Movement Disorders
CLINICAL PRACTICE
REVIEW

Movement Disorders and the Gut: A Review

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Abstract: There is a close link between multiple movement disorders and gastrointestinal dysfunction. Gastrointestinal symptoms may precede the development of the neurologic syndrome or may arise following the neurologic presentation. This review will provide an overview of gastrointestinal accompaniments to several well-known as well as lesser known movement disorders. It will also highlight several disorders which may not be considered primary movement disorders but have an overlapping presentation of both gastrointestinal and movement abnormalities.

Movement disorders often manifest in conjunction with systemic symptoms, including those affecting the gastrointestinal (GI) tract. A bidirectional link between the development of certain movement disorders and their GI accompaniments has also been proposed, due to the intimate relationship between the enteric nervous system (ENS) and central nervous system (CNS). GI dysfunction may arise as a prodromal feature of certain diseases or may occur years after the onset of the movement disorder. This review will focus on primary movement disorders that have accompanying GI signs or symptoms. The clinical features of these GI symptoms will be highlighted and a full description of treatments is not within the scope of this review. Several disorders that have closely overlapping presentations of both movement and GI abnormalities will also be discussed. Methods are outlined in supplementary material Appendix S1.

Primary Movement Disorders with Associated GI Symptoms

Parkinsonism

Parkinson's Disease

There has long been a recognition of an intimate link between the CNS and the gut and this relationship is exemplified by the evolving understanding of Parkinson's disease (PD). The GI tract has not only been implicated in the pathogenesis of PD but also is the site of myriad non-motor symptoms of the disease.

Pathogenesis. PD is characterized by the deposition of misfolded alpha-synuclein protein in formations called Lewy bodies. Lewy body pathology in the CNS, particularly within the substantia nigra, leads to the well-recognized motor features of PD. In 1984, the same pathology was identified in the ENS[1] with later studies demonstrating that the highest rates of alpha-synuclein deposition occur within the submandibular glands and distal esophagus, with lower rates in the colon and rectum.[2]

Pathologic alpha-synuclein has been identified within the GI tract of individuals with prodromal PD up to 20 years prior to diagnosis.[3] Cell-to-cell transmission of alpha-synuclein has been linked with development of PD motor features in nontransgenic mice.[4] This lends support to the proposal that alpha-synuclein pathology may spread up the vagus nerve to the dorsal motor nucleus of the vagus nerve in the CNS via a prion-like mechanism with misfolded alpha-synuclein protein causing neighboring protein to similarly misfold. Prior epidemiological studies have demonstrated a lower risk of developing PD following complete truncal vagotomy (performed for treatment of gastric ulcers) whereas superselective vagotomy (in which only nerves supplying the fundus and body of the stomach are resected, with sparing of vagal innervation to the liver, pancreas, and small intestine) did not have the same protective effect.[5]

Beach and colleagues have challenged this "body-first" theory by demonstrating that alpha-synuclein is not found in the stomach or vagus nerve without also being found in the brain. Autopsy samples from 111 normal elderly subjects, 53 individuals with PD, and 33 with incidental Lewy body disease (ILBD) were stained for alpha-synuclein. Vagus nerve alpha-synuclein was present in 46% and 89% of subjects with ILBD and PD respectively, but was absent in all normal subjects. Similarly, alpha-

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synuclein was found in stomach samples of 17% of subjects with ILBD and 81% of those with PD, but none of those from normal subjects.[6]

Although the specific trigger for the cascade of pathologic changes occurring in sporadic PD has not been established, significant attention has been drawn to the gut microbiome as a possible contributing factor. Dysbiosis describes the disproportionate representation of particular strains of bacteria within the gut. A 2015 study demonstrated that patients with PD were more likely to have significantly decreased levels of *Prevotella* compared with control subjects.[7] *Prevotella* is involved in mucin synthesis and therefore decreased levels of this bacterial subtype may increase intestinal wall permeability. This allows for translocation of bacteria and bacterial secretory products, including endotoxins, thereby increasing local inflammation in the ENS. Although this finding is not specific to patients with PD, it may help to support the theory that alpha-synuclein deposition occurs as a result of an inflammatory environment, whether by bacterial colonization or sterile inflammation. Increased intestinal permeability has previously been demonstrated in individuals with PD with higher rates of alpha-synuclein deposition in the intestinal wall.[8] Alpha-synuclein deposition also occurs in the appendix of healthy individuals and those with PD. The appendix helps to regulate gut immunity and bacterial composition, thus raising the question of whether the appendix is involved in the pathogenesis of PD; however, studies exploring the risk of developing PD after appendectomy have had conflicting results.[9]

Another study demonstrated that the composition of a person's microbiome correlated with motor phenotype, with those having a higher representation of Enterobacteriaceae more likely to fall within the postural instability and gait disorder (PIGD) subtype.[7] Further research will be required to determine whether the microbiome may serve as a biomarker of disease.

Dysfunction. GI dysfunction in PD manifests as myriad non-motor symptoms, with every segment of the GI tract affected.

Drooling

- Drooling describes excessive accumulation or overflow of saliva and occurs in 10–81% of patients with PD.[10] Male sex and more advanced disease are associated with higher frequency of drooling[11] and this non-motor symptom is often more pronounced when a person is in the OFF state. The frequent occurrence of drooling in PD likely is multifactorial, related to a combination of altered salivary secretion, difficulty containing saliva in the oral cavity, and impaired clearance of saliva.[12] Although studies have demonstrated that persons with PD have overall decreased salivary production compared with controls, they do have increased speed of salivary excretion.[13] More severe hypomimia, which manifests with mouth opening, in addition to forward flexed posture, lead to salivary overflow while tongue akinesia, oropharyngeal dysphagia and upper esophageal dysmotility contribute to poor clearance. Patients with PD and drooling have a greater frequency of swallowing,[11] but when cognitive tasks are imposed, swallowing frequency decreases and drooling worsens.[14]

Dysphagia

- Dysphagia, or impaired swallowing, may arise at any time throughout the course of PD, and may be evident at the time of diagnosis.[15] A meta-analysis exploring the prevalence of dysphagia in PD demonstrated that objective evidence of dysphagia may occur in up to 82% of patients, although the symptom is significantly under-reported.[16] Both oropharyngeal and esophageal phases of swallowing are impaired in PD. Triggering of the swallowing reflex is delayed and bradykinesia/akinesia of the oropharyngeal muscles leads to incoordination and slowing of this motor task.[17,18] Manometry studies have demonstrated impaired esophageal motility manifesting as slowed or absent peristalsis, esophageal spasm, or delayed transit from the esophagus to the stomach due to impaired sphincter relaxation.[19] Dysphagia is an important symptom to identify, as it may have serious consequences including aspiration, malnutrition and weight loss.

Gastroparesis

- Gastroparesis, or delayed gastric emptying, occurs in 70–100% of patients with PD,[19] with greater impairment in emptying of solid food. This manifests as early satiety, post-prandial abdominal fullness or pain, bloating, belching, or nausea/vomiting. Other individuals with gastroparesis may be asymptomatic, with diagnosis documented only via formal testing.[20] Because the proximal small intestine is the primary site for levodopa absorption, delayed transit of the medication from the stomach may lead to delayed onset of action or dose failure[21]; gastroparesis, therefore, may contribute to motor fluctuations in the more advanced stages of PD. Over the long term, individuals with gastroparesis may develop food aversion and weight loss may arise. The underlying cause of gastroparesis in PD is not well understood. The interstitial cells of Cajal, the pacemaker cells of the stomach, are preserved in PD, which suggests that pathology may arise via abnormal vagal nerve signaling to the myenteric plexus within the stomach.[22] In keeping with this, vagotomy in mouse models of PD prevents development of gastroparesis.[23] There also is evidence to suggest that individuals with PD have decreased postprandial release of ghrelin, a neuropeptide that acts peripherally to promote gastric motility but also increases dopamine release in the striatum of mouse models of PD.[24] This has fueled research into whether ghrelin may serve as a potential biomarker of disease or as a therapeutic target for neuroprotection.

Helicobacter Pylori

- *Helicobacter pylori* (*H. pylori*) is a gram-negative bacterium that has long been associated with increased risk of gastric ulcer formation and gastric cancer. Though the prevalence of *H. pylori* is equivalent in the general population and the PD population,[25] there are studies suggesting that gastritis from *H. pylori* increases the risk of developing PD.[26] There is insufficient evidence at this time to implicate *H. pylori* infection in the pathophysiology of PD, although the presence of *H. pylori* may play a role in malabsorption and response to medication.[10] *H. pylori* exerts negative effects on ghrelin expression,

leading to gastric hypomotility and delayed transit of levodopa to the small intestine.[27] In addition, direct binding of levodopa by bacterial surface adhesin molecules, production of reactive oxygen species, decreased stomach acidity, and disruption of the GI mucosa in the presence of *H. pylori* all may contribute to impaired absorption of levodopa.[28] Although the pharmacokinetics of levodopa in patients with motor fluctuations are unchanged in the presence or absence of *H. pylori*,[29] several groups have shown that eradication of *H. pylori* decreases motor fluctuations in PD.[30] More recent data from a placebo-controlled trial challenge these prior results and suggest that routine screening for and treatment of *H. pylori* do not lead to improved motor or non-motor function.[31]

Small Intestinal Bacterial Overgrowth

- Small intestinal bacterial overgrowth (SIBO) describes an abnormal accumulation of bacteria within the small intestine, particularly those bacteria typically isolated to the colon. Decreased acidity in the stomach, slowed intestinal motility, and disruption of the protective intestinal mucosal layer may contribute to development of SIBO.[32] SIBO is often intimately tied to the presence or treatment of *H. pylori*, with acid blocking medications (particularly proton pump inhibitors) decreasing the clearance of bacteria in the stomach and small intestine.[10] Clinically, persons with SIBO may develop diarrhea, abdominal pain, or bloating.[32] Patients with PD have a significantly higher rate of SIBO compared with healthy controls and, in addition to the typical clinical symptoms of SIBO, the presence of SIBO also contributes to motor fluctuations.[25] Eradication of SIBO in turn improves motor fluctuations, although the recurrence rate is high.[25]

Constipation

- Constipation is now considered a prodromal feature of PD due to evidence that it may arise up to 20 years prior to the appearance of motor symptoms.[33] There also is evidence to suggest that the degree of prodromal constipation is correlated with the risk of developing PD.[34] Constipation is the most frequently reported GI symptom and colonic transit time is objectively delayed in up to 80% of individuals with PD.[35] In addition to decreased frequency of bowel movements, individuals with PD also may experience functional impairment of defecation due to abnormal coordination of the anorectal musculature. Impaired relaxation or paradoxical contraction of the anal sphincter muscles may be a dystonic phenomenon, particularly as these symptoms may be amplified during the OFF period.[36] Although literature specifically exploring the effect of constipation on motor fluctuations in PD is lacking, impaired colonic motility may increase the risk of SIBO, which has been linked to impaired absorption of levodopa.

Weight Loss

- Greater than half of patients with PD experience weight loss and studies have demonstrated a greater degree of weight loss in patients with PD compared with age-matched controls.[37,38] Weight loss contributes to reduced overall quality of life for affected individuals. Some studies suggest that women with PD tend to lose more weight than men[39] while other studies have challenged this notion.[38] Greater motor impairment, presence of visual hallucinations, dementia, and advanced age also correlate with greater degree of weight loss.[38] The cause of weight loss in PD is not well understood, although the combination of decreased energy intake and excess energy expenditure may play a role. Multiple factors may contribute to decreased caloric intake. Impaired olfaction is a well-established prodromal feature of PD and leads to impaired taste with consequent decreased motivation to eat. The presence of mood disturbances such as depression or apathy can have the same effect. Symptoms related to gastroparesis or medication-induced nausea may lead to food aversion, while other individuals may avoid eating in order to increase ON time. Patients may be functionally limited by dysphagia. Malnutrition may develop in up to 24% of individuals with PD,[40] perhaps due to the aforementioned factors or malabsorption. Both SIBO and the presence of *H. pylori* may impact absorption of nutrients.[10] Dyskinesia contributes to increased energy expenditure and possibly to weight loss, although some studies have challenged this by concluding that weight gain following deep brain stimulation surgery does not correlate with the degree of dyskinesia suppression.[41]

Atypical Parkinsonism

Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is characterized by the onset of cognitive impairment prior to or concurrent with the onset of motor parkinsonism and often is accompanied by visual hallucinations and episodic alteration in awareness. DLB shares many pathologic and clinical features with PD dementia (PDD) and some suggest that these entities exist on a spectrum.[42] The distribution of Lewy bodies in the CNS is more prominent in the cortex and limbic system of patients with DLB; the co-occurrence of Alzheimer's pathology also is more prominent in DLB compared with PDD.[42] Autonomic symptoms in DLB, including constipation, may help to differentiate DLB from Alzheimer's disease clinically and these autonomic symptoms are associated with increased risk of mortality.[43]

Similar to pathologic studies in PD, peripheral deposition of alpha-synuclein has also been demonstrated in DLB with Lewy pathology observed in the stomach, small intestine, and colon.[44] The GI symptoms described in PD presumably occur for similar reasons in DLB, although less attention has been given to the latter.

In a combined group of patients with DLB or PDD, nearly all patients who subjectively reported dysphagia were found to have objective dysfunction on videofluoroscopic swallowing examination, with the pharyngeal phase of swallowing most affected.[45]

Multiple System Atrophy

Multiple system atrophy (MSA) is characterized either by a progressive cerebellar or parkinsonian syndrome in combination with early and severe autonomic dysfunction. On a pathologic level, alpha-synuclein is deposited in the cytoplasm of

oligodendrocytes rather than in neurons. Though less frequently observed in MSA as compared to PD, alpha-synuclein deposition also may be found in peripheral tissue samples, including the colon, in this patient population.[46] Several studies have shown that patients with MSA have bacterial dysbiosis, although the significance of this is unclear.[47] The GI symptoms that arise in MSA mirror those seen in PD. Dysphagia arises earlier in patients with MSA as compared to those with PD, with one study demonstrating the need for diet modification an average of 6 years after symptom onset and the need for tube feeding 7 years after symptom onset.[48] Additional upper GI tract dysfunction is elucidated by studies showing that esophageal peristalsis and distal esophageal contraction are decreased in patients with MSA.[49] The degree of delayed gastric emptying is comparable between populations of patients with MSA and PD.[50] Within the lower GI tract, both constipation and fecal incontinence may arise. Colonic transit time is prolonged in patients with MSA, particularly in the rectosigmoid segment of the colon.[51] Patients with MSA have lower anal squeeze pressure and denervation changes in the external sphincter, both of which likely contribute to fecal incontinence.[51]

Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome manifesting in its classic form with parkinsonism combined with severe postural instability and impaired extraocular movements. PSP is differentiated from the aforementioned synucleinopathies by the pathologic finding of tau inclusions in astrocytes, oligodendrocytes and neurons.[52] Literature outlining GI symptoms in PSP is somewhat limited despite a survey-based study suggesting a high rate of GI dysfunction in this population.[53] Furthermore, studies suggest that early autonomic dysfunction, including constipation, is associated with a faster rate of disease progression.[54] Existing literature does highlight swallowing dysfunction as a common occurrence in PSP with earlier onset in the disease course as compared to PD.[55] More severe impairments in the oral phase of swallowing do distinguish patients with PSP from those with PD, perhaps due to neck hyperextension and a greater degree of cognitive impairment in PSP.[56,57] Interestingly, when compared to patients with PD or MSA, patients with PSP were more akin to healthy controls in measures of esophageal motility.[49]

Chorea

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disorder characterized by progressive impairment in motor, cognitive and psychiatric domains. Although chorea is the most widely recognized movement disorder associated with HD and helps to define the clinical onset of disease, individuals with HD also experience parkinsonism, dystonia, postural instability, and impaired voluntary motor control. HD is an autosomal dominant trinucleotide repeat disorder caused by expansion of the CAG repeat portion in the huntingtin (htt) gene and downstream formation of mutant huntingtin protein. Normal huntingtin is expressed ubiquitously throughout the body. Although the deposition of mutant huntingtin protein is selectively toxic to CNS neurons, particularly in the striatum and cortex, abnormal huntingtin deposition has also been noted in peripheral tissues of HD mouse models and human subjects.[58] This may help to explain the under-recognized systemic symptoms that can accompany the neurologic manifestations of HD. Survey-based studies suggest a high rate of subjective GI dysfunction in individuals with HD; symptoms include swallowing dysfunction, sialorrhea, straining, early abdominal fullness, and fecal incontinence.[59]

Upper GI Tract. Dysphagia is common in HD and pneumonia, likely in part due to aspiration, is one of the leading causes of death in this patient population.[60] Dysphagia and silent aspiration may arise even in the early stages of the disease.[61] Multiple disease characteristics may contribute to the development of swallowing dysfunction. Although advancing motor dysfunction correlates with worsened dysphagia in some studies, others suggest that impaired swallowing may be primarily related to impaired sensory/sensorimotor processing and cognitive dysfunction. This conclusion is extracted from voxel-based imaging in patients with impaired swallowing showing atrophy in parietothalamocerebellar networks with sparing of the striatum.[62] Individuals with HD also have a higher rate of gastritis or esophagitis compared with control populations, although they may be less likely to express subjective symptoms.[63]

Lower GI Tract. Studies in mouse models and in patients with HD have revealed alterations in the gut microbiome, although the implications of this are not well understood.[64,65]

Anorectal dysfunction, manifesting as incontinence or constipation, is significantly more prevalent in individuals with HD compared with healthy controls and may even arise in the premanifest stage.[66] Several studies have shown no evidence of degeneration in Onuf's nucleus, although anal sphincter EMG studies do demonstrate decreased tonic sphincter activity and impaired voluntary activation.[67]

Liver Dysfunction. Using the ^{13}C-methionine breath test as a surrogate for liver mitochondrial function, researchers have demonstrated subclinical liver dysfunction in both manifest and premanifest populations of HD.[68] Furthermore, the decline in mitochondrial function correlated with disease severity in participants with manifest HD.

Pancreatic Dysfunction. Studies have demonstrated a higher prevalence of diabetes mellitus in individuals with HD and impaired glucose tolerance has been noted in both HD mouse models and patients with HD.[58] Although islet cell volume is reduced in mouse models,[69] there is no evidence of this in human subjects.[70] CAG repeat length plays a role in the degree of insulin release, with more highly expanded repeat lengths leading to a reduction of insulin release.[71]

Weight Loss. Weight loss is a common phenomenon in HD, starting in the premanifest stage and increasing throughout the disease course, with advanced HD often associated with cachexia. Studies have demonstrated that the degree of weight loss may correlate with an individual's CAG repeat length, with longer expansions associated with more profound weight loss.[72] Although a person's BMI does not appear to predict age of onset of manifest HD,[73] it may dictate the speed of progression, with lower BMI at disease onset portending more rapid decline in function.[74]

The actual cause for weight loss in HD is not entirely understood. A hypermetabolic state related to hyperkinetic movements and increased energy expenditure could be surmised, but often the greatest degree of weight loss occurs in advanced stages, when individuals no longer experience chorea and are more often severely bradykinetic and bed-bound. One study did demonstrate that increased CAG length is associated with increased production of leptin, a hormone involved in decreased appetite and increased metabolism.[75]

Studies in HD mouse models demonstrate structural changes throughout the GI tract including decreased mucosal thickness in the stomach and large intestine, decreased villus length in the duodenum, and decreased total length of the large intestine; these animals have impaired absorption of nutrients and water. Although malabsorption is present even prior to onset of weight loss in animal models and therefore is not thought to be the initial trigger, the degree of malabsorption does correlate with the rate of weight loss.[76] Similar studies in humans are lacking.

Chorea-Acanthocytosis

Chorea-acanthocytosis (ChAc) is one of a number of neuroacanthocytosis syndromes, caused by autosomal recessive inheritance of mutated VPS13A gene, which encodes the protein chorein. Several motor features of the disease help to formulate a clinical diagnosis, which may be supported by the presence of acanthocytes on blood smear, reduced level of chorein on Western blot, or genetic testing. ChAc manifests with a variety of abnormal movements including chorea, parkinsonism, and dystonia but is most well-recognized for its orofaciolingual features. Individuals with ChAc have a high rate of dysphagia, oral dyskinesias, and oral ulceration as a result of involuntary tongue and cheek biting. Feeding dystonia, a characteristic feature of the disease, occurs in roughly 13% and leads to tongue protrusion when food enters the mouth.[77] Due to difficulty maintaining oral intake, weight loss is common and patients may require gastrostomy tube placement.

Ataxia

Cerebrotendinous Xanthomatosis

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder caused by deficiency in the enzyme sterol 27-hydroxylase leading to abnormal chenodeoxycholic acid synthesis. There is subsequent excess production of cholestanol and cholesterol with deposition of these sterols in the CNS and in peripheral tissues. CNS manifestations of CTX are progressive and include cerebellar ataxia, pyramidal tract signs, polyneuropathy, dystonia, parkinsonism, cognitive impairment and seizures. Peripheral manifestations of CTX include premature cataract formation, tendon xanthomas, and chronic diarrhea. Although the neurologic symptoms typically trigger consideration of CTX, intractable diarrhea may be the earliest feature of the disease, often presenting in early childhood.[78] The cause of intractable diarrhea in CTX is not well understood and patients often undergo extensive GI evaluation prior to formal diagnosis. Despite impaired bile acid synthesis, there is no evidence that fat absorption is impaired in CTX[79] and therefore some have suggested that bile alcohols present in the gut lumen may interfere with gut motility or lead to electrolyte/ fluid disequilibrium or bacterial dysbiosis. Early recognition of CTX as a syndrome is important because supplementation with chenodeoxycholic acid may alleviate, and in some cases resolve GI symptoms and stabilize neurologic symptoms.[79,80,81]

Ataxia Telangiectasia

Ataxia telangiectasia (A-T) is an autosomal recessive disorder caused by mutations in the ATM gene. A-T is characterized by a constellation of neurologic and non-neurologic symptoms. The phenotypic presentation varies widely between individuals, although the classic form presents in early childhood. A-T presents as a progressive ataxic syndrome; however, other hyperkinetic or hypokinetic movement abnormalities also may arise.[82,83] Systemically, A-T is associated with cutaneous and ocular telangiectasias, sensitivity to radiation, immunoglobin deficiency with increased susceptibility to sinopulmonary infections, and endocrine abnormalities such as insulin-resistant diabetes.[84] Due to the involvement of the ATM gene in DNA repair, individuals with A-T also have higher rate of malignancy. GI complications of A-T include dysphagia and difficulty gaining weight, which may lead to failure to thrive. It is not uncommon for individuals with A-T to require insertion of a gastrostomy tube. A-T associated liver pathology also has been described.[85]

Fragile X-Associated Tremor/Ataxia Syndrome

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a degenerative disorder caused by inheritance of an expanded CGG repeat in the FMR1 gene. Whereas individuals with Fragile X syndrome (described later) inherit a repeat length of >200, those with FXTAS inherit a repeat length in the premutation range of 50–200. FXTAS presents clinically with progressive cerebellar ataxia, intention tremor, and/or parkinsonism, typically in the 7th decade of life, with men disproportionately affected.[86] Individuals may experience cognitive and behavioral changes as

the disease progresses. Data on GI manifestations of FXTAS are sparse, though survey-based studies do suggest that individuals report irritable bowel symptoms, constipation, and reflux.[87] With disease progression, individuals may experience dysphagia along with bowel and bladder incontinence.[86] Intranuclear inclusions have been noted in several systemic tissues including, but not limited to, the myenteric plexus of the esophagus and colon.[88]

Myoclonus

Anti-DPPX Encephalitis

Antibodies targeting the dipeptidyl peptidase-like protein 6 (DPPX) are implicated in a relatively recently described autoimmune encephalitis. DPPX is a subunit of the voltage-gated A-type Kv4.2 potassium channel, which is distributed throughout the CNS. The spectrum of clinical disease is variable with the largest review of cases suggesting that encephalopathy and CNS hyperexcitability (defined as myoclonus, hyperekplexia, tremor, or seizures) are common features and occur in 92% and 77% of individuals respectively. A smaller subset of patients developed a syndrome which shares features with PERM (progressive encephalomyelitis, rigidity, and myoclonus).[89] In a small study of 20 seropositive patients, autonomic dysfunction was common with various features of GI dysmotility (diarrhea, gastroparesis, constipation) occurring in nearly half of individuals, often with prodromal weight loss.[90] Studies suggest that DPPX antibodies may elicit hyperexcitability in enteric neurons themselves, which may in part explain the prodromal diarrhea experienced by some individuals.[91]

Triple A Syndrome

Triple A syndrome, also known as Allgrove syndrome (AS), is an inherited disorder that is so named due to its triad of associated symptoms: adrenal insufficiency, achalasia, and alacrima (decreased or absent tear production). Progressive neurologic and autonomic dysfunction may arise; histopathologic studies have revealed reduction in the cardia myenteric ganglia of patients with AS. A 2004 case report describes a patient with prominent myoclonus and a constellation of GI symptoms including esophageal dyskinesia, abdominal pain with diarrhea and recurrent gallstones.[92]

Stereotypy

While it is not within the scope of this paper to address the GI manifestations of autism spectrum disorder as a whole, several neurodevelopmental disorders associated with abnormal movements are important to highlight.

Rett Syndrome

Rett syndrome (RS), predominantly seen in girls, is caused by mutations in the MECP2 gene on the X chromosome and characterized by developmental regression after 6–18 months. Hand stereotypies are the hallmark of this disorder, but numerous other abnormal movements have been described including dystonia, tremor, myoclonus, chorea, ataxia, and rigidity.[93] The GI accompaniments to RS are varied. In a large survey-based study, parents of patients with RS reported that feeding problems and GI symptoms are common, occurring in 81% and 92% of patients with RS respectively. Poorly coordinated chewing and swallowing contributed to prolonged feeding time in 62% and up to 80% of individuals with RS displayed constipation.[94] Biliary tract disease is much less common, occurring in roughly 4% of individuals with RS.[95]

Fragile X Syndrome

Fragile X syndrome (FXS) is a trinucleotide repeat disorder caused by expansion of CGG repeats in the FMR1 gene. It is the most common genetic cause of intellectual disability and is associated with stereotyped hand flapping and motor tics. Data on GI symptoms in FXS are sparse, with diarrhea and reflux estimated to occur in roughly 11% of individuals; connective tissue abnormalities and hypotonia are thought to play a role in the development of reflux in individuals with FXS.[96]

Angelman Syndrome

Angelman syndrome (AS) is a genetically heterogeneous disorder with the most common subtype caused by deletion of the portion of maternal chromosome 15 containing the UBE3A gene.[97] Individuals with AS have a characteristic happy demeanor and experience seizures, intellectual disability, expressive language impairment, and movement abnormalities, including ataxic gait, tremulousness, hand-flapping, and impaired coordination of mouth movements.[98] Difficulty with sucking or swallowing contributes to poor feeding in roughly half of infants with AS. A large retrospective chart review demonstrated that 87% of the individuals with AS experienced GI symptoms with constipation and gastroesophageal reflux reported most frequently.[97]

Other

Anti-IgLON5 Disease

Anti-IgLON5 disease is a more recently recognized autoimmune disorder with heterogeneous manifestations, although most often characterized by significant disturbances in sleep and movement. The associated abnormal movements are varied, but impairments in gait and balance are most frequent, with other individuals displaying chorea, dystonia, or other hyperkinetic movements. The described sleep disturbances include obstructive sleep apnea, stridor, and parasomnias in both REM and non-REM sleep.[99] Data from a small group of patients demonstrated that nearly half experienced autonomic dysfunction, with impairments in urinary function most frequent, followed by impairment in GI motility (constipation or diarrhea) and thermoregulation.[100] Larger studies will be needed to reproduce this data.

Restless Legs Syndrome

Restless legs syndrome (RLS), a sleep-related movement disorder, is characterized by an irresistible urge to move the legs in response to an often poorly described discomfort. Although the pathophysiology of RLS is not definitively known, abnormalities in iron homeostasis, dopamine regulation, and sensorimotor processing have been implicated, with peripheral neuropathy also thought to contribute.[101] Surveys of individuals with RLS suggest that there is a high rate of autonomic dysfunction compared with controls, affecting multiple domains.[102,103] In one study, GI symptoms including dysphagia, drooling, constipation, abdominal fullness, straining for defecation, or fecal incontinence occurred in up to 86% of individuals with RLS not on treatment.[104] There is growing data to support a link between RLS and irritable bowel syndrome (IBS) with one small study showing a 28% prevalence of IBS in the RLS cohort, compared with 4% in controls.[101] A higher rate of SIBO also was noted in the RLS group. The role of intestinal inflammation in the pathophysiology of RLS requires further study.

Disorders with GI/Movement Overlap

The entities discussed above are all disorders that, for the most part, are considered to be neurological disorders in origin, with GI aspects that are secondary. However, there are other disorders that do not fit so neatly into that category, yet afflicted individuals are likely to display both GI and movement disorder symptoms during the course of their illness. Several such disorders will be briefly addressed here, although a more complete description is beyond the scope of this review.

Wilson's Disease

Wilson's disease (WD) is an autosomal recessive disorder that is the result of mutation within the ATP7B gene on chromosome 13. Over 700 mutations, most often missense, have been identified and most affected individuals are compound heterozygotes. Because defective function of ATP7B protein results in impaired biliary excretion of copper, individuals with WD experience gradual accumulation of copper, initially within the liver, but eventually also in other tissues, including the brain. WD can present clinically in several guises: hepatic dysfunction, neurologic dysfunction, psychiatric dysfunction, and still other manifestations. Neurological dysfunction classically includes tremor that may be resting, postural, or action/intention in character. Parkinsonism, dystonia, chorea, and myoclonus also may occur. A more detailed description of the hepatic, neurologic, and other manifestations of WD can be found in other reviews.[105,106]

Separate from hepatic dysfunction, a number of other aspects of GI dysfunction have been described in the setting of WD. In one small study, abnormalities on the Videofluoroscopic Swallow Study were evident in 42.9% of the 21 WD patients studied.[107] Both oral and pharyngeal dysfunction were documented, but esophageal body dysfunction was the most frequent abnormality. Another study investigating gastric abnormalities utilizing gastroscopy documented gastropathy in 65.2% of the 115 patients studied.[108] Gastric or duodenal ulcers were present in 9.6% of patients and esophageal varices were noted in 29.6%. Patients being treated with zinc sulfate had a higher risk for developing gastric injury. Gut microbial dysbiosis also has been reported in WD.[109] The significance of this finding will require further study.

Whipple's Disease

Whipple's disease (WhD) is a rare multisystem disorder caused by infection with the gram-positive bacterium, *Tropheryma whipplei*. It affects males more than females and the average age of onset of symptoms is around age 55. Because of its protean symptomatology, WhD can be devilishly difficult to diagnose. A prodromal stage, often involving joint pain, typically is followed by the development of the classic GI features of WhD, which include diarrhea, abdominal pain, and progressive weight loss.[110] Mesenteric panniculitis, consisting of an inflammatory reaction involving the adipose tissue of the mesentery and characterized by abdominal pain, bloating, constipation, nausea, and vomiting also has been described in WhD.[111] Neurologic involvement in WhD typically is a later development, although it may be the initial feature in approximately 5% of individuals.[112] Neuropsychiatric symptoms eventually become evident in many WhD patients and may be cognitive, psychiatric, or behavioral in nature. Various neurologic features, including cerebellar ataxia and disordered sleep, may appear in WhD but the classic feature of CNS involvement is abnormal movement labeled oculomasticatory myorhythmia, which is considered by some to be pathognomonic of the disorder. Oculomasticatory myorhythmia consists of pendular convergence nystagmus with concurrent slow, rhythmic, synchronous contractions of the masticatory muscles, invariably accompanied by a supranuclear gaze paresis.[112] Prompt diagnosis is important because prolonged antibiotic therapy can produce sustained clinical remission in over 90% of patients. Unfortunately, diagnosis often is delayed for years because of the protean nature of the symptoms and the rarity of the disease itself.

Celiac Disease

The nomenclature and classification of what are now termed gluten-related disorders has become more complicated and detailed in recent years.[112] This brief description will be limited to the autoimmune gluten-related disorders, of which celiac disease (CD) is the prototype. CD is characterized by the presence of gliadin-related IgA antibodies along with the development of small intestinal mucosal injury with villous atrophy, crypt hyperplasia, and increased presence of epithelial lymphocytes. The mucosal damage leads to the appearance of the classic GI symptoms of CD, such as diarrhea, malabsorption, gassy distension, and weight loss. Extraintestinal manifestations of CD also occur, including neurologic features that may become evident in 6–39% of individuals with CD and involve both the central and the peripheral nervous

systems.[113] Among the CNS-related neurologic features, a variety of movement disorder manifestations have been described, including chorea, paroxysmal nonkinesigenic dystonia, and restless legs syndrome. The controversial entity, gluten ataxia, also falls under the umbrella of gluten-related disorders, but further elaboration is beyond the scope of this review.[114] The mainstay of treatment of CD is a gluten-free diet.

Abetalipoproteinemia

Abetalipoproteinemia (ABL) is a rare autosomal recessive disorder caused by a mutation in the microsomal triglyceride transfer protein (MTTP) gene.[115] The consequent deficiency of MTTP results in low levels of total cholesterol, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL). Apolipoprotein B, triglycerides, and chylomicrons are virtually absent and affected individuals are unable to absorb dietary fat and the fat-soluble vitamins E, A, D, and K.[113,115] GI dysfunction, including steatorrhea, diarrhea, vomiting, and failure to thrive typically develops during infancy. Neurological symptoms, such as ataxia, peripheral neuropathy, and myopathy, often do not appear until the teenage years or beyond and are largely attributable to the impaired absorption and resulting deficiency of vitamin E. Movement disorder features in the form of resting and postural tremor also have been described in ABL. High dose oral vitamin E supplementation, along with supplementation of vitamins A, D, and K, and oral essential fatty acids, with restriction of dietary fat intake, are lifelong management strategies.[115]

Conclusion

It is uncommon for movement disorders to occur in isolation. Often, underlying systemic symptoms go hand-in-hand with neurologic disturbances. This is highlighted by the numerous movement disorders with associated GI dysfunction. An interactive relationship between the gut and the brain has been proposed for several of these disorders. Further studies exploring this relationship may lead to discovery of biomarkers to track disease. In addition, recognition and management of these GI symptoms are important, since effective treatment often greatly contributes to the overall quality of life of affected individuals.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique;

LST: 1A, 1B, 1C, 3A, 3B
RFP: 1A, 1B, 1C, 3A, 3B.

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References

1. Qualman SJ, Haupt HM, Yang P, Hamilton SR. Esophageal Lewy bodies associated with ganglion cell loss in achalasia. Similarity to Parkinson's disease. *Gastroenterology* 1984;87(4):848–856. PMID: 6088351.
2. Beach TG, Adler CH, Sue LI, et al. Arizona Parkinson's disease consortium. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. *Acta Neuropathol* 2010; 119(6):689–702. https://doi.org/10.1007/s00401-010-0664-3 Epub 2010 Mar 21. PMID: 20306269; PMCID: PMC2866090.
3. Stokholm MG, Danielsen EH, Hamilton-Dutoit SJ, Borghammer P. Pathological α-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients. *Ann Neurol* 2016;79(6):940–949. https://doi.org/10.1002/ana.24648 Epub 2016 Apr 9. PMID: 27015771.
4. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VMY. Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science* 2012;338(6109):949–953. https://doi.org/10.1126/science.1227157 PMID: 23161999; PMCID: PMC3552321.
5. Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, Sørensen HT. Vagotomy and subsequent risk of Parkinson's disease. *Ann Neurol* 2015;78(4):522–529. https://doi.org/10.1002/ana.24448 Epub 2015 Jul 17. PMID: 26031848.
6. Beach TG, Adler CH, Sue LI, et al. Vagus nerve and stomach synucleinopathy in Parkinson's disease, incidental Lewy body disease, and normal elderly subjects: evidence against the "body-first" hypothesis. *J Parkinsons Dis* 2021;11(4):1833–1843. https://doi.org/10.3233/JPD-212733 PMID: 34151862.
7. Scheperjans F, Aho V, Pereira PA, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord* 2015;30(3):350–358. https://doi.org/10.1002/mds.26069 Epub 2014 Dec 5. PMID: 25476529.
8. Forsyth CB, Shannon KM, Kordower JH, et al. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease. *PLoS One* 2011;6(12):e28032. https://doi.org/10.1371/journal.pone.0028032 Epub 2011 Dec 1. PMID: 22145021; PMCID: PMC3228722.
9. Killinger B, Labrie V. The appendix in Parkinson's disease: From vestigial remnant to vital organ? *J Parkinsons Dis* 2019;9(s2):S345–S358. https://doi.org/10.3233/JPD-191703 PMID: 31609697; PMCID: PMC6839473.
10. Fasano A, Visanji NP, Liu LW, Lang AE, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2015;14(6):625–639. https://doi.org/10.1016/S1474-4422(15)00007-1 PMID: 25987282.
11. Kalf JG, Munneke M, van den Engel-Hoek L, de Swart BJ, Borm GF, Bloem BR, Zwarts MJ. Pathophysiology of diurnal drooling in Parkinson's disease. *Mov Disord* 2011;26(9):1670–1676. https://doi.org/10.1002/mds.23720 Epub 2011 Apr 11. PMID: 21484876.
12. Srivanitchapoom P, Pandey S, Hallett M. Drooling in Parkinson's disease: a review. *Parkinsonism Relat Disord* 2014;20(11):1109–1118. https://doi.org/10.1016/j.parkreldis.2014.08.013 Epub 2014 Aug 27. PMID: 25200111; PMCID: PMC4252747.
13. Nicaretta DH, de Rosso AL, Maliska C, Costa MM. Scintigraphic analysis of the parotid glands in patients with sialorrhea and Parkinson's disease. *Parkinsonism Relat Disord* 2008;14(4):338–341. https://doi.org/10.1016/j.parkreldis.2007.07.008 Epub 2007 Sep 12. PMID: 17855148.
14. Reynolds H, Miller N, Walker R. Drooling in Parkinson's disease: evidence of a role for divided attention. *Dysphagia* 2018;33(6):809–817.

https://doi.org/10.1007/s00455-018-9906-7 Epub 2018 May 21. PMID: 29785679.

15. Noyce AJ, Silveira-Moriyama L, Gilpin P, Ling H, Howard R, Lees AJ. Severe dysphagia as a presentation of Parkinson's disease. *Mov Disord* 2012;27(3):457–458. https://doi.org/10.1002/mds.24006 Epub 2011 Dec 9. PMID: 22161964.

16. Kalf JG, de Swart BJ, Bloem BR, Munneke M. Prevalence of oropharyngeal dysphagia in Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord* 2012;18(4):311–315. https://doi.org/10.1016/j.parkreldis.2011.11.006 Epub 2011 Dec 3. PMID: 22137459.

17. Ertekin C, Tarlaci S, Aydogdu I, et al. Electrophysiological evaluation of pharyngeal phase of swallowing in patients with Parkinson's disease. *Mov Disord* 2002;17(5):942–949. https://doi.org/10.1002/mds.10240 PMID: 12360543.

18. Potulska A, Friedman A, Królicki L, Spychala A. Swallowing disorders in Parkinson's disease. *Parkinsonism Relat Disord* 2003;9(6):349–353. https://doi.org/10.1016/s1353-8020(03)00045-2 PMID: 12853234.

19. Su A, Gandhy R, Barlow C, Triadafilopoulos G. Clinical and manometric characteristics of patients with Parkinson's disease and esophageal symptoms. *Dis Esophagus* 2017;30(4):1–6. https://doi.org/10.1093/dote/dow038 PMID: 28375482.

20. Heetun ZS, Quigley EM. Gastroparesis and Parkinson's disease: a systematic review. *Parkinsonism Relat Disord* 2012;18(5):433–440. https://doi.org/10.1016/j.parkreldis.2011.12.004 Epub 2011 Dec 29. PMID: 22209346.

21. Pfeiffer RF, Isaacson SH, Pahwa R. Clinical implications of gastric complications on levodopa treatment in Parkinson's disease. *Parkinsonism Relat Disord* 2020;76:63–71. https://doi.org/10.1016/j.parkreldis.2020.05.001 Epub 2020 May 11. PMID: 32461054.

22. Heimrich KG, Jacob VYP, Schaller D, Stallmach A, Witte OW, Prell T. Gastric dysmotility in Parkinson's disease is not caused by alterations of the gastric pacemaker cells. *NPJ Parkinsons Dis* 2019;5:15. https://doi.org/10.1038/s41531-019-0087-3 PMID: 31372495; PMCID: PMC6659650.

23. Zheng LF, Song J, Fan RF, et al. The role of the vagal pathway and gastric dopamine in the gastroparesis of rats after a 6-hydroxydopamine microinjection in the substantia nigra. *Acta Physiol (Oxf)* 2014;211(2):434–446. https://doi.org/10.1111/apha.12229 Epub 2014 Feb 19. PMID: 24410908.

24. Unger MM, Möller JC, Mankel K, et al. Postprandial ghrelin response is reduced in patients with Parkinson's disease and idiopathic REM sleep behaviour disorder: A peripheral biomarker for early Parkinson's disease? *J Neurol* 2011;258(6):982–990. https://doi.org/10.1007/s00415-010-5864-1 Epub 2010 Dec 24. PMID: 21181542.

25. Fasano A, Bove F, Gabrielli M, et al. The role of small intestinal bacterial overgrowth in Parkinson's disease. *Mov Disord* 2013;28(9):1241–1249. https://doi.org/10.1002/mds.25522 Epub 2013 May 27. PMID: 23712625.

26. Nielsen HH, Qiu J, Friis S, Wermuth L, Ritz B. Treatment for helicobacter pylori infection and risk of Parkinson's disease in Denmark. *Eur J Neurol* 2012;19(6):864–869. https://doi.org/10.1111/j.1468-1331.2011.03643.x Epub 2012 Jan 17. PMID: 22248366; PMCID: PMC3330170.

27. Isomoto H, Ueno H, Saenko VA, et al. Impact of helicobacter pylori infection on gastric and plasma ghrelin dynamics in humans. *Am J Gastroenterol* 2005;100(8):1711–1720. https://doi.org/10.1111/j.1572-0241.2005.41492.x PMID: 16086706.

28. Niehues M, Hensel A. In-vitro interaction of L-dopa with bacterial adhesins of helicobacter pylori: an explanation for clinicial differences in bioavailability? *J Pharm Pharmacol* 2009;61(10):1303–1307. https://doi.org/10.1211/jpp/61.10.0005 PMID: 19814861.

29. Narożańska E, Białecka M, Adamiak-Giera U, et al. Pharmacokinetics of levodopa in patients with Parkinson disease and motor fluctuations depending on the presence of helicobacter pylori infection. *Clin Neuropharmacol* 2014;37(4):96–99. https://doi.org/10.1097/WNF.0000000000000037 PMID: 24992088.

30. Lee WY, Yoon WT, Shin HY, Jeon SH, Rhee PL. Helicobacter pylori infection and motor fluctuations in patients with Parkinson's disease. *Mov Disord* 2008;23(12):1696–1700. https://doi.org/10.1002/mds.22190 PMID: 18649391.

31. Tan AH, Lim SY, Mahadeva S, et al. Helicobacter pylori eradication in Parkinson's disease: a randomized placebo-controlled trial. *Mov Disord* 2020;35(12):2250–2260. https://doi.org/10.1002/mds.28248 Epub 2020 Sep 7. PMID: 32894625.

32. Grace E, Shaw C, Whelan K, Andreyev HJ. Review article: small intestinal bacterial overgrowth–prevalence, clinical features, current and developing diagnostic tests, and treatment. *Aliment Pharmacol Ther* 2013;38(7):674–688. https://doi.org/10.1111/apt.12456 Epub 2013 Aug 20. PMID: 23957651.

33. Savica R, Carlin JM, Grossardt BR, et al. Medical records documentation of constipation preceding Parkinson disease: a case-control study. *Neurology* 2009;73(21):1752–1758. https://doi.org/10.1212/WNL.0b013e3181c34af5 PMID: 19933976; PMCID: PMC2788809.

34. Lin CH, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. *Parkinsonism Relat Disord* 2014;20(12):1371–1375. https://doi.org/10.1016/j.parkreldis.2014.09.026 Epub 2014 Sep 28. PMID: 25293395.

35. Knudsen K, Krogh K, Østergaard K, Borghammer P. Constipation in parkinson's disease: subjective symptoms, objective markers, and new perspectives. *Mov Disord* 2017;32(1):94–105. https://doi.org/10.1002/mds.26866 Epub 2016 Nov 22. PMID: 27873359.

36. Chung KA, Pfeiffer RF. Gastrointestinal dysfunction in the synucleinopathies. *Clin Auton Res* 2021;31(1):77–99. https://doi.org/10.1007/s10286-020-00745-7 Epub 2020 Nov 27. PMID: 33247399.

37. Abbott RA, Cox M, Markus H, Tomkins A. Diet, body size and micronutrient status in Parkinson's disease. *Eur J Clin Nutr* 1992;46(12):879–884. PMID: 1483417.

38. Uc EY, Struck LK, Rodnitzky RL, Zimmerman B, Dobson J, Evans WJ. Predictors of weight loss in Parkinson's disease. *Mov Disord* 2006;21(7):930–936. https://doi.org/10.1002/mds.20837 PMID: 16534756.

39. Durrieu G, LLau ME, Rascol O, Senard JM, Rascol A, Montastruc JL. Parkinson's disease and weight loss: a study with anthropometric and nutritional assessment. *Clin Auton Res* 1992;2(3):153–157. https://doi.org/10.1007/BF01818955 PMID: 1498561.

40. Sheard JM, Ash S, Silburn PA, Kerr GK. Prevalence of malnutrition in Parkinson's disease: a systematic review. *Nutr Rev* 2011;69(9):520–532. https://doi.org/10.1111/j.1753-4887.2011.00413.x PMID: 21884132.

41. Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease. *Lancet Neurol* 2003;2(2):107–116. https://doi.org/10.1016/s1474-4422(03)00307-7 PMID: 12849267.

42. Jellinger KA. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. *J Neural Transm (Vienna)* 2018;125(4):615–650. https://doi.org/10.1007/s00702-017-1821-9 Epub 2017 Dec 8. PMID: 29222591.

43. Stubendorff K, Aarsland D, Minthon L, Londos E. The impact of autonomic dysfunction on survival in patients with dementia with Lewy bodies and Parkinson's disease with dementia. *PLoS One* 2012;7(10):e45451. https://doi.org/10.1371/journal.pone.0045451 Epub 2012 Oct 1. PMID: 23049679; PMCID: PMC3462171.

44. Ito S, Takao M, Hatsuta H, et al. Alpha-synuclein immunohistochemistry of gastrointestinal and biliary surgical specimens for diagnosis of Lewy body disease. *Int J Clin Exp Pathol* 2014;7(4):1714–1723. PMID: 24817969; PMCID: PMC4014253.

45. Londos E, Hanxsson O, Alm Hirsch I, Janneskog A, Bülow M, Palmqvist S. Dysphagia in Lewy body dementia - a clinical observational study of swallowing function by videofluoroscopic examination. *BMC Neurol* 2013;13:140. https://doi.org/10.1186/1471-2377-13-140 PMID: 24099488; PMCID: PMC4126015.

46. Pouclet H, Lebouvier T, Coron E, et al. Analysis of colonic alpha-synuclein pathology in multiple system atrophy. *Parkinsonism Relat Disord* 2012;18(7):893–895. https://doi.org/10.1016/j.parkreldis.2012.04.020 Epub 2012 May 3. PMID: 22560049.

47. Wan L, Zhou X, Wang C, et al. Corrigendum: alterations of the gut microbiota in multiple system atrophy patients. *Front Neurosci* 2020;14:19. https://doi.org/10.3389/fnins.2020.00019 Erratum for: Front Neurosci. 2019 Oct 18;13:1102. PMID: 32082107; PMCID: PMC7005581.

48. Do HJ, Seo HG, Lee HH, et al. Progression of oropharyngeal dysphagia in patients with multiple system atrophy. *Dysphagia* 2020;35(1):24–31. https://doi.org/10.1007/s00455-019-09990-z Epub 2019 Mar 9. PMID: 30852647.

49. Claus I, Suttrup J, Muhle P, et al. Subtle esophageal motility alterations in Parkinsonian syndromes: Synucleinopathies vs. Tauopathies. *Mov Disord Clin Pract* 2018;5(4):406–412. https://doi.org/10.1002/mdc3.12616 PMID: 30363410; PMCID: PMC6174416.

50. Thomaides T, Karapanayiotides T, Zoukos Y, et al. Gastric emptying after semi-solid food in multiple system atrophy and Parkinson disease.

J Neurol 2005;252(9):1055–1059. https://doi.org/10.1007/s00415-005-0815-y Epub 2005 Apr 4. PMID: 15795792.

51. Sakakibara R, Odaka T, Uchiyama T, et al. Colonic transit time, sphincter EMG, and rectoanal videomanometry in multiple system atrophy. *Mov Disord* 2004;19(8):924–929. https://doi.org/10.1002/mds.20165 PMID: 15300657.
52. Dickson DW. Neuropathologic differentiation of progressive supranuclear palsy and corticobasal degeneration. *J Neurol* 1999;246(Suppl 2): II6–II15. https://doi.org/10.1007/BF03161076 PMID: 10525997.
53. Colosimo C, Morgante L, Antonini A, PRIAMO STUDY GROUP, et al. Non-motor symptoms in atypical and secondary parkinsonism: the PRIAMO study. *J Neurol* 2010;257(1):5–14. https://doi.org/10.1007/s00415-009-5255-7 Epub 2009 Aug 9. PMID: 19669613.
54. Oliveira MCB, Ling H, Lees AJ, Holton JL, De Pablo-Fernandez E, Warner TT. Association of autonomic symptoms with disease progression and survival in progressive supranuclear palsy. *J Neurol Neurosurg Psychiatry* 2019;90(5):555–561. https://doi.org/10.1136/jnnp-2018-319374 Epub 2018 Dec 31. PMID: 30598430.
55. Müller J, Wenning GK, Verny M, et al. Progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders. *Arch Neurol* 2001;58(2):259–264. https://doi.org/10.1001/archneur.58.2.259 PMID: 11176964.
56. Johnston BT, Castell JA, Stumacher S, Colcher A, Gideon RM, Li Q, Castell DO. Comparison of swallowing function in Parkinson's disease and progressive supranuclear palsy. *Mov Disord* 1997;12(3):322–327. https://doi.org/10.1002/mds.870120310 PMID: 9159726.
57. Litvan I, Sastry N, Sonies BC. Characterizing swallowing abnormalities in progressive supranuclear palsy. *Neurology* 1997;48(6):1654–1662. https://doi.org/10.1212/wnl.48.6.1654 PMID: 9191782.
58. Sassone J, Colciago C, Cislaghi G, Silani V, Ciammola A. Huntington's disease: the current state of research with peripheral tissues. *Exp Neurol* 2009;219(2):385–397. https://doi.org/10.1016/j.expneurol.2009.05.012 Epub 2009 May 19. PMID: 19460373.
59. Aziz NA, Anguelova GV, Marinus J, van Dijk JG, Roos RA. Autonomic symptoms in patients and pre-manifest mutation carriers of Huntington's disease. *Eur J Neurol* 2010;17(8):1068–1074. https://doi.org/10.1111/j.1468-1331.2010.02973.x Epub 2010 Feb 24. PMID: 20192977.
60. Lanska DJ, Lanska MJ, Lavine L, Schoenberg BS. Conditions associated with Huntington's disease at death. A case-control study. *Arch Neurol* 1988;45(8):878–880. https://doi.org/10.1001/archneur.1988.00520320068017 PMID: 2969233.
61. Schindler A, Pizzorni N, Sassone J, et al. Fiberoptic endoscopic evaluation of swallowing in early-to-advanced stage Huntington's disease. *Sci Rep* 2020;10(1):15242. https://doi.org/10.1038/s41598-020-72250-w PMID: 32943712; PMCID: PMC7499207.
62. Schumann-Werner B, Dogan I, Mirzazade S, et al. Clinical predictors and neural correlates for compromised swallowing safety in Huntington disease. *Eur J Neurol* 2021;28(9):2855–2862. https://doi.org/10.1111/ene.14953 Epub 2021 Jun 24. PMID: 34077591.
63. Andrich JE, Wobben M, Klotz P, Goetze O, Saft C. Upper gastrointestinal findings in Huntington's disease: patients suffer but do not complain. *J Neural Transm (Vienna)* 2009;116(12):1607–1611. https://doi.org/10.1007/s00702-009-0310-1 Epub 2009 Sep 22. PMID: 19771391.
64. Kong G, Cao KL, Judd LM, Li S, Renoir T, Hannan AJ. Microbiome profiling reveals gut dysbiosis in a transgenic mouse model of Huntington's disease. *Neurobiol Dis* 2020;135:104268. https://doi.org/10.1016/j.nbd.2018.09.001 Epub 2018 Sep 5. PMID: 30194046.
65. Wasser CI, Mercieca EC, Kong G, Hannan AJ, McKeown SJ, Glikmann-Johnston Y, Stout JC. Gut dysbiosis in Huntington's disease: associations among gut microbiota, cognitive performance and clinical outcomes. *Brain Commun* 2020;2(2):fcaa110. https://doi.org/10.1093/braincomms/fcaa110 PMID: 33005892; PMCID: PMC7519724.
66. Kobal J, Matej K, Koželj M, Podnar S. Anorectal dysfunction in Presymptomatic mutation carriers and patients with Huntington's disease. *J Huntingtons Dis* 2018;7(3):259–267. https://doi.org/10.3233/JHD-170280 PMID: 29889076.
67. Kolenc M, Kobal J, Podnar S. No electrophysiological evidence for Onuf's nucleus degeneration causing bladder and bowel symptoms in Huntington's disease patients. *NeurourolUrodyn* 2014;33(5):524–530. https://doi.org/10.1002/nau.22451 Epub 2013 Jun 26. PMID: 23804519.
68. Stüwe SH, Goetze O, Lukas C, et al. Hepatic mitochondrial dysfunction in manifest and premanifest Huntington disease. *Neurology* 2013;80(8):743–746. https://doi.org/10.1212/WNL.0b013e318282514e Epub 2013 Feb 6. PMID: 23390182.
69. Björkqvist M, Fex M, Renström E, et al. The R6/2 transgenic mouse model of Huntington's disease develops diabetes due to deficient beta-cell mass and exocytosis. *Hum Mol Genet* 2005;14(5):565–574. https://doi.org/10.1093/hmg/ddi053 Epub 2005 Jan 13. PMID: 15649949.
70. Bacos K, Björkqvist M, Petersén A, et al. Islet beta-cell area and hormone expression are unaltered in Huntington's disease. *Histochem Cell Biol* 2008;129(5):623–629. https://doi.org/10.1007/s00418-008-0393-z Epub 2008 Feb 8. PMID: 18259770.
71. Boesgaard TW, Nielsen TT, Josefsen K, et al. Huntington's disease does not appear to increase the risk of diabetes mellitus. *J Neuroendocrinol* 2009;21(9):770–776. https://doi.org/10.1111/j.1365-2826.2009.01898.x Epub 2009 Jul 7. PMID: 19602103.
72. Aziz NA, van der Burg JM, Landwehrmeyer GB, Brundin P, Stijnen T, EHDI Study Group, Roos RA. Weight loss in Huntington disease increases with higher CAG repeat number. *Neurology* 2008;71(19):1506–1513. https://doi.org/10.1212/01.wnl.0000334276.09729.0e PMID: 18981372.
73. van der Burg JMM, Weydt P, Landwehrmeyer GB, Aziz NA. Effect of body weight on age at onset in Huntington disease: a Mendelian randomization study. *Neurol Genet* 2021;7(4):e603. https://doi.org/10.1212/NXG.0000000000000603 PMID: 34250226; PMCID: PMC8265577.
74. van der Burg JMM, Gardiner SL, Ludolph AC, Landwehrmeyer GB, Roos RAC, Aziz NA. Body weight is a robust predictor of clinical progression in Huntington disease. *Ann Neurol* 2017;82(3):479–483. https://doi.org/10.1002/ana.25007 Epub 2017 Aug 22. PMID: 28779551.
75. Aziz NA, Pijl H, Frölich M, van der Graaf AW, Roelfsema F, Roos RA. Leptin secretion rate increases with higher CAG repeat number in Huntington's disease patients. *Clin Endocrinol (Oxf)* 2010;73(2):206–211. https://doi.org/10.1111/j.1365-2265.2009.03661.x Epub 2009 Jun 22. PMID: 19548952.
76. van der Burg JM, Winqvist A, Aziz NA, et al. Gastrointestinal dysfunction contributes to weight loss in Huntington's disease mice. *Neurobiol Dis* 2011;44(1):1–8. https://doi.org/10.1016/j.nbd.2011.05.006 Epub 2011 May 23. PMID: 21624468.
77. Urs AB, Augustine J, Khan AA. Chorea-acanthocytosis: a case report with review of Oral manifestations. *Contemp Clin Dent* 2021;12(1):73–75. https://doi.org/10.4103/ccd.ccd_207_20 Epub 2021 Mar 20. PMID: 33967542; PMCID: PMC8092098.
78. Salen G, Steiner RD. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). *J Inherit Metab Dis* 2017;40(6):771–781. https://doi.org/10.1007/s10545-017-0093-8 Epub 2017 Oct 4. PMID: 28980151.
79. van Heijst AF, Wevers RA, Tangerman A, Cruysberg JR, Renier WO, Tolboom JJ. Chronic diarrhoea as a dominating symptom in two children with cerebrotendinous xanthomatosis. *Acta Paediatr* 1996;85(8):932–936. https://doi.org/10.1111/j.1651-2227.1996.tb14189.x PMID: 8863874.
80. Brass EP, Stelten BML, Verrips A. Cerebrotendinous xanthomatosis-associated diarrhea and response to chenodeoxycholic acid treatment. *JIMD Rep* 2020;56(1):105–111. https://doi.org/10.1002/jmd2.12163 PMID: 33204601; PMCID: PMC7653248.AT.
81. Yunisova G, Tufekcioglu Z, Dogu O, et al. Patients with lately diagnosed cerebrotendinous xanthomatosis. *Neurodegener Dis* 2019;19(5–6):218–224. https://doi.org/10.1159/000506770 Epub 2020 Apr 29. PMID: 32349000.
82. Pearson TS. More than ataxia: Hyperkinetic movement disorders in childhood autosomal recessive ataxia syndromes. *Tremor Other Hyperkinet Mov (N Y)* 2016;6:368. https://doi.org/10.7916/D8H70FSS PMID: 27536460; PMCID: PMC4950223.
83. Shaikh AG, Zee DS, Mandir AS, Lederman HM, Crawford TO. Disorders of upper limb movements in ataxia-telangiectasia. *PLoS One* 2013;8(6):e67042. https://doi.org/10.1371/journal.pone.0067042 PMID: 23826191; PMCID: PMC3694953.
84. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. *Orphanet J Rare Dis* 2016;11(1):159. https://doi.org/10.1186/s13023-016-0543-7 PMID: 27884168; PMCID: PMC5123280.
85. Donath H, Woelke S, Theis M, et al. Progressive liver disease in patients with ataxia telangiectasia. *Front Pediatr* 2019;7:458. https://doi.org/10.3389/fped.2019.00458 PMID: 31788461; PMCID: PMC6856634.
86. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *J Invest Med* 2009;57(8):830–836.

https://doi.org/10.2310/JIM.0b013e3181af59c4 PMID: 19574929; PMCID: PMC2787702.

87. Hagerman R, Hagerman P. Advances in clinical and molecular understanding of the FMR1 premutation and fragile X-associated tremor/ataxia syndrome. *Lancet Neurol* 2013;12(8):786–798. https://doi.org/10.1016/S1474-4422(13)70125-X PMID: 23867198; PMCID: PMC3922535.

88. Hunsaker MR, Greco CM, Spath MA, et al. Widespread non-central nervous system organ pathology in fragile X premutation carriers with fragile X-associated tremor/ataxia syndrome and CGG knock-in mice. *Acta Neuropathol* 2011;122(4):467–479. https://doi.org/10.1007/s00401-011-0860-9 Epub 2011 Jul 23. PMID: 21785977; PMCID: PMC3222079.

89. Hara M, Ariño H, Petit-Pedrol M, et al. DPPX antibody-associated encephalitis: Main syndrome and antibody effects. *Neurology* 2017;88(14):1340–1348. https://doi.org/10.1212/WNL.0000000000003796 Epub 2017 Mar 3. PMID: 28258082; PMCID: PMC5379928.

90. Tobin WO, Lennon VA, Komorowski L, et al. DPPX potassium channel antibody: frequency, clinical accompaniments, and outcomes in 20 patients. *Neurology* 2014;83(20):1797–1803. https://doi.org/10.1212/WNL.0000000000000991 Epub 2014 Oct 15. PMID: 25320100; PMCID: PMC4240433.

91. Piepgras J, Höltje M, Michel K, et al. Anti-DPPX encephalitis: pathogenic effects of antibodies on gut and brain neurons. *Neurology* 2015;85(10):890–897. https://doi.org/10.1212/WNL.0000000000001907 Epub 2015 Aug 19. PMID: 26291285; PMCID: PMC4560062.

92. Roubergue A, Apartis E, Vidailhet M, Mignot C, Tullio-Pelet A, Lyonnet S, de Villemeur TB. Myoclonus and generalized digestive dysmotility in triple A syndrome with AAAS gene mutation. *Mov Disord* 2004;19(3):344–346. https://doi.org/10.1002/mds.10660 PMID: 15022193.

93. Temudo T, Ramos E, Dias K, et al. Movement disorders in Rett syndrome: an analysis of 60 patients with detected MECP2 mutation and correlation with mutation type. *Mov Disord* 2008;23(10):1384–1390. https://doi.org/10.1002/mds.22115 PMID: 18512755.

94. Motil KJ, Caeg E, Barrish JO, et al. Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome. *J Pediatr Gastroenterol Nutr* 2012;55(3):292–298. https://doi.org/10.1097/MPG.0b013e31824b6159 PMID: 22331013; PMCID: PMC3393805.

95. Motil KJ, Lane JB, Barrish JO, et al. Biliary tract disease in girls and young women with rett syndrome. *J Pediatr Gastroenterol Nutr* 2019;68(6):799–805. https://doi.org/10.1097/MPG.0000000000002273 PMID: 30664568; PMCID: PMC6534452.

96. Kidd SA, Lachiewicz A, Barbouth D, et al. Fragile X syndrome: a review of associated medical problems. *Pediatrics* 2014;134(5):995–1005. https://doi.org/10.1542/peds.2013-4301 Epub 2014 Oct 6. PMID: 25287458.

97. Glassman LW, Grocott OR, Kunz PA, et al. Prevalence of gastrointestinal symptoms in Angelman syndrome. *Am J Med Genet A* 2017;173(10):2703–2709. https://doi.org/10.1002/ajmg.a.38401 Epub 2017 Aug 16. PMID: 28816003.

98. Williams CA, Driscoll DJ, Dagli AI. Clinical and genetic aspects of Angelman syndrome. *Genet Med* 2010;12(7):385–395. https://doi.org/10.1097/GIM.0b013e3181def138 PMID: 20445456.

99. Gaig C, Compta Y, Heidbreder A, et al. Frequency and characterization of movement disorders in anti-IgLON5 disease. *Neurology* 2021;97(14):e1367–81. https://doi.org/10.1212/WNL.0000000000012639 Epub ahead of print. PMID: 34380749.

100. Honorat JA, Komorowski L, Josephs KA, et al. IgLON5 antibody: Neurological accompaniments and outcomes in 20 patients. *Neurol Neuroimmunol Neuroinflamm* 2017;4(5):e385. https://doi.org/10.1212/NXI.0000000000000385 PMID: 28761904; PMCID: PMC5515599.

101. Weinstock LB, Walters AS. Restless legs syndrome is associated with irritable bowel syndrome and small intestinal bacterial overgrowth. *Sleep Med* 2011;12(6):610–613. https://doi.org/10.1016/j.sleep.2011.03.007 Epub 2011 May 13. PMID: 21570907.

102. Erdal Y, Akdogan O, Nalbantoglu M, Kavasoglu G, Emre U. Autonomic dysfunction in restless legs syndrome. *Sleep Breath* 2020;24(3):995–999. https://doi.org/10.1007/s11325-019-01939-8 Epub 2019 Sep 14. PMID: 31520300.

103. Shneyder N, Adler CH, Hentz JG, et al. Autonomic complaints in patients with restless legs syndrome. *Sleep Med* 2013;14(12):1413–1416. https://doi.org/10.1016/j.sleep.2013.08.781 Epub 2013 Sep 21. PMID: 24152795; PMCID: PMC4105217.

104. Chenini S, Barateau L, Rassu AL, et al. Systematic assessment of autonomic symptoms in restless legs syndrome. *Sleep Med* 2021;80:30–38. https://doi.org/10.1016/j.sleep.2021.01.017 Epub 2021 Jan 18. PMID: 33548567.

105. Pfeiffer RF. Wilson's disease. *Handb Clin Neurol* 2011;100:681–709.

106. Mulroy E, Baschieri F, Magrinelli F, Latorre A, Cortelli P, Bhatia KP. Movement disorders and liver disease. *Mov Disord Clin Pract* 2021;8:828–842.

107. Karhan AN, Aydemir Y, Demir N, et al. Assessment of swallowing function in pediatric patients with Wilson's disease: results of a videofluoroscopic swallowing study. *Arab J Gastroenterol* 2021;22:215–219. https://doi.org/10.1016/j.ajg.2021.05.013.

108. Antczak-Kowalska M, Czlonkowska A, Litwin T, Nehring P, Niewada M, Przybylkowski A. Gastropathy in patients with Wilson disease. *Scand J Gastroenterol* 2020;55:14–17.

109. Cai X, Deng L, Ma X, et al. Altered diversity and composition of gut microbiota in Wilson's disease. *Sci Rep* 2020;10:21825.

110. Meunier M, Puechal X, Hoppé E, et al. Rheumatic and musculoskeletal features of Whipple disease: a report of 29 cases. *J Rheumatol* 2013;40:2061–2066.

111. Verbrugghe L, Verraes K, Vanderschueren S, et al. Mesenteric panniculitis as a presentation of Whipple's disease: case report and review of the literature. *Acta Gastroenterol Belg* 2020;83:666–668.

112. Pfeiffer RF. Gastroenterology and neurology. *Continuum (Minneap Minn)* 2017;23:744–761.

113. Safarpour D, Sharzehi K, Pfeiffer RF. Other neurologic disorders associated with gastrointestinal disease. In: Aminoff MJ, Josephson SA, eds. *Aminoff's Neurology and General Medicine*. 6th ed. London: Academic Press; 2021:201–215.

114. Hadjivassiliou M, Sarrigiannis PG, Shanmuggarajah PD, et al. Clinical characteristics and management of 50 patients with anti-GAD ataxia: gluten-free diet has a major impact. *Cerebellum* 2021;20:179–185.

115. Takahashi M, Okazaki H, Ohashi K, et al. Current diagnosis and management of abetalipoproteinemia. *J Atheroscler Thromb* 2021;28:1009–1019. https://doi.org/10.5551/jat.RV17056. Online ahead of print.

Supporting Information

Supporting information may be found in the online version of this article.

Appendix S1. Supporting Information