REVIEW ARTICLE

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Gastrointestinal Autonomic Dysfunction in Patients with Parkinson's Disease

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ABSTRACT

Currently, gastrointestinal dysfunctions in Parkinson's disease (PD) are well-recognized problems and are known to be an initial symptom in the pathological process that eventually results in PD. Gastrointestinal symptoms may result from the involvement of either the central or enteric nervous systems, or these symptoms may be side effects of antiparkinsonian medications. Weight loss, excessive salivation, dysphagia, nausea/gastroparesis, constipation, and defecation dysfunction all may occur. Increased identification and early detection of these symptoms can result in a significant improvement in the quality of life for PD patients.

Key Words
Parkinson's disease; Gastrointestinal dysfunctions; Enteric nervous system; Pathophysiology; Assessment.

INTRODUCTION

Currently, gastrointestinal dysfunctions in Parkinson's disease (PD) are well-recognized problems and are known to be the initial symptoms in the pathological process that eventually results in PD.[1] Many types of PD-associated gastrointestinal dysfunctions have been identified, including weight loss, dental deterioration, excessive salivation, dysphagia, esophageal dysmotility, gastroparesis, decreased bowel movement, constipation and defecation dysfunction.[2-4] Even in the early stage of the disease, patients with PD are likely to suffer from gastrointestinal dysfunction, and these symptoms eventually occur in the advanced stage as well.[5,6] These symptoms can impact other PD symptoms and are the second-most significant predictor of the quality of life for people living with PD.[7]

Despite recent progress in the recognition of gastrointestinal dysfunctions, there is a paucity of clinical trial data on the management of gastrointestinal symptoms in PD. In this paper, the clinical presentation, evaluation, pathophysiology, and treatment of each gastrointestinal symptom in PD will be discussed.

Weight loss

Weight loss is common in PD and was found in 52% of individuals with PD at the onset of the disease.[8] The amount of weight loss is usually modest, although it can exceed 12.8 kg in 22% of PD patients.[8] The underlying pathophysiological mechanisms of this unintended weight loss are not known. Medical evaluations for an alternative medical cause should also be performed for patients experiencing severe weight loss. Possible contributors include 1) either reduced energy intake or increased energy expenditure, 2) olfactory impairment with a consequent reduction in the sense of taste, 3) dysphagia, and 4) a complex interplay between changes in the dopaminergic systems caused by PD coupled with changes induced by anti-parkinsonian medication.[9,10] In contrast to the weight loss that develops as part of PD itself, there is an average weight gain of 13% within 16.3 months and increased appetite following the subthalamic nucleus deep brain stimulation surgery for PD.[11]

Excessive saliva and sialorrhea

Excessive saliva with or without drooling occurs in 70–78% of PD patients, and sialorrhea can lead to aspiration and subsequent aspiration pneumonia.[12,13] Recent studies using simple questionnaires or sialometry have shown that drooling reflects impaired automatic swallowing rather than excessive saliva production.[14,15] The excessive salivation may be due to dysfunctions in the dorsal motor nucleus of the vagus (DMV), which can affect the muscles controlling deglutition and esophageal motility.[16] Salivary secretion is actually reduced in PD, even in the early stage of disease.[15] Dry mouth often precedes the onset of motor symptoms in PD.[5] A recent study has found alpha-synuclein (α-SYN) inclusion in minor salivary glands and Lewy body pathology in the submandibular gland,[17,18] although the pathological implication in PD patients is not clear. Another recent study determined that dribbling saliva while awake occurs in 28% of PD patients, and nocturnal drooling occurs in 58% of PD patients. The patients who exhibited drooling were older and had more severe PD, longer disease duration, worse scores for dysphagia, and more severe involuntary mouth opening.[19] Additionally, the researchers found that diurnal drooling typically appeared later in the disease course and was associated with involuntary mouth opening and swallowing dysfunction.[19]

Several methods for assessing sialorrhea in PD have been employed, but no objective bedside methods have been developed. An easily administered clinical rating scale would be of more use to the practicing neurologist for documenting the severity of sialorrhea and treatment response. Scales used to evaluate the severity of sialorrhea in PD include the Drooling Severity and Frequency Scale, the Drooling Rating Scale, the Unified PD Rating Scale item number 6, and the Sialorrhea Clinical Scale for PD.[20]

Use of chewing gum or hard candy is encouraged, and this approach may be effective for patients with mild symptoms.[2] For patients with moderate to severe symptoms, pharmacological treatments are warranted. Oral anticholinergic drugs, such as trihexyphenidyl hydrochloride and benzatropine mesylate, are prescribed in an attempt to "dry up" the excess saliva, even though the side effects of these medicines include cognitive dysfunction, urinary retention and constipation.[21] Alternatively, topical anticholinergics can be administered sublingually to control sialorrhea and avoid systemic side effects.[22,23] Periodical intraparotid injection of botulinum toxin

A or B is also effective in eradicating excess saliva in PD patients.[24] Surgical approaches, such as tympanic neurectomy (with sectioning of the Jacobson's nerve and the chorda tympani), have been successfully used in the treatment of refractory drooling in various neurological disorders, including PD.[25]

Dysphagia

Dysphagia occurs in 10% to over 80% of PD patients.[12,13,26-28] Survey studies have suggested that approximately 50% of PD patients report symptomatic dysphagia, yet clinical assessments using barium swallowing tests and videofluoroscopy can detect abnormalities in more than 75–97% of cases with the risk of silent aspiration.[29-31] Although the dysphagia typically occurs in the relatively late stages of PD,[32] it may be an early or presenting symptom in some cases.[33,34]

Dysphagia is a disorder that affects not only swallowing but also the entire complex motor cascade, beginning prior to swallowing and ending when a bolus passes through the lower esophageal sphincter. All stages of swallowing—preoral, oral, lingual, pharyngeal, and esophageal—may be affected by PD.[35,36] Dysphagia can result when the motor symptoms of PD involve the oropharyngeal muscles or can occur from defective coordination of the oropharyngeal and esophageal musculature due to brainstem dysfunction. Recent neuropathological studies have clearly shown that the DMV is affected early in the course of the disease.[37-41] Additionally, esophageal dysphagia might be associated with Lewy bodies or the loss of the neurons within the esophageal myenteric plexus.[42] In addition to the pathophysiological abnormalities, dysphagia can also occur as a side effect of medications.[43]

The most typical abnormality found in PD is a prolongation of the swallowing reaction time.[44] Dysregulated feeding during the preoral phase may be caused by parkinsonian motor symptoms as well as mental dysfunctions such as impulsive feeding. Multiple abnormalities during the oropharyngeal phase have also been found, including decreased mastication and lip sealing, delayed bolus transit, disordered fragmented transfer and peristalsis, vallecular and pyriform sinus residues, delayed swallowing reflexes, and deficits in laryngeal movement.[31,33,45] A majority of PD patients experienced repetitive swallow attempts (double or triple swallow pattern) for a single bolus.[34] This abnormal swallow pattern was distinctly associated with abnormal peristalsis, including failed peristalsis and incomplete bolus transit. These abnormalities can cumulate in increased risk of aspiration. Esophageal dysfunction may also responsible for dysphagia in PD, and esophageal dysmotility often manifests with repetitive proximal esophageal contractions, slowed esophageal transit, aperistalsis, reduced pressure of the lower esophageal sphincter and achalasia.[21]

Treatment of dysphagia has not been approved universally. Non-pharmacological techniques such as chin-down swallowing and use of the National Dysphasia Diet Program may be useful in some patients.[46] Optimizing dopaminergic medication can be beneficial for some patients.[31,47] Swallowing training to learn voluntary airway protection techniques may also be beneficial. Percutaneous endoscopic gastrostomy placement may become necessary in the face of severe, intractable dysphagia, but such severity is rare in PD.[48]

Gastric dysfunction

Although nausea in PD occurs very commonly due to dopaminergic medication, nausea may also develop in untreated PD patients due to underlying gastroparesis (impaired gastric emptying). Gastric dysfunction may be associated with α-SYN pathology in the submucosal Meissner's plexus with extension into the gastric mucosa and in proximity to the fundic glands.[49] Gastroparesis can be characterized by symptoms such as postprandial bloating or abdominal discomfort, early satiety, nausea, and weight loss.[13] In 28 untreated patients with PD, the average time to empty half of the gastric contents (i.e., the half-gastric emptying time) was 59 min compared to 44 min in a group of healthy control individuals.[50] Impaired gastric emptying may also interfere with levodopa absorption by delaying the onset of action for levodopa or causing a complete dose failure.[50]

If the gastric dysfunction symptoms are mild, diet control using small, frequent meals, walking 1 to 2 hours after meals, avoiding high fat and fiber foods, and lying down after meals are encouraged.[3] When pharmacological treatments are needed, the use of domperidone, a peripheral-acting D2 receptor antagonist, has been shown to improve both gastric emptying and levodopa absorption.[51] However, domperidone possesses cardiac electrophysiological

properties similar to those of class III antiarrhythmic agents and can prolong the QTc interval and predispose individuals to ventricular arrhythmias. Therefore, performing a baseline electrocardiogram (ECG) and testing serum potassium prior to the initiation of therapy are generally recommended. If a QT interval of > 450 ms in males and > 470 ms in females is detected on the baseline ECG or if sustained hypokalemia is detected, the patient should not receive domperidone therapy.[52] The Pharmacovigilance Working Party of the European Medicines Agency has also identified an increased risk of serious ventricular arrhythmias or sudden cardiac death associated with domperidone, particularly in patients older than 60 years or in patients taking daily doses of more than 30 mg.[51] Intravenous infusion of erythromycin is another potential treatment approach for the short-term management of gastroparesis,[53] but concerns over sustained efficacy, antimicrobial resistance and arrhythmogenic effects limit its long-term use.

Small intestinal bacterial overgrowth

Small intestinal bacterial overgrowth (SIBO) is associated with malabsorption due to a bacterial density above 10^5 colony-forming units/mL of small intestinal aspirate and/or the presence of colonic-type species.[54] Recently, SIBO has been implicated as a gastrointestinal dysfunction in PD, and the prevalence of SIBO in PD ranged from 54% to 67% (in contrast, one large study of 294 older German adults without PD reported a 15.6% prevalence).[55-59] SIBO in PD could be associated with worse on-medication motor scores and more severe motor fluctuations.[60] The eradication of SIBO using rifaximin 400 mg 3 times a day for 7 days resulted in improvement in motor fluctuations without affecting the pharmacokinetics of levodopa.[56] Therefore, it can be postulated that impaired gut motility in PD leads to SIBO, which may in turn induce a secondary inflammatory response in the gut mucosa and impair levodopa absorption.

Constipation

Constipation may occur in more than 50% of PD patients.[61] The proposed mechanism is slow transit through the colon. Colon transit time has been found to be up to twice as long in PD patients compared with controls.[62-64] The accumulation of Lewy bodies in enteric neurons may explain this finding, which may result primarily from impaired reflex relaxation of the distal smooth muscle due to loss of inhibitory motor neurons.[65] Additionally, fluctuations in the severity of anorectal abnormalities in response to dopaminergic medications have been documented, demonstrating that this symptom can also be associated with medication.[66] Constipation often occurs early in the disease course and may predate motor features by several years. A study of more than 6,000 men without PD showed that the future risk of PD increases four-fold in men who had less than one bowel movement a day compared to men who had more than one.[67] Subsequent autopsy studies on subjects with no clinical signs of parkinsonism prior to death suggested that late-life constipation is associated with incidental Lewy bodies in the substantia nigra and locus ceruleus as well as decreased substantia nigra neuron density.[68,69]

The treatment of constipation may begin with conservative, non-pharmacological methods. Patients are advised to increase fluid intake, maximize dietary fiber, increase exercise and discontinue medications known to exacerbate constipation. If conservative treatments fail, pharmacological treatment can be attempted with various laxatives (either bulk-forming laxatives such as psyllium or osmotic laxatives such as milk of magnesia or polyethylene glycol).[70,71] Although studies in PD have yet to determine the ideal treatment for PD-associated constipation, prokinetic agents such as prucalopride can be used in patients with medically intractable constipation,[72] albeit with caution because these agents may lead to worse parkinsonian motor symptoms.

Defecation dysfunction

Defecation dysfunction in patients with PD may be associated with abnormalities found during colonic inertia to the anal outlet,[73] and clinical symptoms of difficulty with the act of defecation include excessive straining, pain, and incomplete evacuation. Defecation dysfunction is a consequence of the uncoordinated action of the muscles involved with defecation.[74] Relaxation of the puborectalis muscle allows for opening of the anorectal angle and perineal descent, which facilitates fecal expulsion. Outlet obstruction may occur when both the puborectalis muscle and the external anal sphincters do not relax sufficiently.[75,76] During defecation, failure of

relaxation in both the external anal sphincter and the puborectalis muscles can produce a functional outlet obstruction. This dysfunction has been considered as a focal dystonic phenomenon.[75] The functional outlet obstruction may cause both excessive straining and a sense of incomplete emptying. The obstruction may also make defecation painful. Development of the functional outlet obstruction is more frequent in PD and affects more than 60% of PD patients.[77]

Improvement in defecation dysfunction has been reported after subcutaneous injection of the dopamine agonist apomorphine or Botulinum toxin injections into the external anal sphincter and/or puborectalis muscle.[75,76,78]

Pathological implications

Extensive studies of clinical human materials have shown almost all patients with PD display Lewy pathology within their enteric nervous system (ENS).[17] Furthermore, Braak et al.[49] suggested that these lesions in enteric neurons develop early in the course of disease prior to the appearance of pathology in the substantia nigra neurons. Therefore, the ENS could be critically involved in the pathophysiology of the disease.[79]

Dopaminergic neurons are also relatively abundant in the plexuses of the upper gastrointestinal tract, accounting for 15% to 20% of the total number of enteric neurons, whereas their proportion dwindles to 2–4% in the large intestine.[80] As stated previously, constipation and defecation dysfunction typically precede motor manifestations of PD.[67] Whereas gastroparesis symptoms also precede motor manifestations, the prevalence of these symptoms was not significantly different from that of the controls. Even though there is a rostrocaudal gradient of α-SYN neuropathology in the ENS in the early stages of PD with a higher burden in the upper gut compared to the lower gut, constipation and defecation dysfunction were the only prominent premotor gastrointestinal symptoms of PD.[5]

Examining the gastrointestinal tract by endoscopy is a simple way to evaluate α-SYN deposits; however, quantification of α-SYN deposits and subsequent determination of a positive result remains somewhat ambiguous. Several issues should be considered, including the population studied, the thickness of the tissue, the site of biopsy (ascending colon vs. transverse colon vs. descending colon), the number of sections, the sample numbers of subjects, available histological techniques, and the timing of detection.[81,82]

Conclusion

In PD patients with gastrointestinal disorders, the PD-related healthcare costs and non PD-related healthcare costs are significantly increased. Additionally, emergency admissions and the number of comorbidity-related therapeutics are also increased.[7]

It is essential to be aware of the various gastrointestinal manifestations of PD to facilitate prompt recognition and effective therapeutic intervention for these potentially distressing symptoms. Treatment of dysphagia, gastroparesis, and defecation dysfunction are particularly challenging. More clinical trials are needed to guide clinicians in the management of these symptoms, and more research is needed to clarify the mechanisms underlying disordered gastrointestinal motility in PD.

Conflicts of Interest

The authors have no financial conflicts of interest.

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