Pediatric enteric neuropathies: diagnosis and current management

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Purpose of review
Neurointestinal diseases are increasingly recognized as causes of significant gastrointestinal morbidity in children. This review highlights the most common pediatric enteric neuropathies and their diagnosis and management, emphasizing insights and discoveries from the most recent literature available.

Recent findings
The embryologic and histopathologic causes of enteric neuropathies are varied. They range from congenital aganglionosis in Hirschsprung disease, to autoimmune-mediated loss of neuronal subtypes in esophageal achalasia and Chagas disease, to degenerative neuropathies in some cases of chronic intestinal pseudo-obstruction and gastroparesis. Increased awareness of the clinical presentation and diagnostic evaluation of these conditions is essential as it allows for earlier initiation of treatment and improved outcomes. Most current therapies, which include medical management, neurostimulation, and operative intervention, aim to minimize the symptoms caused by these conditions. The evidence base for many of these treatments in children is poor, and multiinstitutional prospective studies are needed. An innovative therapy on the horizon involves using neuronal stem cell transplantation to treat the underlying disorder by replacing the missing or damaged neurons in these diseases.

Summary
Although recent advances in basic and clinical neurogastroenterology have significantly improved our awareness and understanding of enteric neuropathies, the efficacy of current treatment approaches is limited. The development of novel therapies, including pharmacologic modulators of neurointestinal function, neurostimulation to enhance gut motility, and neuronal cell-based therapies, is essential to improve the long-term outcomes in children with these disorders.

Keywords
enteric nervous system, enteric neuropathy, Hirschsprung disease, neurointestinal disease

INTRODUCTION

Normal gastrointestinal function relies on the enteric nervous system (ENS), a complex network of neurons and glia in the gut wall that regulate motor, sensory, absorptive, secretory, and multiple other aspects of gastrointestinal homeostasis. Comprising cells that arise from the embryonic neural crest, the ENS is organized in two major ganglionated plexuses, myenteric and submucosal, and functions independently of central nervous system input (Fig. 1). Many diseases of the gastrointestinal tract have a neuropathic cause (Table 1) and lead to significant morbidity due to abnormalities in motor and/or sensory gastrointestinal function. Some conditions are developmental in origin, caused by abnormal formation of the ENS. Others are acquired in later life due to infection, immune-mediated inflammation, or neuronal degeneration. In this review, we highlight the most common enteric neuropathies affecting children, review our current understanding of their pathophysiology, and discuss current and emerging approaches to their diagnosis and treatment.

HIRSCHSPRUNG DISEASE

Hirschsprung disease (HSCR) is the most common congenital neurointestinal disease with an

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KEY POINTS

- Enteric neuropathies result from congenital defects in enteric nervous system development or from acquired loss of enteric neurons due to infection, immune-mediated inflammation, or neuronal degeneration.
- The most common pediatric enteric neuropathies include Hirschsprung disease, esophageal achalasia, gastroparesis, chronic intestinal pseudo-obstruction, and neuropathic constipation.
- Although current therapies aim primarily to alleviate symptoms, neuronal stem cell transplantation is being explored as a way of treating the underlying pathophysiology by replacing damaged or missing neurons in these conditions.

incidence of one in 5000 live births. It is caused by the failure of enteric neural crest-derived cells, which give rise to the ENS, to complete their craniocaudal migration from the foregut to the end of the bowel [1], leaving the distal end aganglionic and therefore devoid of motility. Recent work has demonstrated that abnormal proliferation, differentiation, and migration of the neural crest-derived cells underlie the development of HSCR [2▪▪,3]. This disease usually presents in newborns with failure to pass meconium within the first 48 h of life, abdominal distension, emesis, and feeding difficulty. The aganglionosis is 'short-segment' (i.e., limited to the rectosigmoid) in 80% of cases, with the remainder extending more proximally, sometimes involving the whole colon or even the entire intestine [2▪▪].

HSCR has a complex, non-Mendelian inheritance pattern complicated by variable penetrance and clinical expression. Mutations in greater than 10 genes have been identified, but nearly all patients have a coding or noncoding mutation in the *RET* gene, which is critical for ENS development. Several genetic syndromes are associated with HSCR, including Down syndrome in 10% of cases, Shah–Waardenburg, Haddad syndrome, and Mowat–Wilson syndrome [2▪▪]. Although a contrast enema showing a caliber change between proximal dilated bowel and distal aganglionic bowel raises suspicion

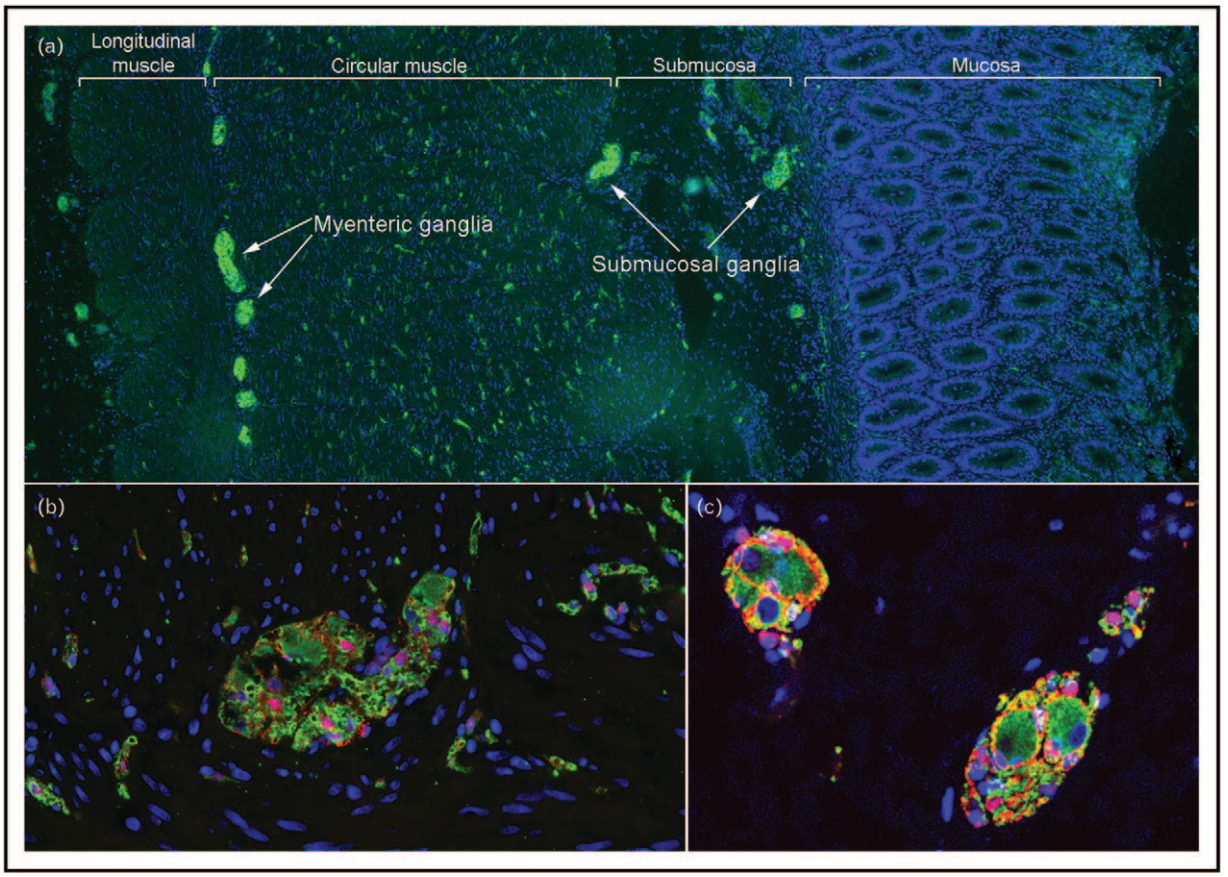

FIGURE 1. Enteric nervous system. Immunohistochemistry shows the enteric nervous system organized in two concentric rings of ganglia located in the myenteric and submucosal plexuses (a). Magnified views of a myenteric ganglion (b) and a submucosal ganglion (c) demonstrate the presence of both enteric neurons (Tuj1 antibody, green) and glial cells (S100 antibody, red), with nuclei stained with DAPI (4′,6-diamidino-2-phenylindole, blue).

Table 1. Enteric neuronal phenotype associated with pediatric neurointestinal diseases

Enteric neuropathy	Enteric neuronal phenotype
Hirschsprung disease	Enteric ganglia absent along variable lengths of distal bowel
Intestinal neuronal dysplasia, type B	Colonic submucosal hyperganglionosis in children >1 year of age
Esophageal achalasia	Autoimmunity leading to loss of inhibitory enteric neurons in esophageal myenteric plexus
Gastroparesis	Variable findings, including loss of ICC, hypoganglionosis, or neuronal inflammation (myenteric ganglionitis) in stomach
CIPO	Neuropathic cases are associated with neuronal inflammation, usually affecting the myenteric plexus
Neurogenic constipation	Variable histology, with some cases exhibiting reduced neurons, glial cells, or ICCs; neurotransmitter imbalance may also contribute
Chagas disease	Autoimmune-mediated inflammatory enteric neuropathy leading to degeneration of neurons in the gastrointestinal tract

CIPO, chronic intestinal pseudo-obstruction; ICC, interstitial cells of Cajal.

in the appropriate clinical setting, the diagnosis is established by rectal biopsy showing absence of ganglion cells and often the presence of hypertrophic nerves. Ancillary tests are helpful and recently calretinin immunohistochemistry, showing absent calretinin-immunoreactive fibers in the submucosa and lamina propria, is replacing the traditional acetylcholinesterase histochemical stain that has been fraught with unreliability [4].

The treatment of HSCR remains surgical, with single-stage transanal endorectal pullthrough procedures, with or without laparoscopy, representing the most common approach for short-segment disease. Both Soave and Swenson transanal procedures are performed, and no significant difference in outcomes (hospital stay, obstructive symptoms, or enterocolitis incidence) has been observed [5]. Current research is focusing on long-term outcomes and the recognition that bowel function is not nearly as good as previously thought. In a meta-analysis of transanal pullthroughs, 14% experienced persistent bowel dysfunction, including 53% with constipation, 29% with Hirschsprung-associated enterocolitis (HAEC), and 18% with incontinence or soiling [6]. A recent longer term study of transanal endorectal pullthroughs with 15-year follow-up found that 54% of patients had soiling and 44% developed postoperative HAEC, with bowel function reduced in children with an associated syndrome [7▪▪]. The same group analyzed long-term bowel function and quality of life with matched controls and found significant impairment in fecal control during childhood. Control improved with age, but stooling frequency remained persistently higher. Quality of life was satisfactory, but the importance of psychosocial support for the child and the family is emphasized [8].

One cause of postpullthrough morbidity is the 'transition zone pullthrough', in which the proximal resection margin contains abnormally ganglionated bowel. The transition zone, defined by partial circumferential aganglionosis, hypoganglionosis, and/or submucosal nerve hypertrophy, was shown to extend up to 5 cm proximal to the aganglionic segment [9]. Based on this observation, routine resection of a 5 cm proximal margin should be performed and may improve outcomes. Postpullthrough complications, including fecal incontinence, obstructive symptoms, and HAEC, adversely impact not only gastrointestinal function but also quality of life, including psychological, behavioral, and/or developmental outcomes [10]. Early identification and treatment of these complications utilizing multidisciplinary teams is of critical importance, including involvement of adult specialists as these children transition to adulthood.

INTESTINAL NEURONAL DYSPLASIA

Intestinal neuronal dysplasia (IND) type B, which comprises more than 95% of IND cases, presents as chronic constipation usually during childhood. The diagnosis is made by biopsy showing submucosal hyperganglionosis in the colon. The specific histopathologic criteria have been controversial. One set of criteria based on expert opinion includes the presence of giant submucosal ganglia defined as containing more than eight ganglion cells per ganglion in at least 20% of submucosal ganglia examined. The diagnosis must be made on frozen section and should not be made before 1 year of age because submucosal hyperganglionosis occurs normally in infants [11].

IND has been found in isolation or in the transition zone proximal to the aganglionic segment in HSCR. In the latter scenario, it has been proposed to cause persistent obstructive symptoms after pullthrough surgery [12] but whether this is true is

debated [13]. IND remains a controversial entity, with some suggesting that its histologic features are secondary to chronic obstruction rather than a primary cause of constipation. Regardless, treatment is similar to that of chronic constipation, with some severe cases requiring surgery, including sphincterotomy, diverting colostomy, or colectomy [14].

ESOPHAGEAL ACHALASIA

Esophageal achalasia is uncommon in children, with an incidence of 0.1 per 100 000 [15,16▪] and an average age at diagnosis of 11 years [17,18]. The disease is characterized by impaired relaxation of the lower esophageal sphincter (LES) and abnormal esophageal motility, resulting in dysphagia and regurgitation, often with retrosternal chest discomfort and weight loss. Its pathophysiology is due to the loss of inhibitory neurons in the esophageal myenteric plexus that release nitric oxide, which is required for LES relaxation [2▪▪]. The disease is thought to be autoimmune, with autoantibodies reacting against enteric neurons and leading to an imbalance of excitatory (cholinergic) over inhibitory (nitrergic) innervation [19].

The diagnosis is made by esophagram and manometry. A contrast study typically shows a dilated esophagus with abnormal peristalsis and delayed emptying through a narrow esophagogastric junction, giving a 'bird's beak' appearance [19]. Characteristic manometric findings include high resting LES pressure, failure of LES relaxation after swallowing, and absence of peristaltic contractions in the esophagus. The optimal treatment in children remains controversial due to inadequate comparative data on which to base recommendations [20]. Initial treatment with botulinum toxin injection into the LES is only temporizing, requiring subsequent Heller myotomy in 85% of cases in a recent retrospective review [17]. Endoscopic pneumatic dilatation is commonly performed, but has been associated with a high rate of retreatment for persistent or recurrent symptoms, ranging from 71 to 88% [16▪,18], leading some to recommend Heller myotomy as first-line therapy for newly diagnosed children.

A Heller myotomy has long been the gold standard among pediatric surgeons. The procedure is usually laparoscopic and often includes a partial fundoplication to minimize the risk of postmyotomy reflux. However, reported results after Heller myotomy are mixed, with repeat myotomy or pneumatic dilation required in 15–29% of patients for recurrent dysphagia [16▪,21]. In a prospective double-blind trial, laparoscopic myotomy and pneumatic dilation yielded equivalent results at 2-year follow-up in 184 patients [22]. Interestingly, in subgroup analysis, younger patients (aged under 40 years) were more likely to require redilation after pneumatic dilation, suggesting age-dependent differences in outcome and consistent with the poorer long-term results observed in children.

Peroral endoscopic myotomy (POEM) is a new approach that leverages natural orifice transluminal endoscopic surgery to perform endoscopic myotomy. Experience in children is limited. A recent study comparing pediatric laparoscopic myotomy and POEM found that the latter had shorter operative time, longer myotomy, fewer complications, faster time to feeding, and shorter hospital stay, with equivalent outcomes [15]. Another study of 10 children included Eckhardt score, timed barium swallow, and high-resolution manometry 1 year after POEM and found significantly improved scores on these measures and complete symptom resolution [23]. The current lack of evidence supporting one treatment approach over another, combined with the rarity of achalasia in children, has led to wide variation in practice [24]. Well designed multiinstitutional studies are needed to improve treatment and prevent the adverse impact this disease has on a child's long-term quality of life [16▪].

GASTROPARESIS

Gastroparesis refers to delayed gastric emptying in the absence of mechanical obstruction. Symptoms include postprandial bloating and pain, early satiety, nausea, and vomiting. Although the prevalence among children is unknown, the past decade has seen a dramatic increase in gastroparesis-associated hospitalizations [25]. In children, 70% of gastroparesis is idiopathic or postviral, with the remaining 30% due to medications or postsurgery. Various pathophysiologic causes have been proposed, including abnormalities of extrinsic gastric innervation, loss of interstitial cells of Cajal (ICCs), hypoganglionosis, and inflammatory degeneration of myenteric neurons [2▪▪]. The diagnosis is suspected clinically and confirmed by gastric emptying scintigraphy, which measures the time to empty a ^{99}Tc sulfur colloid meal from the stomach. A 4-h solid meal scan is the optimal test and can be completed by most children, excluding the very young [26].

The mainstay of treatment for pediatric gastroparesis includes dietary modification and medications (prokinetic drugs, antiemetics, and appetite stimulants) with the goal of maintaining fluid and nutrition status and relieving symptoms. For intractable cases, surgical options include

gastrostomy, jejunostomy, gastric emptying procedures, and intrapyloric Botox injection, but these have met with limited success [27]. Gastric electrical stimulation (GES) is a promising new approach that has been shown to be effective in treating the nausea and vomiting, even while not improving gastric emptying. GES involves delivery of low-energy electrical stimulation via electrodes implanted into the stomach [28▪▪]. The largest pediatric study to date included 97 children, 67 of whom had permanent pulse generators implanted and exhibited significant and sustained symptomatic improvement [29▪▪]. Additional studies are needed to confirm these findings and to determine mechanisms of action, predictors of success, and long-term efficacy.

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

Chronic intestinal pseudo-obstruction (CIPO) is a rare and severe motility disorder characterized by recurrent or continuous symptoms of intestinal obstruction in the absence of a fixed obstructive lesion [3]. Symptoms are often nonspecific, delaying the diagnosis and contributing to morbidity. CIPO accounts for 15% of cases of chronic intestinal failure in children. Most cases are idiopathic, whereas some occur secondary to systemic disease, including myxedema, Duchenne muscular dystrophy, hypothyroidism, hypoparathyroidism, celiac disease, Chagas disease, and mitochondrial disorders [2▪▪]. The pathophysiology of primary CIPO can be neuropathic, mesenchymopathic, or myopathic, depending on whether the abnormality lies with the enteric neurons, ICCs, or smooth muscle, respectively. Neuropathic CIPO is often due to degenerative loss of enteric neurons or to an inflammatory neuropathy within the enteric ganglia and/or nerve processes [30]. Although the prognosis in children is better for neuropathic, rather than myopathic, CIPO [31], the disease remains chronic and often debilitating, and often with no definitive therapy available.

Treatment requires a multidisciplinary team of surgeons, gastroenterologists, pathologists, nutritionists, and psychologists aimed at avoiding the many associated complications, including intestinal failure, small intestinal bacterial overgrowth, central line-associated bloodstream infections, sepsis, and, when possible, improving gut motility and function [32▪]. Treatment therefore includes nutritional support with enteral nutrition, parenteral nutrition when needed, nonopioid analgesics, antibiotics, and prokinetics. The role of surgery is limited to central venous access, ostomy for intestinal decompression, feeding tubes, appendicostomy or cecostomy for antegrade enemas [3], and, in end-stage CIPO, bowel transplantation. Immunomodulatory therapy may have a role in treating immune-mediated neuropathies, but the evidence remains limited to small case series [2▪▪].

NEUROGENIC CONSTIPATION

Chronic constipation is a common functional gastrointestinal disorder that affects up to 30% of children. Three principal subtypes exist: normal transit (functional constipation), slow transit constipation (STC), and obstructed defecation. Tissue obtained from colectomies performed for severe STC show an underlying enteric neuropathy in some patients, including reductions in neuronal cell bodies and processes, enteric glia, and ICCs [2▪▪]. A study of children with severe STC showed that abnormal colonic manometry was associated with histopathological findings involving neurons, ICCs, and smooth muscle [33]. Colonic dysmotility may be due to neurotransmitter imbalance, such as an excess of nitric oxide in the myenteric plexus, which could inhibit contractile activity [34]. However, the role of neurotransmitters remains unclear as multiple studies on a variety of mediators have yielded contradictory results.

Treatment of chronic constipation begins with medical management using laxatives, including bulk-formers (fiber), stool softeners, lubricants (mineral oil), hyperosmotic agents (lactulose and polyethylene glycol), stimulants (bisocodyl and senna), serotonin agonists (prucalopride), and other newer agents [5-Hydroxytryptamine receptor 4 (5-HT4) agonists, ileal bile acid transporters, and ghrelin agonists] [35,36]. Cases refractory to medications may benefit from surgical intervention, but a thorough diagnostic evaluation is essential prior to embarking on an operation. The workup should be tailored to the individual child and can include anorectal and/or colonic manometry, colon transit study, and contrast enema. Depending on the results, intestinal diversion, various types of colectomy, and antegrade colonic enema procedures have all proven to be beneficial, but the evidence supporting each of these is poor and larger, more rigorous studies are needed [37,38▪].

CHAGAS DISEASE

Chagas disease is caused by the parasite *Trypanosoma cruzi* and transmitted to humans by *Reduviidae* beetles, known as 'kissing bugs'. Infection can also occur via vertical or blood-borne transmission, nonvectorial modes that represent a major source of infection [39]. Chagas disease is endemic in Central and South America, but present worldwide, with

over 6 million people infected and over 12 000 deaths annually [40]. Symptoms during the acute infectious phase, which lasts weeks to months, are mild and self-resolving. In 20–30% of patients, a symptomatic chronic phase occurs, often many years later, with cardiac, neurologic, and gastrointestinal consequences [41]. Although any segment of the gastrointestinal tract can be affected and result in dysmotility, the esophagus and colon are most often involved, leading to megaesophagus and megacolon, respectively. Interestingly, gastrointestinal involvement is geographically distinct, with esophageal involvement more common in Brazil and megacolon more often seen in Chile [42]. The megaesophagus is often called 'Chagasic achalasia' due to its similarities to idiopathic achalasia, although an important difference is the loss of both excitatory and inhibitory innervation in Chagasic achalasia as opposed to selective loss of inhibitory innervation in the idiopathic form [43].

Chagas disease is characterized by the degenerative loss of enteric ganglia due to immune infiltration in the myenteric plexus. This results from autoimmunity due to a flagellum-associated surface protein (Fl-160) that mimics a protein expressed by mammalian enteric neurons [44]. Patients with gastrointestinal disease can also have circulating antibodies against the type 2 muscarinic acetylcholine receptor expressed on smooth muscle cells, leading to muscle contraction and contributing to achalasia [45].

Treatment of Chagas disease is based on antiparasitic drugs in the acute phase and symptom management in the chronic phase. Drug treatment includes nifurtimox and benznidazole, but these have variable efficacy and significant side effects [42]. Management of chronic gastrointestinal involvement, such as megaesophagus and megacolon, are similar to idiopathic achalasia and constipation with megacolon, respectively. There is a growing emphasis on prevention through the use of vector control strategies, including insecticides [46], as well as the importance of testing pregnant women and screening and treating infants with congenital Chagas disease [47].

FUTURE DIRECTIONS

An area of active and promising investigation is the development of neuronal cell transplantation for HSCR and other neurointestinal diseases [48▪▪]. The identification and isolation of neuronal progenitor cells from the human postnatal intestine [49,50] raises the intriguing possibility of transplanting these cells to replace missing or abnormal neurons in patients with enteric neuropathies. Recent studies successfully transplanted enteric neuronal progenitors isolated from the intestine or differentiated from pluripotent stem cells into mouse models of HSCR [51,52▪▪], but improvement in gut function has yet to be convincingly demonstrated. The initiation of pilot studies in humans is on the horizon.

CONCLUSION

Neurointestinal diseases represent a diverse group of conditions associated with significant morbidity. We have presented those most commonly encountered in childhood, but many other enteric neuropathies exist, including hypoganglionosis, ganglioneuromatosis, neuronal intranuclear inclusion disease, ganglionitis, degenerative neuropathy, and so on [53]. An increased awareness of these conditions, including their clinical presentation and their pathologic features, is needed to improve the care we deliver to affected patients. Unfortunately, for most of these diseases, definitive treatments are lacking and current therapies aim only to alleviate symptoms. As our understanding of ENS biology and of neurointestinal pathophysiology improves, so too will our ability to treat these challenging clinical conditions.

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Conflicts of interest

There are no conflicts of interest.

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