Gastroparesis in Parkinson Disease

Subjects: Neurosciences

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Patients with Parkinson disease (PD) experience a range of non-motor symptoms, including gastrointestinal symptoms. These symptoms can be present in the prodromal phase of the disease. Recent advances in pathophysiology reveal that α-synuclein aggregates that form Lewy bodies and neurites, the hallmark of PD, are present in the enteric nervous system and may precede motor symptoms. Gastroparesis is one of the gastrointestinal involvements of PD and is characterized by delayed gastric emptying of solid food in the absence of mechanical obstruction. Gastroparesis has been reported in nearly 45% of PD. The cardinal symptoms include early satiety, postprandial fullness, nausea, and vomiting. The diagnosis requires an appropriate test to confirm delayed gastric emptying, such as gastric scintigraphy, or breath test. Gastroparesis can lead to malnutrition and impairment of quality of life. Moreover, it might interfere with the absorption of antiparkinsonian drugs. The treatment includes dietary modifications, and pharmacologic agents both to accelerate gastric emptying and relieve symptoms.

Keywords: Parkinson disease ; gastroparesis ; alpha-synuclein ; vagus nerve

1. Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder, after Alzheimer disease. It affects 2–3% of the population over 65 years and is more common in men [1]. Worldwide incidence estimates of Parkinson's disease range from 5 to >35 new cases per 100,000 individuals yearly. Parkinson's disease is rare before 50, but the incidence increases 5–10-fold from the sixth to the ninth decade of life.[2] The triad of parkinsonism is defined by motor symptoms that are rigidity, bradykinesia, and tremors [3]. However, the majority of patients with PD reveal a variety of non-motor symptoms, either as a specific complaint or upon specific questioning [4][5]. Gastrointestinal (GI) dysfunction in PD was already described by James Parkinson in 1817 in his first description of the disease [6]. Although historically overlooked [7], interest in GI manifestations has been increasing in the past decades. Several studies revealed five GI features—excess saliva, dysphagia, nausea (mainly related to delayed gastric emptying), decreased bowel movement frequency, and difficulty with defecation—as occurring more frequently in PD patients as compared to aged controls [8][9].

GI manifestations can occur at an early stage of PD and may precede motor symptoms in some cases by several years [10][11]. These disturbances impact the quality of life and are a common reason for emergency room visits and hospitalizations [12][13][14]. Gastroparesis, in particular, contributes to malnutrition and weight loss which is frequent in patients with PD [15]. In addition to its clinical aspect, the idea that PD may have its genesis in the gut has received increasing attention.

2. Pathophysiology of GI Dysfunction in PD

Gastric motility and secretory functions are regulated by an extrinsic neuronal network composed of the sympathetic and parasympathetic systems, and an intrinsic neuronal semiautonomous network, the enteric nervous system (ENS). The ENS consists of myenteric (or Auerbach's) plexus and submucous (or Meissner's) plexus [16][17]. The myenteric plexus runs between circular and longitudinal muscle layers for the whole length of the gut and primarily provides motor innervation, whereas the submucous plexus plays a role in the control of secretion. The parasympathetic pathway is mainly driven by the vagus nerve, and by the sacral nerves for the distal part of the colon. The extrinsic system cooperates with the intrinsic network, and with the central nervous system. Intramural circuits of the ENS and efferent vagal nerves innervate motor neurons. Excitatory and inhibitory motor neurons drive the motility of the gastric smooth muscle. Interactions between the brainstem and ENS in the form of vago-vagal reflexes determine patterns of normal gastric motor activity [18].

The neuropathological hallmarks of PD are neuronal loss in the substantia nigra, leading to dopamine deficiency, and abnormal α-synuclein accumulation in the brain, with intracellular aggregates leading to the formation of Lewy bodies, or Lewy neurites [19]. The presence of Lewy bodies has been described in the GI tract and especially in the esophagus and

colon since 1984 [20]. Mucosal biopsy samples harvested from the colon, stomach, and duodenum, have shown that misfolded α-synuclein is present in the ENS from the early stages in patients with PD and even 8 years before the onset of motor symptoms [21]. Myenteric neurons of the whole GI tract represent one of the earliest sites of α-synuclein accumulation, and this deposition occurs with a rostro-caudal gradient throughout the ENS [22]. High levels of Lewy bodies are also found in the central nervous system and in the dorsal motor nucleus of the vagus nerve (DMV) which has a strong influence on GI motility [23]. The causes of this distribution are unknown, although deposition follows the distribution of visceromotor projection neurons.

3. Gastroparesis

3.1. Prevalence in PD

Gastroparesis is a disorder defined by delayed gastric emptying of solid food in the absence of mechanical obstruction [24]. The main symptoms include early satiety after eating, postprandial fullness, nausea, vomiting, belching, and bloating. Severe forms lead to weight loss and impaired quality of life [25]. The prevalence of gastroparesis in PD has not been formally assessed. Impaired gastric emptying seems to be common reaching 70% to 100% of PD patients in a study using scintigraphy measurement [26]. However, this delayed emptying could be asymptomatic, with subjective symptoms present only in 25% to 45% of patients [27]. Interestingly, a recent study identified a subgroup of PD patients with accelerated gastric emptying [28]. Gastroparesis may occur in early and untreated PD, but its frequency seems to be higher in advanced disease [26][29]. The severity of gastroparesis is also correlated with the severity of motor impairment [30].

3.2. Pathophysiology

Delayed gastric emptying is associated with antral hypomotility and in some patients with pyloric sphincter dysfunction. Both mechanisms are caused by neuromuscular dysfunction. Extrinsic excitatory innervation is addressed from the vagus nerve and interacts with the intrinsic nerves of the ENS. In the smooth muscle layer, the interstitial cells of Cajal convey the signal to smooth muscle cells and are regarded as gastric pacemakers. These pacemaker cells do not seem to be altered in PD, suggesting that disturbance occurs either in the vagus nerve or in the myenteric plexus [31]. Alteration in a cholinergic anti-inflammatory pathway has also been demonstrated on an animal model of PD, which could lead to gastric muscular inflammation and muscular macrophage accumulation [32]. This muscular macrophage accumulation in the gastric wall has been described in idiopathic gastroparesis.

3.3. Diagnostic Criteria

Clinical assessment of the symptoms should be performed with a reproducible and validated scale to allow a better follow-up and to standardize clinical trials on gastroparesis [33][34]. The Gastric Cardinal Symptom Index (GCSI) is to date the best validated score, based on the evaluation of nine items, scored from 0 to 5, (nausea, retching, vomiting, stomach fullness, early satiety, postprandial fullness, loss of appetite, bloating, stomach distension). The global score is then calculated on a range from 0 to 5, and is used to assess the effects of treatment, but not as a diagnostic tool to decide whether a patient should perform diagnostic tests.

4. Treatment

4.1. Dietary Modifications

Therapeutic strategy first relies on dietary modification and is generally used for all patients. Patients are recommended to eat small meals and to avoid foods high in fat and indigestible fibers [35]. A small-particle-size diet has been shown to reduce upper GI symptoms in diabetic gastroparesis [36]. Thus, snacking and more frequent meals to maintain caloric intake are needed. Caloric liquids such as soups are also often well tolerated and recommended. In severe cases, vitamin deficiencies should be detected and supplemented. Rarely, feeding tube or parenteral nutrition can be necessary [37].

4.2. Pharmalogical Treatment

Most of the medical treatments used for gastroparesis have not been validated in the specific context of gastric dysmotility due to PD. Prokinetic drugs, and in the first step peripheral dopamine antagonist drugs, are the most commonly used medication. D2 receptor antagonists that cross the brain–blood barrier, including metoclopramide, are contraindicated in PD. By contrast, domperidone is a D2 receptor antagonist acting peripherally as it does not cross the brain–blood barrier, and it may be used to accelerate gastric emptying and relieve nausea and vomiting [38]. Of note, domperidone is associated with cardiac arrhythmia risks and is thus not approved by FDA [39][40]. However, recent data are reassuring on the safety profile of the drug used in the right settings, and domperidone should be considered as an option in

gastroparetic PD patients [41]. Motilin receptor agonists, including erythromycin and azithromycin, are not appropriate for extended use owing to drug interactions (especially for erythromycin), to QT prolongation, and to their association with tachyphylaxis with loss of efficacy over a few weeks [42]. A selective 5-HT_4 receptor agonist, prucalopride, lacking cardiac side effects, is yet approved for the treatment of constipation and has been shown to improve gastric emptying in small open labeled studies in PD [43][44]. One small study reported improvement in gastric emptying with nizatidine, a histamine H2-receptor antagonist, in patients with PD [45]. This drug could also be used to treat some of the reflux symptoms associated with gastroparesis [46]. Finally, ghrelin antagonists such as relamorelin are being assessed as potential prokinetic agents and seem to be effective in improving symptoms and gastric emptying in patients with diabetic gastroparesis in two phase 2 trials [47][48].

4.3. Interventional Techniques

Several instrumental techniques are now available for patients who do not respond to medical treatment. In some patients, gastroparesis is associated with pyloric sphincter dysfunction, and endoscopic therapies targeting the pylorus have thus been assessed. Botulinum toxin injections in the pyloric sphincter may alleviate gastroparesis, with data also presented in patients with PD [49]. However, two double-blinded studies failed to show improvement with this technique compared with placebo [50][51]. It may provide temporary relief, but not sustained improvement, lasting on average 3 months. Endoscopic pyloric dilation has been less commonly evaluated in gastroparesis, and not in PD, but could also allow a temporary relief in some patients [52]. Recently, gastric endoscopic pyloromyotomy has been developed for refractory patients, and reveals improvement in gastric emptying and symptomatic scores, with a more sustained relief in 66% of patients at 1 year [53][54]. This technique also has not been assessed in PD, and controlled trials are still missing.

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