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Review

Gastrointestinal Manifestations of Parkinson's Disease Survey of the Recent Literature

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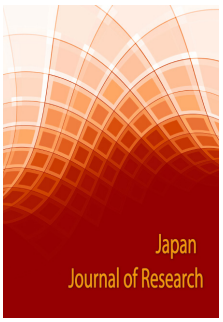

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor symptoms such as bradykinesia, rigidity, rest tremor, and postural instability. However, visceral- symptoms are also a significant part of the disease spectrum, with gastrointestinal (GI) manifestations being among the most common and debilitating. This review is one of the recent literature on the gastroenterological manifestations of PD. This includes dysphagia, esophageal motility disorders, gastroparesis, constipation, pelvic floor dyssynergia, nausea and vomiting, contraindicated medications, and SIBO[small intestine bacterial overgrowth].

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor symptoms such as bradykinesia, rigidity, rest tremor, and postural instability. However, visceral-motor symptoms are also a significant part of the disease spectrum, with gastrointestinal (GI) manifestations being among the most common and debilitating. These GI symptoms can precede the onset of motor symptoms, often making them the initial presentation of the disease. The GI tract is extensively innervated by the enteric nervous system (ENS), which is affected by the same pathological process of alpha-synuclein aggregation seen in the central nervous system in PD. This leads to a range of GI symptoms, including dysphagia, gastroparesis, nausea and vomiting, abdominal distension, and constipation.

Dysphagia

Dysphagia, or difficulty swallowing, can occur at any stage of PD and can lead to complications such as aspiration pneumonia. The pathophysiology of dysphagia in PD is complex. Up to 8 out of 10 patients with PD may report difficulty swallowing [1]. Dysphagia is a common symptom of Parkinson's disease (PD), affecting up to 80% of PD patients [2]. It can lead to severe complications such as malnutrition, dehydration, and aspiration pneumonia, which is a leading cause of death in PD. Marois C, et al [3]. report that dysphagia accounts for about 50% of referrals for percutaneous gastrostomy tube placements in this population. For some patients with dysphagia, speech therapists can provide strategies and exercises to improve swallowing function.

The management of dysphagia in PD is a significant clinical challenge and requires a multidisciplinary approach. The first step in the management of dysphagia in PD is a thorough assessment. This typically involves a clinical swallowing examination, which can provide valuable information about the patient's swallowing function and the risk of aspiration. Instrumental assessments such as video-fluoroscopic swallowing study or fiberoptic endoscopic evaluation of swallowing may be required in some cases. Once the presence and severity of dysphagia have been established, a management plan can be developed. This typically involves a combination of compensatory strategies, swallowing exercises, and dietary modifications. Compensatory strategies are techniques that can be used to facilitate safer. Swallowing exercises can help to improve the strength and coordination of the muscles involved in swallowing.

These include exercises to improve tongue strength, laryngeal elevation, and pharyngeal contraction. The effectiveness of these exercises can be enhanced by incorporating principles of motor learning, such as intensive, repetitive, and task-specific training. Dietary modifications can also play a vital role in the management of dysphagia in PD. This may involve altering the texture of foods and liquids to make them more accessible and safer to swallow. For example, foods may need to be pureed or minced, and liquids may need to be thickened. A dietitian can provide valuable guidance on making these modifications while ensuring that the patient's nutritional needs are

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met. In severe cases of dysphagia where oral intake is not safe or sufficient, alternative methods of nutrition may need to be considered. This may involve using a feeding tube, such as a nasogastric tube or a percutaneous endoscopic gastrostomy (PEG) tube. Serotonin-modulating agents are recommended as the first-line agents for IEM in PD [4]. The most commonly prescribed of these is prucalopride, which has a high affinity and specificity for 5-HT4 receptors, resulting in the release of acetylcholine to promote motility throughout the gut and in the treatment of IEM, potentially enhancing the primary peristalsis of the esophagus [5].

Gastroparesis

Gastroparesis, or delayed gastric emptying, is another common GI manifestation in PD. Gastroparesis is one of the most common GI symptoms in PD, reported to occur in up to 87% of patients. The most common disorders of esophageal motility found in PD, per Chicago classification criteria, are ineffective esophageal motility (IEM), distal esophageal spasm (DES),and esophagogastric junction outflow obstruction [6,7].

Symptoms attributed to gastroparesis include bloating, abdominal fullness, and nausea. These symptoms can be particularly troublesome as they can interfere with the absorption of levodopa, the mainstay of PD treatment, leading to fluctuations in motor symptoms. Thirty-four percent of such patients have concomitant severe to very severe constipation, and the increasing severity of constipation is associated with increasing symptoms of gastroparesis [8].

The first step in managing gastroparesis in PD is a thorough assessment. This includes of course a physical examination and a detailed history of the patient's symptoms. Gastric emptying scintigraphy correlates poorly with symptom severity and lacks reproducibility, commonly turning negative if repeat testing is performed on the same person in whom it was recently positive (and vice versa) [9].

Recently, two randomized controlled trials evaluating prucalopride, a 5-HT4 agonist, in gastroparesis have shown mixed results in symptom improvement [10,11].

Once the presence and severity of gastroparesis have been established, a management plan can be developed. This involves a combination of dietary modifications, pharmacological treatments, and, in some cases, more invasive interventions. Gastroparesis may be managed with dietary modifications such as small, frequent meals and avoiding high-fat and high-fiber foods. Prokinetic agents can also be used to enhance gastric emptying. However, these agents should be used with caution in PD due to the potential for worsening of motor symptoms. [See contraindicated drugs below]

Other methods may include gastric electrical stimulation, a surgical procedure that involves the implantation of a device to stimulate the stomach muscles, and botulinum toxin injections into the pylorus, the opening from the stomach into the small intestine. However, the evidence for these interventions in PD is limited, and they are generally reserved for severe, refractory cases.

Constipation

Constipation has consistently been demonstrated to appear well in advance of motor symptoms—even up to 20 years before PD diagnosis. Constipation is a common non-motor symptom of PD, affecting up to 87% of patients. It is often one of the earliest symptoms, occurring before the onset of motor symptoms.

It can precede the onset of motor symptoms by several years, making it a potential early marker for the disease. The management of constipation in PD is a significant clinical challenge that requires a comprehensive and individualized approach. Initial treatment begins with dietary and lifestyle interventions, including an increase in fiber and water intake, as well as exercise and mobility. Nearly 80% of patients with PD demonstrate prolonged colonic transit time [12].

Osmotic laxatives and lubiprostone have both been shown to be efficacious in prospective studies of patients with PD [13].

One study of patients with Parkinsonism treated with linaclotide or prucalopride found these medications to be effective and well-tolerated, with a higher proportion reporting satisfaction with linaclotide [14].

Managing constipation in PD

Managing constipation in PD involves lifestyle modifications with increased dietary fiber and fluid intake. Additional treatment includes bulk-forming laxatives, such as psyllium, which can help increase stool bulk and promote bowel movements. Osmotic laxatives, such as polyethylene glycol and lactulose, can help to soften the stool by increasing the amount of water in the bowel. Stimulant laxatives, such as senna and bisacodyl, can be used for short-term relief of acute constipation. Prokinetic agents, such as prucalopride, can enhance gut motility and may benefit some patients. However, their use in PD is limited by the potential for worsening motor symptoms. In one study of Parkinson's patients with constipation, it was found that treatment with a beta-blocker significantly lowered the risk of constipation. According to Pagano G, et al., [15] this may be due to the beneficial effects of beta-blockade on a dysregulated autonomic nervous system.

In cases where conservative measures and pharmacological treatments are ineffective, more invasive interventions may be considered. Biofeedback therapy can help to improve defecatory mechanics and is effective in some patients with PD. Sacral nerve stimulation, a surgical procedure involving implanting a device to stimulate the sacral nerves, may also benefit some patients.

Pelvic floor dyssynergia

Pelvic floor dyssynergia is an abnormality of coordination in the abdominal, recto-anal, and pelvic floor muscles, resulting in difficulty or inability to achieve defecation [16,17]. Patients with dyssynergic defecation complain of excessive straining and a feeling of incomplete evacuation. Defecatory dysfunction is also reported in up to 58.9% of patients. The pathophysiology of constipation in PD involves degeneration of the enteric nervous system, autonomic dysfunction, and the side effects of antiparkinsonian medications

In patients for whom dyssynergia is suspected, additional testing with high-resolution anorectal manometry with balloon expulsion is warranted to distinguish pelvic floor dyssynergia for patients with PD, as they are abnormal in nearly 90% of patients with PD with constipation [18].

Nausea and vomiting

Nausea and vomiting are highly prevalent features of PD, with gastroparesis being present in at least 70% of cases [9,19].

Ordinary GI Medications which blocks central D2 receptors with some of these drugs also blocking cholinergic, muscarinic, and histaminergic receptors, are contraindicated in PD. These

contraindicated drugs include Prochlorperazine (Compazine), promethazine (Phenergan), Metoclopramide (Reglan), (Buspar), Haloperidol (Haldol), Olanzapine (Zyprexa) Amoxapine (Asendin) [4].

SIBO [SMALL INTESTINE BACTERIAL OVERGROWTH]

Chronic bloating often poses a therapeutic challenge. Approximately 1 in 4 patients with PD suffer from bloating [20]

SIBO is emerging as an important microbiome-associated condition. Using well-validated catheters and techniques optimized for small bowel microbiome assessment, SIBO appears best defined using the threshold of ≥103 CFU/mL because this concentration seems to be a key microbial tipping point both for disruption of the microbiome and for the development of GI symptoms. The most critical disruptors in SIBO appear to be E coli and species of *Klebsiella*, and specific strains are likely responsible for most overgrowth in SIBO.

Metabolic data support augmentation of H2- and H2S-producing pathways in subjects with SIBO, defined by high-throughput sequencing, supporting the current clinical use of breath testing.

16S rRNA sequencing shows that 2 key genera, Escherichia and *Klebsiella*, account for most bacterial overgrowth in SIBO. Moreover, *Escherichia* and *Klebsiella* are associated with disruptive changes to the microbiome proportional to their abundance, consistent with the recent identification of E coli as a disruptor in the small bowel.

Escherichia and *Klebsiella* effect these changes both independently and synergistically. Regarding symptoms, *Escherichia* is associated with bloating and diarrhea, whereas *Klebsiella* has a greater association with abdominal pain, consistent with recent studies identifying K aerogenes as a major histamine producer potentially linked to visceral hypersensitivity.

Pathways enriched in SIBO subjects include pathways involved in the degradation and fermentation of sugars, particularly pyruvate fermentation pathways coupled with aerobic/anaerobic respiration and sulfate-reducing pathways. Changes in these pathways also correlated with GI symptoms in SIBO subjects, including diarrhea, bloating, urgency, and abdominal pain.

Given the higher prevalence in this population of PD, one should test for SIBO in patients with these symptoms and treat (typically with a 14-day course of rifaximin, which has been shown in most to improve symptoms attributed to SIBO) [21].

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