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REVIEW

Gut dysfunction in Parkinson's disease

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Abstract

Early involvement of gut is observed in Parkinson's disease (PD) and symptoms such as constipation may precede motor symptoms. α-Synuclein pathology is extensively evident in the gut and appears to follow a rostrocaudal gradient. The gut may act as the starting point of PD pathology with spread toward the central nervous system. This spread of the synuclein pathology raises the possibility of prion-like propagation in PD pathogenesis. Recently, the role of gut microbiota in PD pathogenesis has received attention and some phenotypic correlation has also been shown. The extensive involvement of the gut in PD even in its early stages has led to the evaluation of enteric α-synuclein as a possible biomarker of early PD. The clinical manifestations of gastrointestinal dysfunction in PD include malnutrition, oral and dental disorders, sialorrhea, dysphagia, gastroparesis, constipation, and defecatory dysfunction. These conditions are quite distressing for the patients and require relevant investigations and adequate management. Treatment usually involves both pharmacological and non-pharmacological measures. One important aspect of gut dysfunction is its contribution to the clinical fluctuations in PD. Dysphagia and gastroparesis lead to inadequate absorption of oral anti-PD medications. These lead to response fluctuations, particularly delayed-on and no-on, and there is significant relationship between levodopa pharmacokinetics and gastric emptying in patients with PD. Therefore, in such cases, alternative routes of administration or drug delivery systems may be required.

Key words: Parkinson's disease; Gut dysfunction; Sialorrhea; Dysphagia; Gastroparesis; Constipation; Gut microbiota

Core tip: Gut is involved in early Parkinson's disease (PD) with extensive synuclein pathology, following a rostrocaudal gradient along the gastrointestinal system. It may act as the starting point of PD pathology with

prion-like spread toward the central nervous system. The clinical manifestations include malnutrition, oral and dental disorders, sialorrhea, dysphagia, gastroparesis, constipation, and defecatory dysfunction. These are distressing for the patients and need to be managed properly by pharmacological or non-pharmacological measures. Gut dysfunction also leads to response fluctuations in PD and this may require alternative routes of administration or drug delivery systems for anti-PD medications.

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder affecting people across the globe. It is clinically defined by its motor features such as bradykinesia, rigidity, rest tremor, and postural impairment[1]. However, "non-motor" features of PD play a vital role in the disease process, and recently this has gained increasing significance, clinically as well as from the etiopathogenesis point of view. Non-motor manifestations such as loss of sense of smell and taste, rapid eye movement sleep behavior disorder, and clinical evidence of autonomic dysfunction can predate motor features by years and sometimes can dominate the clinical picture[2].

Gastrointestinal (GI) or gut dysfunction in PD can be because of both motor and non-motor (dysautonomic) impairment. A better description of gut dysfunction in PD is available, and it is now established that GI disturbances are common and affect virtually all levels of the GI system[3]. Although initially considered to be late manifestations of PD, GI disturbances are present early in the course of the disease in relatively high frequency[4]. The gut dysfunction includes drooling, dental problems, diminished taste, swallowing disorders, impaired gastric emptying, weight loss, and constipation. Other than clinical gut manifestations, the GI system is a significant contributor to the pathogenesis of PD and gut may even act as route for the spread of pathology to the central nervous system (CNS). Moreover, early involvement of gut is considered a possible presymptomatic stage of PD.

In this review, we aim to discuss gut dysfunction in PD including the role of gut synuclein as biomarker for early PD. We also summarize various GI manifestations along with their management.

GUT PATHOLOGY IN PD

PD is classified as synucleinopathy. It is pathologically characterized by the presence of Lewy neurites and Lewy bodies in the brain, which are abnormal inclusions consisting of nearly insoluble aggregates within cellular processes and somata of involved neurons. These are chiefly made of α-synuclein along with ubiquitin and phosphorylated neurofilaments[5]. Until now, postmortem detection of α-synuclein aggregation in brain by immunohistochemistry along with neuronal loss in substantia nigra is considered gold standard for definite diagnosis of PD[6]. For pathological diagnosis of PD in early stages, alternative approaches are studied including identification of Lewy bodies and α-synuclein in extra-CNS locations , and the gut appears to be a promising area because of its accessibility.

Table 1 Gut pathology in Parkinson's disease

Distribution of gut pathology	Pathology spreading from the gut	Gut microbiota
Rostrocaudal gradient of α-synuclein pathology	Crossing the gut barrier	Modulation of gut-brain axis
Place of colon and vermiform appendix	Dual-hit hypothesis	Helicobacter pylori and small intestinal bacterial overgrowth
	Prion-like propagation	Clinical phenotypic correlation

Distribution of gut pathology

Distribution of α-synuclein pathology in gut in relation to its nature, appearance, staining properties, and distribution along the GI system has been documented (Table 1). A rostrocaudal gradient of α-synuclein associated histopathology within GI system is likely. Earlier studies showed characteristic inclusions that were histologically and ultrastructurally identical to Lewy bodies in Auerbach's and Meissner's plexuses, which were abundant in the lower esophagus[7]. Another study confirmed the highest involvement in lower esophagus and submandibular gland followed by stomach and small intestine, whereas colon and rectum had the lowest involvement[8]. This rostrocaudal gradient along enteric nervous system (ENS) coincides with the distribution of vagal innervation from dorsal motor nucleus of vagus (DMV)[9]. However, this gradient is not unequivocally evident in all studies[10]. Interestingly, a recent study on patients with no history of neurological disease showed vermiform appendix enriched in α-synuclein in its mucosal plexus. The authors concluded that appendix may be used as candidate anatomical locus for the initiation of enteric α-synuclein aggregation[11].

Spreading from the gut?

As the pathological involvement of gut is unfolding, a hypothesis that gut/ENS may act as initiation point of PD pathology or route to centripetal involvement of CNS has gained importance. Braak *et al*[12] suggested

that pathology may be caused by a pathogen that can penetrate the mucosal barrier of the GI tract and, via postganglionic enteric neurons, reaches the CNS along preganglionic fibers derived from the vagus by retrograde axonal and transneuronal transport, thus reaching selectively vulnerable subcortical nuclei.

In addition, a dual-hit hypothesis is proposed, which suggests that a neurotropic pathogen, probably viral, enters the brain via two routes-nasal and gastric-following swallowing of nasal secretions in saliva. These secretions might contain a neurotropic pathogen that penetrates the epithelial lining and reaches preganglionic parasympathetic motor neurons of the vagus nerve by transsynaptic transmission through axons of Meissner's plexus. This would allow retrograde transport into the medulla, followed by caudo-rostral propagation to substantia nigra[13]. The early involvement of ENS has also been demonstrated in an animal study, which concluded that ENS abnormalities preceded CNS changes[14].

This hypothesis of spread of synuclein pathology across various sections of nervous system has suggested another aspect of PD pathogenesis, that is, the possibility of prion-like propagation. This is based on two recent reports showing Lewy bodies in grafted neurons in subjects with PD suggesting probable spread of α-synuclein aggregates from host to graft neurons[15,16]. Studies on animal models of PD have shown that intracerebral injection of exogenous α-synuclein induces a progressive α-synuclein immunoreactive staining pattern suggestive of α-synuclein pathology propagation via a prion-like process[6].

Role of gut microbiota

Furthermore, the emerging role of gut microbiota adds to the contribution of GI system in PD. Microbiota may interact with gut-brain axis through different mechanisms, most importantly *via* modulation of intestinal barrier[17]. In PD, gut microbiota changes associated with intestinal inflammation may contribute to α-synuclein misfolding. Moreover, priming of the innate immune system by gut microbiota may enhance the inflammatory response to α-synuclein. The role of peripherally-induced inflammation inflicting damage on dopaminergic neurons has also been studied in animals[18]. The role of *Helicobacter pylori* (*H. pylori*) in PD has been investigated. A Cochrane review concluded that there is limited evidence to suggest that *H. pylori* eradication improves absorption of levodopa and consequently motor symptoms[19]. However, a recent study showed that *H. pylori* infection is linked with worse motor severity of PD[20]. The study investigating the contribution of small intestinal bacterial overgrowth (SIBO) to pathophysiology of motor fluctuations in PD showed that SIBO eradication resulted in improved motor fluctuations without affecting pharmacokinetics of levodopa[21]. Recently, a study explored the relation of gut microbiota with clinical phenotype of PD and compared fecal microbiomes of patients with PD with control subjects and showed a reduction of *Prevotellaceae* in PD. Moreover, the relative abundance of *Enterobacteriaceae* was positively related with the severity of postural instability and gait difficulty[22]. These findings offer some insight into the possible effect of gut microbiota on PD.

Enteric α-synuclein as a biomarker of early PD

Because of extensive involvement of the GI tract and its easy accessibility, there is growing interest to utilize enteric α-synuclein as a possible biomarker of early PD. However, some reports were critical about gut biopsy utilization. A study showed that there was no neuronal loss in myenteric plexus in PD and that Lewy body pathology parallels parasympathetic autonomic input from DMV[23]. Pathologic species or strain of α-synuclein, considered to be responsible for PD pathology, have been detected using immunoreactive staining of α-synuclein, and future studies should concentrate on α-synuclein immunoreactivity for identifying these specific species. However, although studies have utilized antibodies reactive for phosphorylated α-synuclein as a marker of pathologic α-synuclein in the GI tract[24], α-synuclein phosphorylation may be a normal event in adult human brain[25]. Based on recent evidence that soluble, oligomeric aggregates of α-synuclein may ultimately be pathogenic, it was suggested that antibodies reactive to oligomeric forms of α-synuclein could improve specificity and sensitivity for pathological staining in the GI tract[6]. The other concern about gut sampling is the appropriate site for biopsy. Although colonic biopsy shows positive results, a recent evaluation of the procedure has questioned its applicability in the current form[26]. Another recent study on colonic mucosal biopsy showed elevated levels of aggregated hyperphosphorylated α-synuclein in both PD and control subjects and suggested that the colonic deposition of α-synuclein cannot be a useful diagnostic test for PD[27]. One option may be to use vagally innervated segments of the GI tract for biopsy. Conversely, biopsy of submandibular salivary glands appears to be useful. These glands have high intensity of PD pathology, and their feasibility and applicability have been demonstrated[28,29]. Thus, further studies for evaluating the role of enteric α-synuclein as a biomarker for PD should be conducted, including search for optimal biopsy site as well as methods of tissue sampling/preparation and possible pathological α-synuclein targets.

CLINICAL MANIFESTATIONS OF GI DYSFUNCTION

Malnutrition

PD is associated with weight alteration, which maybe either loss or gain of weight. Unintended weight loss

Table 2 Sialorrhea

Mechanism	Treatment
Swallowing dysfunction Abnormal head posture Unintentional mouth opening due to hypomimia	Oral Glycopyrrolate Sublingual Ipratropium bromide spray Intra-oral Tropicamide films Behavioral modification Intra-salivary gland Botulinum neurotoxin injection Radiotherapy

is common[30] and correlates with worsened quality of life (QOL)[31]. Malnourishment in PD is linked to reduced food intake because of loss of appetite and GI dysfunction such as dysphagia, constipation, and early satiety[32]. It is associated with increased severity and duration of disease, psychiatric symptoms such as depression or anxiety, and fatigue[30,33,34]. The decreased body mass index during initial 6 mo of follow-up in PD was an indicator for future risk of dementia[35]. Increasing levodopa dosages were associated with the risk of malnutrition[36]. Micronutrient deficiencies, particularly vitamin D deficiency/insufficiency are common in PD[37] and these may be related to malnutrition, immobility, and sunlight deprivation. Patients with PD may have low bone mineral density and osteoporosis. Levodopa therapy causes vitamin B_{12} and folic acid deficiency with hyperhomocysteinemia and may contribute to osteoporosis[38]. Increasing evidence suggests that impaired insulin signaling and mitochondrial dysfunction lead to neurodegeneration, and these processes might also contribute to weight loss in PD.

Recent studies have shown that PD may be associated with weight gain[39,40]. Moreover, compulsive eating and weight gain have been related to dopamine agonist use[41]. Also deep brain stimulation (DBS) of subthalamic nucleus (STN) has been associated with post-operative weight gain[42].

Malnutrition in PD needs early intervention and patients should be advised regarding lifestyle changes, exercise, and dietary supplementation. Adverse effects of dopaminergic therapy must also be considered. Bisphosphonates, supplementation of vitamin D and calcium is useful in osteoporosis in PD[38].

Oral and dental disorders

Patients with PD have poor oral hygiene. They have fewer remaining teeth, more caries, gingival recession, and increased tooth mobility. The poor oral health may be because of lower frequencies of tooth brushing, motor impairment, apathy, depression, and cognitive impairment[43,44]. There are reports of PD being associated with bruxism, temporomandibular disorders, and subjective taste impairment. Burning mouth syndrome is more common in PD and this could be because of decreased dopamine levels and dopamine dysregulation[45]. A patient was found to develop burning mouth syndrome with carbidopa/levodopa, which improved when this was replaced with pramipexole[46].

Sialorrhea

Drooling is an important component of PD, which leads to worse QOL and significant social and emotional consequences[47,48]. Its frequency varies from 10% to 84% probably because of lack of standard definition and criteria for diagnosing drooling[49]. Drooling in PD has been linked to dysphagia with less efficient swallowing[50-52] rather than increased salivary production (Table 2). Studies have reported decrease in salivary production in PD[53]. Drooling was correlated with unintentional mouth opening because of hypomimia, abnormal head posture[52], and dysarthria[54]. Other features associated with drooling are longer disease duration[55], disease severity[56], dementia[57], hallucinations[47],orthostatic hypotension, and a history of using antidepressants[49].

Drooling increases the risk of silent aspiration and laryngeal penetration of saliva in patients with PD[58], therefore, this must be addressed in all affected patients. Its treatment consists of pharmacological and non-pharmacological measures. Glycopyrrolate is effective in reducing sialorrhea in patients with PD[59]. Studies have demonstrated benefit from anticholinergics used as topical preparations with less systemic adverse effects. These include sublingual ipratropium bromide spray[60] and intra-oral tropicamide films[61]. Another effective and safe option is the use of ultrasound-guided intra-salivary gland injection of botulinum neurotoxin (both botulinum toxin A and B)[62,63]. The non-pharmacological approaches include chewing gum and behavioral modification[49]. Radiotherapy is effective in the treatment of sialorrhea and it can be used in cases refractory to medical therapy[64,65].

Dysphagia

Dysphagia is an important component of PD, which adversely affects QOL[66]. As shown by a meta-analysis, patients are less likely to voluntarily complain about dysphagia, which revealed a pooled frequency estimate of 35% for subjective dysphagia and of 82% for objectively measured dysphagia[67]. Dysphagia in PD may be due to dysfunction of oral, pharyngeal, and esophageal phases of swallowing[68]. Several abnormalities have been described and oropharyngeal bradykinesia and incoordination plays an important role in PD[69]. However, contributors to pathophysiology of dysphagia are much widespread. Recent studies have shown the involvement of cortical areas in dysphagia[70,71]. The role of central cholinergic dysfunction in dysphagia has also been suggested[72]. Pathology has also been demonstrated in pharyngeal motor and sensory nerves[73,74]. Dysphagia has been

Table 3 Dysphagia

Evaluation	Treatment
Bedside screening	Compensatory maneuvers
Cough reflex testing	Rehabilitation maneuvers
Modified barium swallow studies	Expiratory muscle strength training
Videofluoroscopy	Video-assisted swallowing therapy
Manometry	Rotigotine transdermal patch
Fiberoptic endoscopic evaluation of swallowing	Percutaneous endoscopic gastrostomy placement

associated with male gender, older age, longer disease duration, dementia, depression, and severity of motor symptoms[75-77]. Although dysphagia is considered to arise in later parts of the disease, it is present in early stages of PD, particularly when a multimodal approach is used for its assessment[78,79]. This can be evaluated by bedside screening such as swallow trial, videofluoroscopy of swallowing act, fiberoptic endoscopic evaluation of swallowing, manometry, modified barium swallow studies, and cough reflex testing (Table 3)[80-83].

Besides causing difficulty in ingesting food and medicine, dysphagia in PD with prolonged swallowing time is associated with the risk of aspiration pneumonia[84,85]. Therefore, dysphagia needs to be diagnosed and treated early. Treatment options include compensatory maneuvers such as thickening liquids to nectar or honey consistency, chin-tuck maneuver, frequency/multiple swallowing technique, and rehabilitation maneuvers such as exercises of tongue strengthening and control along with vocal exercises[86]. Logopedic dysphagia treatment by an experienced speech therapist consists of oral motor exercises, airway-protecting maneuvers, and postural compensation[87]. Other options such as expiratory muscle strength training and video-assisted swallowing therapy may be effective[88]. Percutaneous endoscopic gastrostomy placement may be rarely needed in severe dysphagia[3]. Role of levodopa in improving dysphagia has been found conflicting[89,90]. A recent study showed that rotigotine transdermal patch improved swallowing in PD patients with dysphagia[91]. Effect of DBS on dysphagia in PD remains debatable[92]. However, unilateral STN-DBS appears to have adverse effect on the swallowing function in contrast to unilateral globus pallidus internus DBS[93].

Gastric dysfunction

Gastroparesis is quite common in PD, observed in about 70%-100% of subjects and may be present in both early and advanced stages of the disease[94-96]. The severity of motor impairment is correlated with gastroparesis in PD[97]. The symptoms of delayed gastric emptying include nausea, vomiting, early satiety, and postprandial fullness, and can lead to weight loss, malnutrition and dehydration. Delayed gastric emptying is defined as > 60% retention at 2 h postprandially and/or > 10% retention at 4 h, using 4-h imaging protocol after ingestion of a radioactive technetium Tc 99m-labeled solid food[98]. Alternatively, breath tests using nonradioactive ^{13}C-sodium octanoate bound into solid meal may be employed for evaluating gastric emptying[99]. Other methods used to assess gastric motility in PD are real time visualization by magnetic resonance imaging[100] and electrogastrography[101].

A major impact of gastroparesis on PD is the occurrence of response fluctuations, particularly delayed-on (delay in onset of "on-phase") to no-on (without "on-phase") with levodopa, and significant relationship were indicated between levodopa pharmacokinetics and gastric emptying[102,103]. In contrast, it has been suggested that levodopa itself can lead to the development of delayed gastric emptying[96]. Therefore, management of gastroparesis is essential. Other than dietary changes and exercise, one may use pharmacotherapy using domperidone. Although domperidone is useful in treating gastroparesis without interference with antiparkinsonism treatment[104], concerns have been raised about its arrhythmogenic potential with risk of long QT syndrome[105]. Recent studies have shown improvement of gastroparesis with Nizatidine[106], and the role of ghrelin agonist needs further evaluation[107]. Moreover, low levels of vitamin D has been suggested to contribute to gastric dysmotility in PD, but this finding needs further corroboration[108]. Benefits from botulinum neurotoxin injection in the pyloric sphincter[109] and STN-DBS[110] have been reported. In refractory cases, gastric electrical stimulation may be attempted (Table 4)[111].

To circumvent levodopa pharmacokinetic derangements associated with gastroparesis, several options have been studied. These include orally dissolving or soluble formulations[112,113]. Levodopa-carbidopa intestinal gel, subcutaneous apomorphine, and rotigotine patch are beneficial in gastroparesis as well as severe dysphagia[114,115]. STN-DBS is a useful surgical option[116].

H. pylori infection and small intestinal bacterial overgrowth

The other aspect of gastric involvement in motor fluctuations is the putative role of *H. pylori*. Investigations for *H. pylori* infection include serology, urea breath test, and stool antigen test[117]. There are mixed views on effect of *H. pylori* infection; however, recent studies show that *H. pylori* infection is associated with worse motor severity of PD[20]. Therefore, *H. pylori* eradication preferably using a combination regimen is indicated. Similarly, the role of SIBO has been evaluated. SIBO is diagnosed by culture of intestinal aspirates, or more practically, by hydrogen lactulose, and glucose breath tests[118]. Treatment for SIBO in PD is indicated as recent studies show improvement in motor fluctuations following eradication of SIBO[21].

Table 4 Gastroparesis

Evaluation	Treatment	Modifications of dopaminergic agents
Gastric emptying scintigraphy	Domperidone	Orally dissolving or soluble formulations
^{13}C-sodium octanoate breath test	Nizatidine	Levodopa-carbidopa intestinal gel
Electrogastrography	Ghrelin agonist	Rotigotine patch
	Botulinum neurotoxin injection into the pyloric sphincter	Subcutaneous Apomorphine
	STN DBS	
	Gastric electrical stimulation	

STN: Subthalamic nucleus; DBS: Deep brain stimulation.

Table 5 Constipation and defecatory dysfunction

Mechanism	Evaluation	Treatment
Slow transit constipation	Radiopaque marker study for colonic transit	High fiber diet, psyllium, proper fluid intake
	Wireless motility capsule	Adjustment of anticholinergics and dopaminergic agents
		Macrogol[1]
		Lubiprostone[2]
Dyssynergic defecation	Anorectal manometry	Biofeedback therapy
	Rectal balloon expulsion	Botulinum neurotoxin injection into the puborectalis
	Defecography	

[1]Macrogol-polyethylene glycol (an osmotic laxative); [2]Lubiprostone-chloride channel activator (increases fluid secretion in the intestine).

Constipation and defecatory dysfunction

Constipation is probably the commonest GI manifestation in PD and is present in more than 50% of the cases. It is approximately two to four times commoner in patients with PD than in controls[119]. Constipation and defecatory dysfunction is found in early stages of PD[120], and in fact, studies have shown that constipation can predate motor symptoms of PD by even 20 years[121]. Thus, constipation is one of the earliest manifestations of PD. Interestingly, studies have shown increased occurrence of future PD in persons with constipation, which may be in a dose-dependent manner[122,123].

One mechanism is prolonged colon transit time[124]. Another dysfunction is defecatory pelvic floor dyssynergia or functional pelvic outlet obstruction by paradoxical contraction of striated anal sphincter muscles during straining for defecation, which is considered dystonia in some studies[120,125]. Constipation is a known adverse effect of drugs used in PD, such as anticholinergics and dopaminergic agents; however, intrinsic disease pathophysiology may be responsible for it. The use of beta-blockers in PD is associated with lower risk of constipation, whereas dopaminergic treatments tend to increase it[126]. Conversely, levodopa improves paradoxical sphincter contraction and anorectal constipation in patients with PD[127] supporting the presence of more than one mechanism for constipation in PD[128]. Likewise, symptoms include infrequent bowel movements, unsuccessful attempts at defecation, and a sense of incomplete rectal emptying at defecation[129].

In general, evaluation of chronic constipation usually comprises clinical assessment by digital anorectal examination followed by relevant investigations (Table 5). Colonic transit is evaluated by radiopaque markers, scintigraphy, or wireless motility capsule, and defecatory disorder is assessed by anorectal manometry, rectal balloon expulsion, or defecography[130]. In patients with PD, mostly colon transit time and manometry are utilized. Additionally, electromyography of external anal sphincter has been used to demonstrate neurogenic changes[124]. The treatment starts with high fiber diet, proper fluid intake, psyllium, and physiotherapy. However, many patients require additional treatment. The effective options for slow transit constipation in PD are Macrogol and lubiprostone; Nizatidine was also effective (Table 5)[131-133]. Other drugs such as prucalopride needs to be considered in PD. Treatment for dyssynergic defecation include biofeedback therapy and levodopa or apomorphine injections[134,135]. Botulinum neurotoxin type A injection into puborectalis muscle under ultrasonographic guidance is useful for dyssynergic outlet-obstruction constipation[134,136].

Apart from constipation and defecatory dysfunction, existence of fecal incontinence in PD has been described and its frequency may be significant[119].

CONCLUSION

In PD, gut is affected early and extensively. It appears to participate in pathogenesis of the disease. Further studies are required to understand whether it indeed acts as an initiation point in PD pathology and if so, its mechanism of involvement including the role of gut microbiota. To establish the potential role of enteric α-synuclein as a biomarker of early PD, studies are needed with adequate reproducibility regarding optimal sampling site and technique and appropriate pathogenic targets. The GI manifestations in PD are distressing for patients with significant morbidity and complications. Therefore, these should be identified promptly and treated. This requires the clinician to pay due attention to these symptoms during the evaluation of PD patient. The management of these conditions may be tricky as it includes not only symptomatic treatment but also optimization of anti-Parkinsonian drugs, particularly anticholinergics and dopaminergic agents. Studies on novel therapeutic agents and non-pharmacotherapeutic interventions would be helpful. Moreover, newer dopaminergic drug delivery systems should be studied to circumvent dysfunctional gut.

The role of DBS in these conditions needs further evaluation.

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