, sleep disorder, depression, and hyposmia [77–79]. Most of the GI dysfunctions are accompanied by inflammatory processes which play a critical role in the pathology of PD. Already in 1965, it was described that the increased prevalence of peptic ulcer is prodromal to idiopathic parkinsonism [80]. In a well-characterized model of experimental colitis peripheral inflammation is usually induced by oral dextran sulfate sodium (DSS) administration [81]. The mice quickly develop symptoms similar to those observed in UC patients including hematochezia diarrhea and loss of body weight. Villarán et al. used the experimental colitis model to show that inflammatory responses in the gut lead to an increase in the levels of inflammatory markers in the substantia nigra (SN) including TNF-α, GFAP and IL-6 [18]. In the study, the rats were injected with lipopolysaccharide (LPS) in the SN and the study concluded that experimental colitis reinforced the inflammatory and deleterious effects of LPS and loss of dopaminergic neurons [18]. Also, chronic mild gut inflammation induced by a low con-
centration of DSS in the drinking water (0.5%) is sufficient to accelerate the onset of motor dysfunction in an animal model of PD, a mouse overexpressing human mutant (A53T) α-syn [82]. The authors observed that the age of onset of motor dysfunction was significantly earlier, and α-syn pathology and dopamine neuron degeneration were exacerbated in DSS-treated PD mice [82].

The question remains whether the peripheral inflammation must be of gut origin or whether peripheral inflammation, as such, is a risk factor by itself, and not only as a factor contributing to neurodegeneration. Carrageenan, an extract of Irish moss (Chondrus crispus), is commonly used to produce short-lasting acute inflammation and hyperalgesia in animal models [83]. In 2012, a Spanish group tested the influence of a mild to moderate peripheral inflammation (injection of carrageenan into the paws of rats) on the degeneration of dopaminergic neurons in an animal model based on the intranigral LPS injection [84]. Here as well, the challenge with carrageenan increased the detrimental effects of the intranigral injection of LPS on dopaminergic neuron survival and was accompanied by increased serum levels of TNF-α, IL-1β, IL-6 and C-reactive protein; activation of microglia, loss of astrocytes and damages to the BBB. Recently, this has been supported by a report showing that DSS-induced experimental colitis increases systemic inflammation which then results in cortical inflammation via up-regulation of serum cytokines [85]. Mice with acute or subchronic gut inflammation manifest early changes in the nigrostriatal dopaminergic homeostasis, dopaminergic neuron death, and increased levels of nigral pro-inflammatory markers and renin-angiotensin system (RAS) pro-inflammatory activity [86]. Interestingly, there was no significant increase in colonic α-syn and phosphorylated (p)-α-syn expression during the relatively short survival period. Moreover, in the same study a decrease in dopaminergic function (i.e., central dopaminergic degeneration) led to GI disturbances and an increase in GI inflammatory responses [86]. This neural bidirectional gut-brain interaction may explain the early gut disturbances observed in parkinsonian patients, and the increased vulnerability of nigral dopaminergic neurons following gut inflammation [87].

The above-mentioned animal studies link inflammatory processes in the GI tract to loss of dopaminergic neurons and by that suggest a mechanism of how GI inflammation may contribute to the development or progression of parkinsonian symptoms.

A very recent, elegant animal study has presented another evidence for a critical role of intestinal inflammation and α-syn accumulation in the initiation and progression of PD. Grathwohl et al. have recapitulated human PD pathology in an animal model showing that α-syn accumulates in the large intestine of α-syn transgenic as well as wildtype mice subjected to experimental colitis and that this process seemed to be modulated by monocyte/macrophage-related signaling [88]. Interestingly, experimental colitis in transgenic mice at a young age led to an exacerbation of α-syn pathology in the brain later in life resulting in severe neurodegeneration. Unfortunately, the authors did not perform vagotomy which could be a convincing evidence for the involvement of vagal nerve in transfer of α-syn pathology. In another 2019 study, Resnikoff et al. utilized nonhuman primates, common marmosets, with colitis to show that inflammation may trigger α-syn pathology in the ENS of the gut. Marmosets with colitis had significantly increased expression of inflammatory markers and p-α-syn, and decreased expression of α-syn in the colonic myenteric ganglia [89].

GASTROINTESTINAL TRACT INFLAMMATION OF PATIENTS WITH PD

GI symptoms are among the most bothersome of PD symptoms. In a cohort study from the early 90s it has been shown that those symptoms occurred more frequently in PD patients than in controls including abnormal salivation, dysphagia, nausea, constipation, and defecatory dysfunction. Except for defecatory dysfunction, symptoms did not correlate with treatment but instead correlated with disease severity [90, 91].

Lewy pathology affects the GI tract in PD [92–94]. PD mice show a strong immune response in the gut [95], and colonic biopsies of PD patients show evidence of a structural dysfunction of the intestinal barrier, reinforcing the idea of a role of the GI tract in the initiation and/or the progression of the disease [96, 97]. Enteric inflammation occurs in PD which further strengthen the role of peripheral inflammation in the pathophysiology of PD [16]. Further, in non-human primates, colitis-associated inflammation is concomitant to alterations in α-syn and p-α-syn expression in colonic myenteric ganglia [89]. Autopsy studies performed on human subjects with
Lewy Body disorders have consistently shown that α-syn aggregates are found in the ENS in nearly every case examined [92, 93, 98]. Still there is a lack of evidence from prodromal PD GI samples which could help to establish a better link between PD initiation and GI inflammation.

CNS glial activation, characterized by micro- and astrogliosis, is a well-defined feature of an activated neuroinflammatory response. The ENS likewise contains a prominent component of glial cells, the so-called enteric glial cells, which, like astrocytes of the CNS, contribute to support, protect, and maintain the neural network [99]. Enteric glial cells have different physiological roles depending on their location within the GI wall [100]. They are located in the GI mucosa beneath the epithelial cells and have an influence on the epithelial barrier function. Both IBD and PD have been associated with GI barrier dysfunction and furthermore, the GI symptoms that occur in PD might in part be caused by enteric glial dysfunction [96, 101]. Enteric glial cells are in a close proximity of gut epithelial cells, and similarly to their counterparts in the CNS they may affect intestinal permeability through the release of several mediators, directly controlling epithelial barrier functions [102]. Abnormalities in the form of morphological changes have also been found in patients with IBD [103]. Enteric inflammation in PD is closely associated with glial dysregulation and evidence suggests that enteric glial cells are key players in regulating gastrointestinal inflammation [16]. Intestinal permeability in PD correlates with levels of α-syn as well as indicators of oxidative stress [104].

Devos et al. performed a study where a putative co-occurrence of gut inflammation in PD patients was investigated. It was concluded that the mRNA-expression levels of pro-inflammatory cytokines were significantly elevated in the ascending colon of PD patients [16]. Levels of the commonly used enteric glial markers GFAP and Sox-10 were strongly correlated with the amount of several pro-inflammatory cytokines, including IL-6, which is released after enteric glial cell activation [105]. The pro-inflammatory profile of cytokines seen in patients with PD was very similar to the cytokine profile seen in patients with IBD. For example, an increase in the expression of IL-1β and TNF-α have been associated with both PD and IBD [106, 107]. It is important to emphasize that not all PD-patient show identical pro-inflammatory profiles.

Recently, calprotectin, a fecal marker of intestinal inflammation, as well as alpha-1-antitrypsin and zonulin (both fecal markers of intestinal permeability) have shown to be significantly elevated in PD patients when compared to controls [23]. Interestingly, the inflammatory marker profile in PD patients shared some similarities to what has been reported in IBD [108]. Another study from the same year analyzed immune and angiogenesis factors in stool to assess the GI inflammatory state in PD patients, their healthy spouses, and unrelated healthy control subjects [13]. In this study, they found elevated levels of proinflammatory factors such as IL-1α, IL-1β, chemokine ligand 8 (CXCL8) and C-reactive protein (CRP). Additionally, the authors showed that disease-associated patterns in levels of immune factors did not change with PD duration which suggests that intestinal inflammation is not exclusively present in advanced disease state. Based on that they hypothesize that intestinal inflammation is an early manifestation of PD that could contribute to the development of neuropathology rather than an effect arising in response to extensive GI neurodegeneration.

### ALPHA-SYNUCLEIN AND IBD

As mentioned earlier, in PD, the presynaptic protein α-syn undergoes pathological changes, including phosphorylation and aggregation leading to the formation of Lewy bodies, which can be also found in neurons of the ENS. Therefore, yet another natural evidence suggesting a relationship between colonic inflammation and PD would be the search for α-syn aggregates in ENS of GI patients. CD patients show a significant 2-3-fold increase in the levels of α-syn protein in the non-inflamed and inflamed area of GI tract when compared to controls. Interestingly, these differences were not observed in UC patients, and there were no differences in the immunoreactivity for α-syn or p-α-syn between large intestine samples from CD, UC and controls [109]. The authors suggested that some of the pro-inflammatory cytokines and/or para-inflammatory responses that are activated in CD, but not in UC, are involved in the regulation of α-syn expression. Soon after, a new study showed substantial intracellular α-syn staining in infiltrating monocytic cells from colonic biopsies in 8/11 UC cases, and 4/11 patients with CD and almost none in healthy individuals [88].

Accumulation of α-syn is not necessarily specific to IBD but it is also related to GI inflammation and α-syn is a regulator of the immune system including
certain innate immune cells [110, 111]. A study from 2017 on pediatric patients, reported a positive correlation between the expression of α-syn in the enteric neurites of the upper GI tract and the degree of acute and chronic inflammation in the intestinal wall [112]. This study also reported an intra-patient increase in expression of α-syn before and after norovirus infection.

Extracellular α-syn may accumulate due to impairment of the microglial phagocytic molecular machinery. It has been shown that excess α-syn compromises phagocytosis as demonstrated by measuring fibrillar α-syn uptake in iPSC-derived macrophages from PD patients with α-syn (SNCA) A53T and SNCA triplication [113].

It is worthy of note that α-syn aggregates are also seen in the ENS of normally aging subjects [114], especially in the appendix [115]. A recent comprehensive epidemiological study describing decreased incidence of PD in patients that had appendectomies illustrate a relationship between PD and GI tract health and function [116]. This suggests that the normal human appendix contains pathogenic forms of α-syn that affect the risk of developing PD.

Overall, these reports provide some evidence for the hypothesis that colonic inflammation is capable of altering α-syn in the ENS, however, induction of this protein within the ENS may be a part of the normal immune defense mechanism [112, 117, 118].

**GUT-BRAIN AXIS THEORY**

Based on increasing experimental evidence as to the connection between the intestinal environment and the CNS, the so-called ‘gut-brain axis theory’ has been proposed which consists of bidirectional communication between the CNS and the ENS, linking emotional and cognitive centers of the brain with peripheral intestinal functions [119].

According to this hypothesis, PD can be a consequence of intestinal dysbiosis and/or intestinal barrier dysfunction caused by an unknown pathogen within the GI. Such dysbiosis may be a reason for α-syn aggregation in submucosal neurons and/or impact immune and inflammatory pathways leading to the peripheral and central immune activation and inflammation.

IBD is clearly associated with intestinal dysbiosis, however, no single microbe or microbial milieu has been proven causal. Recent advances in next-generation sequencing technologies have identified alterations in the composition and function of the gut microbiota. The decrease of bacteria with anti-inflammatory capacities and the increase of bacteria with inflammatory capacities are observed in patients with IBD when compared to healthy individuals [120, 121]. Similar to IBD, PD patients exhibit a pro-inflammatory microbiota profile with a reduction in beneficial products such as short chain fatty acids [12, 122–125]. Colonization of α-syn overexpressing mice with microbiota from PD-affected patients enhances physical impairments compared to microbiota transplants from healthy human donors. Further, short chain fatty acids (SCFA), produced by the intestinal microbiome, increased the presence of α-syn aggregates in the basal ganglia and SN [126]. Certain microbiome derived SCFA have also been implicated as modulators of microglia cell development and activation [127].

The gut microbiome and its effect on PD is not within the scope of the present review as it is covered by others in this special issue of the Journal of Parkinson’s disease. However, evidence indicates that communication between the microbiota and the brain involves the vagus nerve, which transmits information from the luminal environment to the CNS. In fact, neurochemical and behavioral effects were not present in vagotomized mice, identifying the vagus as the major modulatory constitutive communication pathway between microbiota and the brain [128]. α-syn from PD patient brain lysate injected into the gastric wall of rodents is taken up and transported retrogradely over a long distance via the vagal nerves from the gut to the dorsal motor nucleus of the brainstem in a time-dependent manner [129]. A very recent study provides an immunohistochemical evidence for propagation of initially localized enteric α-syn pathology through the autonomic nervous system to the brain in a transgenic rodent model [130]. This is yet another indication suggesting the exclusive link between the brain and the gut, and a pathway to spread the pathological protein to the brain according to the Braak’s theory [5, 131]. Further, their model also shows secondary anterograde (vagus-to-stomach) spreading of α-syn which is the first indication of bidirectional α-syn propagation via the vagus nerve [130]. In yet another animal study pathological α-syn preformed fibrils were injected into the duodenal and pyloric muscularis layer causing retrograde, polysynaptic spreading of pathology into the brain which was further hampered by truncal vagotomy [132]. This supported an earlier evidence based on the rotenone gavage animal model showing...
that PD-like pathology progression occurs through sympathetic and parasympathetic nerves and that the scission of these nerves is sufficient to stop the progression of the pathology into the CNS [133].

Pathological forms of α-syn delivered directly to the ENS are able to cause a GI phenotype in the form of reduced colonic motility in an animal model [134]. Interestingly, the data from this study suggest that α-syn can be transported from ENS to the CNS brainstem in both rodents and non-human primates, however, the pathology was neither sustained, nor did it spread. The different outcomes of animal studies can be due to different methodologies and models, including lower amounts and different forms of delivered pathological α-syn, time after injection and site of injection. Thus, the hypothesis of gut to brain propagation is still highly debated in the field and evidence in humans is still controversial [135].

In cohort studies with follow-up from northern Europe, individuals who underwent truncal vagotomy had a lower risk of developing PD than age- and sex-matched control individuals [136–138]. A larger population-based study is still needed as the evidence is inconsistent and the existing attempts had limited statistical power to examine the potential long-term effect of truncal vagotomy on PD.

CONCLUSIONS

The relatively new idea that the earliest stages of PD may occur in the GI tracts has been gaining attraction in recent years. Increasing evidence supports the hypothesis of pathological interplay between peripheral and CNS innate immunity probably contributes to initiation and progression of PD. The chronic activation of pro-inflammatory mechanisms, which occurs in autoimmune conditions, has been increasingly recognized as a critical contributor of neurodegenerative disorders. Given the potentially critical role of GI pathology in PD pathogenesis, there is reason to suspect that IBD or its treatments may impact PD risk, thus, clinicians should be aware of PD symptoms in IBD patients. More biomarker and observational studies are needed to identify IBD patients at risk to develop PD in order to start potential new therapies for PD. It is, however, important to state at this point that IBD only increases the risk of developing PD, and only a small fraction of IBD patients develops PD [65]. For a given IBD patient the risk of getting PD is still very small and the probability of not getting the diagnosis is >95–97%. Inflammation of the GI is only one of many symptoms on the list of changes in the gut and its associated neural structures in PD patients thus IBD might be just one of many sources of intestinal inflammation. The Braak’s theory of pathological changes typically developing in predictable stages was strengthened by the observation that in post-mortem samples of PD patients, Lewy bodies are seen in both the brain and the GI nervous system that controls the function of the gut. The vagus nerve may be the relevant route through which PD pathological factors travel from the GI tract to the brain, but the convincing evidence still needs to be provided.

The obvious question is the mechanism by which the inflammation state in the GI tract can contribute to the dopaminergic degeneration in different circumstances and different PD patients. Those mechanisms may involve:

1) GI accumulation of α-syn that retrogradely and slowly is being transported to the CNS, Parallel, but similar processes that simultaneously affect central and peripheral dopaminergic neurons.

2) Peripheral inflammation, due to chronically inflamed gut, may trigger α-syn deposition, increase the permeability of the gut and the BBB leading to neuroinflammation.

3) Inadequate signaling and metabolites from the gut microbiome may occur in addition to the dysregulation of the gut-brain dopaminergic crosstalk.

It is still possible that PD begins in a different region of the body or is a systemic disease in which the final stage manifests as a neurodegenerative disorder. Non-motor symptoms often precede the onset of motor dysfunction. PD patients have been observed to have more psychological, musculoskeletal, and cardiovascular symptoms and hence visit their general practitioners more often than control subjects during the prodromal phase [139].

A new conceptual model for PD pathogenesis proposed by Johnson et al., in which disease-associated factors are divided into three categories: triggers, facilitators, and aggravators, describes in an elegant manner a multifactorial etiology of PD [140]. Based on this model, pharmacological therapies aiming at slowing or arresting PD progression should not only be given to patients enriched for the appropriate target, but also be administered in the relevant phases of the disease [140].
Therefore, a clear knowledge of the mechanisms implicated in gut/immune/nervous communication could help improve the diagnostic and therapeutic tools leading to better quality of life of the patients, reducing the exacerbation of PD symptoms, and delaying the progression of the disease.

**CONFLICT OF INTEREST**

The author has no conflict of interest to report.

**REFERENCES**


systematic review and meta-analysis. Dig Liver Dis 51, 38-42.


