Gastrointestinal symptoms of Parkinson’s disease: A systematic review from pathogenesis to management

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Abstract

The identification of Parkinson’s disease (PD) is mainly dependent on motor symptoms, while the non-motor symptoms exist even decades ahead of the PD diagnosis. According to Braak’s hypothesis, the enteric plexus is the first affected site during the pathological development of PD, and gastrointestinal (GI) symptoms appear during the onset of the disease. Although GI symptoms decrease the life quality of patients with PD, there is often less focus on GI symptoms compared with motor symptoms. In this review, we summarize the pathophysiological basis, clinical manifestation, diagnosis, and treatment of GI symptoms in patients with PD. We also discuss the treatment and research dilemmas, as well as the research direction in the near future.

Keywords: Parkinson’s disease; Non-motor symptoms; Gastrointestinal symptoms; Brain-gut axis; Management

1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disease, and its incidence is increasing annually. It is estimated that the number of patients with PD in China will rise to about 5 million in 2030, accounting for almost half of the number of patients with PD worldwide. In addition to the motor symptoms, non-motor symptoms contribute to the impaired quality of life, severe disability, and shortened life span in advanced PD. The common non-motor symptoms of PD are gastrointestinal (GI) symptoms, REM sleep behavior disorder, and anosmia. Epidemiological research suggests that GI symptoms affect more than 80% of patients with PD, which is far greater than the incidence among the healthy population[1-4]. In addition, GI symptoms, including drooling, dysphagia, gastroparesis, constipation, fecal impaction, and intestinal pseudo-obstruction, often occur for years or even decades before the diagnosis of PD, indicating a close association with PD[5]. However, the recognition and treatment of GI symptoms in patients with PD have not been systematically summarized, and a standardized consensus has not been reached. Autopsy reports show that the intestine is the first and typical site to be pathologically affected, suggesting that PD may arise from the intestine. Clinical and in vivo studies have confirmed that intestinal α-synuclein aggregation may spread to...
the central nervous system (CNS) through the vagus nerve. Recent research has suggested that the gut microbiota may contribute to PD\[^{26}\]; however, the specific underlying mechanism remains elusive. Therefore, it is of great significance to focus on the GI symptoms and pathological changes in patients with PD, and consequently develop standardized identification and management. Herein, we systematically elaborate the clinical manifestations, pathogenesis, diagnosis, and management of GI symptoms in patients with PD (Figure 1).

2. Clinical manifestation and epidemiology

2.1. Drooling

Excessive salivation is a known issue in PD that has a negative impact on social interactions and may even lead to depression. Studies have shown that more than one-third of patients with advanced PD have excessive salivation, which the 8-item PD questionnaire indicates is significantly related to decreased quality of life\[^{27}\]. Excessive salivation is also caused by swallowing dysfunction. The pathological changes of CNS structures and innervating nerves of the oropharyngeal muscle groups are responsible for swallowing dysfunction, which results in saliva accumulation and excessive salivation. A retrospective analysis of 728 patients with PD demonstrated that the prevalence of dysphagia was higher among patients with excessive salivation than in patients without excessive salivation\[^{28}\], which further suggests that the excessive salivation may be caused by dysphagia. The study also reported that the rate of salivation increases with age. The reason and potential mechanism for this increased salivation warrant further investigation.

2.2. Dysphagia

Around 35% of patients with PD report having subjective symptoms of dysphagia during the course of their disease, and more than 80% of patients are diagnosed with dysphagia by objective measures\[^{29,10}\]. Dysphagia is related to movement disorder of the oropharyngeal muscles, which leads to slow and uncoordinated swallowing action. However, the etiopathogenesis of dysphagia is unclear. Swallowing dysfunction is considered to be caused by degeneration of the basal ganglia, substantia nigra (SN) region, and brainstem\[^{10,13}\]. Dysphagia leads to reduced eating, malnutrition, and even aspiration pneumonia, which are important causes of death in patients with PD\[^{11-13}\]. The prevalence and severity of dysphagia increase significantly as PD progresses. As dysphagia involves lesions in the SN region and muscle dyskinesia, some scholars believe that dysphagia should be classified as an atypical motor symptom. The application of antiparkinsonian drugs partially improves the swallowing function.

2.3. Gastroparesis

Gastroparesis refers to the delayed emptying of solid food without mechanical obstruction. The clinical manifestations of gastroparesis include abdominal distension, hiccups, nausea, and vomiting. Impaired gastric emptying caused by gastric dysmotility is common in patients with PD, but not all patients display subjective symptoms. Up to 50% of patients with PD have abdominal distention, and 15% have nausea and vomiting\[^{14}\]. Gastroparesis may occur in the early stage of PD or even before the PD diagnosis. The prevalence of gastroparesis seems to be higher in the later stages of PD, and the severity of gastroparesis is correlated with motor symptoms. The occurrence of gastroparesis is also related to the slowing down of GI muscle movement. Furthermore, there are a few reported cases of rapid gastric emptying in PD, which may be due to uncoordinated action of GI muscle groups. Gastroparesis leads to decreased efficacy or dyskinesia, which increases the difficulty of treatment\[^{19}\].

2.4. Constipation

Constipation is a common GI symptom that is characterized by reduced defecation frequency, firm stools, and dysphasia. At present, the diagnosis of constipation is mainly based on the Rome IV criteria and the patient's subjective feeling. For constipation to be diagnosed, the symptoms must have been present for at least 6 months and must have been experienced within the past 3 months. A patient is diagnosed with constipation if they have two or more of the following defecation-related manifestations in more than 25% of their defecations: Straining, massive or hard feces, incomplete bowel movement, anal obstruction, manual evacuation, and less than 3 spontaneous defecations per week\[^{16}\]. The estimated prevalence of constipation worldwide is 15–20% in people older than 60 years\[^{17}\] and 20.0–37.3% in people older than 84 years\[^{17,18}\]. In patients with PD, constipation is very common, with a prevalence of around 80%\[^{14-16}\]. In most cases, constipation significantly reduces the quality of life. In addition, constipation in older adults can lead to fecal impaction and intestinal pseudo-obstruction, which collectively form a serious issue. Constipation can precede motor symptoms by up to 20 years, indicating that constipation could be a warning for the onset of PD. Multiple prospective and retrospective studies have shown that people with constipation have a higher risk of PD development.

3. Pathophysiology of GI symptoms

The typical neuropathological manifestations of PD are abnormal α-synuclein aggregation and Lewy body (LB) formation, resulting in the loss of dopaminergic neurons in the SN region. It is well known that the loss of
dopaminergic neurons in the SN region leads to the motor symptoms of PD, while the GI symptoms are derived from pathological changes in the swallowing center, peripheral nerves that control the swallowing muscles, and enteric nervous system (ENS).

In general, drooling is caused by increased salivary secretion or decreased swallowing. Patients with PD often have reduced salivary secretion[8,19]. Pathological studies have showed that LBs exist in the superior cervical ganglion, cervical sympathetic trunk, peripheral vagus nerve, and submandibular gland, thereby damaging the salivary secretion[20]. Therefore, dysphagia is considered the cause of excessive salivation in patients with PD.

The pathophysiological mechanism of dysphagia in PD has not been fully clarified. The present studies suggest that both dopaminergic and non-dopaminergic systems are implicated in dysphagia. Many swallowing associated projection fibers converged on the dopaminergic basal ganglia system, which plays an important role in swallowing. Functional MRI has shown that both the putamen and globus pallidus are activated in healthy volunteers during swallowing[10,21], confirming the important role of the basal ganglia nervous system in the swallowing function. Thus, dopamine deficiency impairs the swallowing function of patients with PD, and dysphagia is relieved by L-DOPA preparation. Autopsy studies of patients with PD have found α-synuclein aggregation in the swallowing center of the medulla oblongata and the peripheral sensory nerves and motor nerves innervating the pharyngeal muscle[22], suggesting that central and peripheral mechanisms are involved in the dysphagia of patients with PD.

The retardation of GI motility leads to gastroparesis and constipation, and severe constipation leads to fecal impaction and intestinal pseudo-obstruction. GI motility dysfunction is thought to be caused by pathological changes of the ENS. The two main groups of ganglia in the ENS are the intermuscular ganglia and submucosal ganglia[23,24]. Abnormal α-synuclein accumulation in the ENS leads to slow GI movement. Pathological analysis of the GI symptoms of PD shows that the typical pathological features are distributed from the gut to the brain, which supports the suggestion that PD is a systemic disease. It should be noted that the pathological changes appear in the gut before the CNS, and the occurrence of GI symptoms such as constipation may occur decades before the diagnosis of PD[14]. Thus, it has been suggested that PD may originate in the intestine.

In 2003, Braak et al. proposed that α-synuclein accumulation, the typical pathohistological manifestation of PD, affects the ENS (Stages 1 and 2) decades before affecting the CNS (stages 3 and 4)[25,26], indicating that the GI tract may be part of the course of PD. The Braak staging system attracted wide attention to the pathological GI changes of patients with PD. It is well established that
the dorsal vagal nucleus is first affected by LBs in the CNS. However, LBs are not a unique pathological hallmark of CNS and have also been found in the GI tract, including the esophagus, stomach, small intestine, colon, and rectum. Interestingly, LBs occur in the GI tract before the dorsal vagal nucleus. The frequency of LB detection decreases along the GI tract from the esophagus to the rectum, displaying a distance-dependent distribution. The reason for this LB distribution pattern has not been studied and may be related to the distance from the brain. Therefore, it has been hypothesized that PD originates from the intestine.

The neural network is divided into the CNS and the peripheral nervous system (PNS). In the mid-19th century, abundant neural networks were found in the intestinal wall and defined as the ENS, which is an important part of the PNS. The ENS shares many similarities with the CNS and contains 80–100 million neurons, which are supported by glial cells, and various neurotransmitters have been identified. The ENS produces the same amount of dopamine as the brain, providing half of the dopamine for the body. Dopamine is an important neurotransmitter in the brain, and its deficiency is the direct cause of PD. In addition, the ENS provides more than 95% of the serotonin in the body, and serotonin deficiency in the brain is associated with depression. This line of evidence indicates that the gut and brain share high degrees of similarity in both structure and function. Therefore, the ENS is also called the “second brain”.

The ENS communicates with the CNS through the vagus nerve. The ENS contains a large number and wide variety of complex microbiota. The human intestine contains about $10^{13}–10^{14}$ bacteria (i.e., intestinal flora), consisting of more than 1000 species with 100 times more genes than humans. Because the intestinal flora has a heightened sensitivity to changes from the outside world, microbiota composition and metabolites tend to fluctuate immediately in response to the changes, leading to activation of the immune and inflammatory systems, which then feed this information back to the CNS. Therefore, the ENS is a pivot bridge between the external environment and the brain. Structurally, the ENS and the brain are connected through the vagus nerve. Functionally, the gut and brain form a complex neuroendocrine immune network with a strong biphasic regulation. The close connection in structure and function suggests the critical link between the gut and brain. However, the relationship between PD and the gut needs further study. An association between complete vagotomy and a lower incidence of PD has been shown in a large epidemiological study in Denmark and in a transgenic PD mouse model. Kim et al. demonstrated the gradual transfer of $\alpha$-synuclein from the intestine to the brain through the vagus nerve, which consequently causes the degeneration of dopaminergic neurons as well as PD-like motor symptoms. The metabolites of the gut microbiota are short-chain fatty acids (SCFAs), which stimulate microglia activation and promote $\alpha$-synuclein-dependent motor symptoms. Microbiota from patients with PD aggravate motor symptoms in mice. Overall, the evidence suggests that PD may arise from the GI tract, and the gut pathology spreads to the brain through the vagus nerve and gut immune inflammation network.

## 4. Evaluation and management

### 4.1. Drooling

#### 4.1.1. Assessment of salivation

The excessive salivation in PD may be attributed to the rate of salivary secretion and saliva swallowing. A study used technetium-99m scintigraphy to show that the salivary secretion is the same in patients with PD and healthy controls. However, salivary secretion in response to discrete stimuli is significantly higher in patients with PD with excessive salivation. Regarding salivary swallowing, barium swallowing and fluoroscopy evaluation in patients with PD with excessive salivation proved that the severity of dysphagia is directly related to the severity of excessive salivation. A study of the maximum tongue pressure during swallowing showed that animal models and patients with PD have a slow tongue extension speed and significantly longer average tongue pressing time than normal controls. Furthermore, the maximum tongue pressure is lower in patients with advanced PD than in patients with early or moderate PD, and the oropharyngeal transport time is negatively correlated with the tongue movement speed.

#### 4.1.2. Management

The main methods used to manage drooling are drug therapy and non-pharmacological therapy.

Drug therapies include anticholinergic drugs and botulinum toxin (BoNT). Anticholinergic drugs include sublingual atropine, sublingual bromine ipratropium spray, oral pyruvate, and oral tropicamide. The Movement Disorder Society has stated that pyruvate is effective, but there is no evidence for its long-term effectiveness. The mechanism of BoNT is to inhibit the release of acetylcholine. The two serotypes of BoNT are BoNT-A and BoNT-B, which have both been studied in patients with PD with excessive salivation. Local injection of BoNT into the salivary gland inhibits the activities of cholinergic parasympathetic nerves and postganglionic sympathetic nerves, resulting in decreased salivary secretion. BoNT-A and BoNT-B are effective in controlling salivation.
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symptoms in patients with PD. BoNT-A and BoNT-B have an onset time of 1 week and the effects last for about 3–5 months after injection. Ultrasound-guided BoNT injection may be more effective and safer.

Non-pharmaceutical therapies include behavioral therapy and radiotherapy. Behavioral therapy, such as chewing gum and advising patients to swallow at a fixed time, can help patients with PD to alleviate excessive saliva[6]. At 1 month after receiving 12 Gy bilateral radiation therapy in the parotid and submandibular glands, patients with PD show significant improvements in excessive saliva, and this effect lasts for 1 year[42]. However, radiotherapy can only be used as adjuvant therapy in refractory cases.

4.2. Dysphagia

4.2.1. Evaluation

Patients with PD have problems such as transporting food slowly in the oral phase, oral tremoring, and reduced tongue movement. The swallowing function of patients with PD is evaluated using barium swallow radiography[43], fluoroscopy[44], and the Munich dysphagia test[45]. In addition, patients with PD have insufficient relaxation of the upper esophageal sphincter[46]. Patients with severe PD show a significant decrease in velopharyngeal and oropharyngeal pressure. Therefore, high-resolution pharyngeal manometry is used to detect subtle abnormalities by quantifying the swallowing pressure of patients with PD. Evaluating the swallowing pressure is helpful to understand the neuromuscular dysfunction caused by abnormal pressure during swallowing in patients with PD[47].

4.2.2. Management

The treatment of esophageal dysfunction in patients with PD is rare and difficult. At present, there is no effective drug to improve swallowing function. Levodopa is thought to improve the swallowing function because dopaminergic substitutes improve posture, breathing, and tongue movement[48]. Non-pharmaceutical techniques, such as chin-down swallowing and the addition of thickening agent[49], and Lee Silverman speech therapy[50], have also been shown to partially improve the swallowing function of patients with PD. Impaired cricopharyngeal relaxation can be improved by surgical cricopharyngeal myotomy[51] or BoNT injection[52]. However, this operation increases the risk of aspiration in patients with esophageal dyskinesia or lower esophageal sphincter dysfunction with gastroesophageal reflux. Percutaneous endoscopic gastrostomy may be necessary for severe and refractory dysphagia, but is rarely performed in patients with PD because of the invasiveness of the procedure[53].

4.3. Gastroparesis

4.3.1. Evaluation

Gastric emptying scintigraphy is the gold standard for evaluating gastric emptying. Patients ingest a scrambled egg meal labeled with 18.5–37 MBq of technetium-99m sulfur colloid, and then, continuous imaging is performed for 120 min (1 min per frame) to enable the calculation of the half-life of gastric emptying[44]. Gastric emptying is also evaluated using the 13C-sodium acetate breath test[55]. Gastroparesis symptoms can be evaluated by daily diary questionnaire, which is simple and easy to implement[56]. In addition, the three-dimensional transmission system is a new approach to calculate the transmission time and motion mode of the GI region based on the position of an ingested wireless electromagnetic capsule[57]. In contrast to gastric emptying scintigraphy, the three-dimensional transmission method can be carried out in the patient's residence, and is safe and well tolerated because it is carried out under near-normal physiological conditions; it can also evaluate the function of the small intestine. The reliability of the data acquired from the three-dimensional transmission system is similar to that of gastric emptying scintigraphy.

4.3.2. Management

In patients with gastric emptying disorders, the use of macrolide drugs such as erythromycin or azithromycin shortens the half-life of gastric emptying[44]. Nizatidine, a selective histamine H2 receptor antagonist and a cholinomimetic, improves gastric emptying in patients with PD[59]. TZP-102 is an effective agonist of oral ghrelin that improves the symptoms of type 2A diabetic gastroparesis[55]. However, there is no persuasive evidence that BoNT injection into the pylorus significantly alleviates the subjective symptoms and improves the objective measurements of gastroparesis[56]. Subthalamic deep brain stimulation (STN-DBS) may improve the dysfunction of patients with PD by regulating the nervous system that controls GI function[58]. Permanent gastric electrical stimulation achieves a good response in 71% of patients with intractable gastroparesis during 2 years of follow-up[59]. In patients with PD, the extract of the dietary herb Rikkunshito shortens gastric emptying assessed by the 13C-sodium acetate expiration breath test[55].

4.4. Constipation

4.4.1. Evaluation

The Rome III criteria have been widely used in the evaluation of functional intestinal diseases since being published in 2006, and Part C3 is used in the evaluation of functional constipation. The Rome standard is an internationally recognized objective definition of constipation that mainly focuses on six symptoms[60];
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In PD, constipation occurs due to slow colonic transmission and/or outlet obstruction. Therefore, constipation in patients with PD is often assessed using physiological evaluation methods, such as the evaluation of the colonic transit time, high-resolution anorectal manometry, and MRI defecography. Patients with PD have a significantly prolonged colonic transit time, while anorectal manometry shows reduced basic anal sphincter pressures, prospective phase adjustments on squeeze, and a hypercontractual external sphincter response to the rectosphincteric reflex. However, subjective constipation in PD is poorly correlated with physiological results. Especially for patients with refractory symptoms, physiological examinations should be combined to evaluate both the colonic transport and the anorectal function for systematic evaluation and appropriate symptom management.

4.4.2. Management

The treatment of constipation in PD should be comprehensive. On top of a healthy diet, it is supplemented with drug therapy, physical therapy, microbial flora adjustment and so on. After treatment, the symptoms of constipation could be improved in some PD patients. The relevant key literature is summarized in Table 1.

4.4.2.1. Medication

Effective treatments for constipation in patients without PD are also generally effective in patients with PD, such as increasing the fiber intake and taking permeable or irritant laxatives. In patients with PD, 4 weeks of psyllium administration increase the fecal frequency without changing the colonic transport or anorectal function. However, fiber should be avoided in patients with gastroparesis because fiber could delay gastric emptying. Osmotic laxatives are widely used in the general population and are also useful for patients with PD. A double-blind controlled trial showed that isotonic polyethylene glycol electrolyte solution improves constipation in patients with PD. The solution is well tolerated and only causes diarrhea and nausea in a small number of patients. The UPDRS score confirmed that the treatment does not affect PD motor symptoms. However, while taking osmotic laxatives, the patient’s cardiac and renal function should be monitored. Based on clinical experience, irritant laxatives (such as senna and bisacodyl) also play a certain role in constipation in patients with PD, but are generally recommended for occupational use as a rescue therapy.

Lubiprostone plays a role locally in the small intestine by activating the type 2 chloride channel in the intestinal apical cell membrane and inducing the secretion of liquid and electrolytes to speed up the transport time of the small intestine and colon. Compared with placebo, lubiprostone improves the constipation scale, visual analysis scale scores, and daily defecation volume. Furthermore, lubiprostone only causes mild adverse reactions, most frequently comprising loose stools in 48% of patients. However, the severity of these symptoms is mild and will not lead to treatment interruption.

Squalamine rapidly restores the intrinsic primary afferent neuron excitability of the ENS to promote intestinal propulsion, which may be effective in the treatment of constipation in patients with PD. Ent-01 oral tablet (a synthetic squalamine salt) may increase the number of spontaneous defecations per week in 80% of patients through local stimulation of the ENS. An ongoing double-blind, placebo-controlled study reported that the common adverse events of Ent-01 include nausea in 21/44 patients (47%) and diarrhea in 18/44 patients (40%).

Cisapride increases the release of acetylcholine from the myenteric plexus. A preliminary study of 20 patients with PD found that cisapride accelerates colonic transmission and improves constipation, with no “excessive effects” such as adverse reactions and diarrhea.

Mosapride is a selective 5-HT4 receptor agonist that promotes the release of acetylcholine from intestinal cholinergic neurons. In contrast to cisapride, mosapride does not block K+ channels or D2 dopaminergic receptors. Evaluation of the colonic transit time before and after treatment in 14 patients with PD with constipation showed that mosapride citrate enhances the movement of the lower GI tract, thus improving constipation without causing serious adverse reactions. In a 6-OHDA rat model, the novel oral active growth hormone-releasing peptide agonist HM01 crosses the blood–brain barrier and alleviates PD-related constipation, suggesting potential

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<td>Abdominal massage[79]</td>
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benefits for PD with GI diseases\textsuperscript{85}. Another 5-HT4 receptor agonist, tegaserod, is approved for the treatment of chronic idiopathic constipation. A study of five patients with PD-related constipation suggested that tegaserod is well tolerated and improves the defecation frequency and fecal consistency of most patients\textsuperscript{79}. However, another randomized controlled trial with a small sample size found that tegaserod had no significant effect on constipation in patients with PD\textsuperscript{77}.

One study that treated 18 patients with PD with outlet constipation with ultrasound-guided injections of BoNT-A on both sides of the puborectal muscle found a lower pressure during training and an improved anorectal angle on defecography after treatment. This suggests that such BoNT-A injections are effective for obstructive constipation in patients with PD\textsuperscript{74}. However, the effect only lasts for 3 months, so repeated injections may be required to maintain clinical improvement. Another study also reported that BoNT is effective and safe for outlet obstruction in PD\textsuperscript{65}.

### 4.4.2.2. Physical therapy

Functional magnetic stimulation for 3 weeks significantly reduces the colonic transit time and the Knowles-Eccersley-Scott symptom questionnaire scores by helping to straighten the anorectal angle, making the rectal contents enter the anal canal smoothly and improving constipation\textsuperscript{78}. Colonic electrical stimulation also alleviates colonic transmission delay in a rotenone-induced PD model\textsuperscript{78}. Abdominal massage, as an adjunct to the management of constipation, offers an acceptable and potentially beneficial intervention for patients with PD\textsuperscript{70}. STN-DBS increases anal compression pressure in patients with PD, but does not improve anorectal dyssynergia, suggesting that the subthalamic nucleus is involved in the voluntary control of anorectal movement in patients with PD\textsuperscript{86}. A study of 10 patients showed that STN-DBS improves constipation as assessed by a subjective questionnaire\textsuperscript{86}.

### 4.4.2.3. Microbial flora adjustment

A randomized, double-blind, placebo-controlled trial confirmed that the consumption of fermented milk containing a variety of probiotic strains and prebiotic fibers is better than placebo in improving constipation in patients with PD\textsuperscript{82}. Probiotics increase the number of spontaneous bowel movements, which improves the constipation severity score\textsuperscript{68}, and only cause mild adverse reactions such as abdominal discomfort in less than 5% of patients. A before-after trial also found that probiotics improve constipation\textsuperscript{69}. However, the long-term effect of probiotics needs further investigation.

One case report showed that fecal microbiota transplantation (FMT) temporarily improves PD symptoms, such as tremoring, and continuously improves constipation\textsuperscript{61}. Another study showed that FMT tends to improve the Wexner constipation score in patients with PD, but the effect did not reach statistical significance compared with the control group\textsuperscript{73}. FMT is relatively complex and immature, and there is no fixed standard regarding the source of strains. Furthermore, FMT can only improve the microorganisms in the lumen rather than the mucosal microbiome\textsuperscript{84}, and its improvement of motor symptoms only lasts for several days. Therefore, the application of FMT in PD needs to be treated with caution.

### 4.4.2.4. Others

A healthy diet, such as the Mediterranean diet, can reduce the occurrence of prodromal symptoms of PD, including constipation\textsuperscript{85}. However, a study currently investigating whether the Mediterranean diet improves constipation and other symptoms of PD have not yet been published\textsuperscript{86}. Acupuncture and traditional Chinese medicine may also play a role in the treatment of PD\textsuperscript{97,98}. In sitting position, it is more difficult to defecate due to the contraction of the puborectal muscles. Therefore, the “squatting position” is recommended to relax the puborectal muscles to enable the elimination of feces more easily and completely\textsuperscript{99}. 

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**Table 1. (Continued)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Study design</th>
<th>Evaluation method</th>
<th>Results</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiawei-Liuunjzi Tang\textsuperscript{90}</td>
<td>Double-blind, randomized, placebo-controlled ($n=59$ vs. $57$)</td>
<td>UPDRS questionnaires</td>
<td>Effective</td>
<td>Dyspepsia (8.9%)</td>
</tr>
<tr>
<td>Abdominal massage\textsuperscript{76,79}</td>
<td>Qualitative study ($n=7$ vs. $7$)</td>
<td>Interview</td>
<td>Effective (4/7)</td>
<td>No</td>
</tr>
<tr>
<td>Isosmotic macrogol solution\textsuperscript{76}</td>
<td>Double-blind, placebo-controlled study ($n=29$ vs. $28$)</td>
<td>Stool frequency, straining, stool consistency, use of rectal laxatives as a rescue therapy</td>
<td>Effective</td>
<td>Nausea (1/29) and diarrhea (1/29)</td>
</tr>
<tr>
<td>Psyllium\textsuperscript{81}</td>
<td>Randomized controlled pilot study ($n=4$ vs. $3$)</td>
<td>Stool diary, stool weight, colonic transit time, and anorectal manometry</td>
<td>Effective</td>
<td>No</td>
</tr>
</tbody>
</table>
5. Brain-gut axis and PD

Since Braak’s staging system was reported\(^{100}\), more attention has been paid to the role of the brain-gut axis in the pathogenesis of PD. Structurally, the brain and intestine are associated through the vagus nerve and the ENS\(^{101}\). However, due to the existence of the intestinal barrier, it is unclear how the submucosal plexus interacts directly with intestinal microorganisms. In 2015, Bohorquez et al. found a direct synaptic connection between enteroendocrine cells and the submucosal plexus through a retrograde rabies virus tracing technique\(^{102}\). Moreover, enteroendocrine cells are an \(\alpha\)-synuclein-positive cell type\(^{103}\). Various intestinal factors change the \(\alpha\)-synuclein in intestinal tissue into abnormal \(\alpha\)-synuclein, which then forms a template. This template, as a seed, enters the vagus nerve through the synapse link between intestinal endocrine cells and intestinal nerves, and is then transmitted to the CNS by endocytosis, exocytosis, and other prion-like pathways; other pathways such as neurotransmitters and SCFAs may also be involved\(^{101}\). These findings prove that \(\alpha\)-synuclein transmission into the CNS is structurally possible.

GI symptoms are quite common in patients with PD, and patients with constipation have a greater risk of PD (Figure 2)\(^{104}\). When \(\alpha\)-synuclein is injected into the intestinal wall, \(\alpha\)-synuclein is also found in the vagus nerve\(^{105}\). PD can be induced by oral toxins or changes in intestinal flora\(^{106}\). Pathological deposition of \(\alpha\)-synuclein is also found in the intestine, and this deposition follows the rostral-caudal gradient, which may also be related to the density of vagus nerve distribution. Epidemiological investigations show that vagotomy reduces the risk of PD\(^{107,108}\). This line of evidence suggests that PD may indeed originate from the intestine.

There are still some questions about the transmission of \(\alpha\)-synuclein. For example, in one study, \(\alpha\)-synuclein deposition was not found in the ENS, but was found in the CNS\(^{109}\). Based on these findings, it cannot be ruled out that \(\alpha\)-synuclein originates from the CNS, although this may be due to the detection method. Therefore, it is very important to explore reliable detection methods and distinguish different configurations of \(\alpha\)-synuclein. Because \(\alpha\)-synuclein exists in both synaptic cells and all nucleated cells, it is essential to ascertain how to avoid the influence of \(\alpha\)-synuclein in the nucleus. Transplantation of the fecal flora from patients with PD induces the symptoms of PD in mice with overexpression of \(\alpha\)-synuclein but not in mice without overexpression of \(\alpha\)-synuclein\(^{110}\). Epidemiologically, constipation is a common but not universal feature of early PD\(^{110}\). Thus, the intestine plays a certain role in the pathogenesis of PD but is not the only contributing factor. In A53T \(\alpha\)-synuclein mice, non-motor symptoms, such as constipation, are reported to occur before motor symptoms. Insoluble \(\alpha\)-synuclein and its aggregation are found in the intestinal neurons of the myenteric plexus and submucosal plexus. The \(\alpha\)-synuclein overexpression is actually systemic in this transgenic mouse strain, and \(\alpha\)-synuclein should be accumulated in all tissues. Therefore, the occurrence of
constipation before the onset of motor symptoms indicates the vulnerability and susceptibility of the intestinal nerves. Because of its susceptibility, GI dysfunction acts like a sentry in PD rather than a pathogenic cause\(^{[1]}\). Recent research has found that there is a nigro-vagal monosynaptic pathway controlling gastric tension and gastric motility in the rat model of PD induced by 6-hydroxydopamine, which suggests that GI symptoms may be a manifestation of dopamine deficiency outside the CNS\(^{[1]}\).

The etiology of PD is often compared to prion disease (Creutzfeldt-Jakob disease) because its pathology may arise from the vagus nerve. Creutzfeldt-Jakob disease is divided into sporadic and familial Creutzfeldt-Jakob disease. The pathogens of sporadic and familial Creutzfeldt-Jakob disease originate from the PNS and CNS, respectively. Analogously, PD can be divided into two subtypes that originate from the PNS or occur idiopathically in the CNS\(^{[1]}\). Different subtypes of PD may show specific phenotypes and prognoses. Patients with constipation have more serious axial symptoms, indicating that the progress of PD is relatively fast in these patients, especially those who develop constipation before the onset of motor symptoms, suggesting that axial symptoms and constipation are interactive factors in PD\(^{[1]}\). Similarly, patients with constipation are at greater risk of dementia\(^{[1]}\). This suggests that patients with PD that originates from the intestine may have different characteristics regarding phenotype and even pathogenesis.

Patients with PD have GI symptoms, regardless of whether PD originates in the gut or whether GI dysfunction is one of the manifestations of PD outside the CNS.

6. Challenges

At present, there is no fundamental solution to the GI symptoms of PD. The current treatment is mainly based on the physical function of the digestive tract itself, such as increasing the viscosity of food, increasing the osmotic pressure of the intestinal tract, and locally promoting GI peristalsis. However, these treatments cannot radically alleviate the symptoms of PD, such as excessive salivation and constipation. Moreover, most effects of the current treatments can only be maintained for a certain period. For example, the tension relief achieved through the injection of BoNT is generally maintained for 3 months, and the regulation of intestinal flora by the ingestion of beneficial microbes is sustained for several days.

The main reason for the poor management of PD-related GI symptoms is that the GI symptoms of PD and even the mechanism of PD itself are not yet completely clear. The GI symptoms cannot be completely relieved by dopamine replacement, which suggests that the motor symptoms of PD and GI symptoms may have different mechanisms. If PD does originate from the intestine, novel PD treatment methods may include improving the intestinal flora, regulating intestinal function, and supplementing corresponding SCFAs and branched chain fatty acids. However, there is currently insufficient evidence to prove that PD originates from the intestine.

If PD is an overall degenerative disease, neurons such as SN dopaminergic neurons, locus coeruleus noradrenergic neurons, and the dorsal vagus nucleus are more vulnerable because of their long axons, greater number of branches, higher energy consumption, and greater damage caused by free radicals. Thus, the treatment of PD and related GI symptoms should include methods to protect neurons from damage.

7. Conclusions

There is no doubt that GI dysfunction exists in PD and seriously decreases quality of life. However, it remains unclear whether GI dysfunction is part of the symptoms of PD or an initial cause of PD. Although there are many available treatments for GI symptoms, including compound drugs, natural herbs, physical stimulation, and a healthy diet, it is still difficult to treat PD-related GI symptoms, especially in patients with advanced PD. Therefore, further drug research and development is needed. In addition, more in-depth clinical and basic research is warranted to uncover the causes of the intestinal symptoms of PD.

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Conflict of interest

The authors report no conflicts of interest.

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