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REVIEW PAPER

Hirschsprung disease and other intestinal neuropathies in children

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ABSTRACT

Proper intestinal motility depends on interaction between muscles, nerve cells, and tendinous connective tissue of muscularis propria. Intestinal motility disorders refer to varied intestinal neuromuscular pathologies, including enteric neuropathies. The most common symptoms of these diseases are delayed passage of meconium in newborns and chronic constipation in infants and older children. If organic causes of clinical features are detected, a further multidisciplinary team approach for the management of these patients is recommended. Entities discussed in this review include Hirschsprung disease, hypoganglionosis, intestinal neuronal dysplasia, ganglioneuromatosis, and chronic intestinal pseudo-obstruction. Emphasis is given to the clinical symptoms and diagnostic features that distinguish these conditions enabling faster diagnosis and appropriate treatment.

KEY WORDS:

chronic constipation, intestinal motility disorder, delayed passage of meconium, Hirschsprung disease.

INTRODUCTION

The digestive system is innervated through enteric nervous system (ENS), which is a complex web of neurons and glia in the bowel wall. It is necessary for the proper functioning of the gastrointestinal tract and plays an important role in peristalsis, water balance, hormone secretions, and intestinal bowel homeostasis. ENS dysfunctions lead to intestinal dysganglionosis, which was classified by Scharli in 1995 (Table 1) [1].

The purpose of the work is to describe anomalies of the intestinal motor functions like Hirschsprung disease (HD), hypoganglionosis (HG), intestinal neuronal dysplasia (IND), ganglioneuromatosis (DIG), chronic intestinal pseudo-obstruction (CIPO).

HIRSCHSPRUNG DISEASE

Congenital aganglionic megacolon or HD is related to complete absence of neuronal ganglion cells in the myenteric (Auerbach's) and submucosal (Meissner's) plexuses of the rectum and a variable length of contiguous proximal intestine. The first description made by Harald Hirschsprung in medical literature dates from 1887 and

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TABLE 1. Dysganglionosis classification according to Scharli

Type	Characteristic
Agenetic type	Congenital aganglionosis (Hirschsprung disease) Acquired aganglionosis (Chagas' disease)
Hypogenetic type	Hypoganglionosis
Dysgenetic type	Intestinal neuronal dysplasia type A Intestinal neuronal dysplasia type B
Combination of different forms	Agangliosis + hypoganliosis Agangliosis + intestinal neuronal dysplasia type B Hypoganglionosis + intestinal neuronal dysplasia type B
Dysmorphic type	Ganglion cell immaturity Ganglion cell degeneration

refers to two boys with severe constipation. This disorder is the most common enteric neuropathy, which affects 1 in 5000 live births with a male-to-female ratio of 4 : 1. Male predominance decreases in cases with more extensive aganglionosis [2]. About 30% of cases are connected with other congenital defect syndromes, especially Down syndrome (trisomy 21). Genetic anomalies associated with HD include Bardet-Biedl syndrome (BBS), cartilage-hair hypoplasia, Goldberg-Shprintzen syndrome, Mowat-Wilson syndrome, Waardenburg syndrome type 4, multiple endocrine neoplasia type 2 (MEN 2) syndrome, and others [3]. In addition, the significant risk of HD occurrence is higher for first-, second-, and fourth-degree relatives than in the general population [4]. Mutation in any gene associated with enteric nervous system development may lead to congenital aganglionic megacolon. Nowadays, approximately 20 gene mutations have been detected as linked with the disease. The rearranged during transfection (RET) gene is the first one described and relates to 50% of familial and 15–35% of sporadic cases of HD [5]. Other genes that have been identified include: glial cell-derived neurotrophic factor (GDNF), family receptor alpha-1 (GFRα1), neutrin (NRTN), endothelin B receptor (EDNRB), Endothelin-3 (ET3), paired-like homeobox 2B (PHOX2b), SRY-related HMG-box 10 (SOX10), neuregulin 1 (NRG1), neuregulin 2 (NRG2), NADPH oxidase 5 (NOX5), and sonic hedgehog homologue (SHH) genes [2, 6, 7]. Recent, extensive studies have revealed that members of the protocadherin genes (PCDHA1, PCDHA9) are candidate genes for HD [8]. Also, epigenetic and epitranscriptomic regulations play relevant roles in ENS development. Failures of transcriptomics, microRNAs, chromatin-associated protein complex, histone modifications, and DNA methylation and demethylation are important in the pathogenesis of disease [9]. Maternal fever in the first trimester of pregnancy may be a risk factor for HD [2].

HD is a part of the neurocristopathies, a group of diseases related to abnormal development of neural crest cells. Normally, neuroblast migration from the neural crest begins at four weeks of gestation and ends at seven weeks of gestation. A defect of the cell transfer results in a lack of neuronal ganglion in the distal colon [10]. Symptoms of the disease are linked with tonic state of the aganglionic segment, inability of colonic movement, and relaxation in the internal anal sphincter. Approximately 80% of cases represent short-segment HD with the aganglionic part present in the rectosigmoid region. Less common forms are long-segment HD extending from the rectum, sigmoid colon, and colon up to the splenic flexure, and total colonic aganglionosis (TCA). Ultra-short segment HD (USSHD) is characterised by aganglionosis extending 2 to 4 cm proximal to the internal anal sphincter [2]. Affected infants present with distal intestinal obstruction (DIO), i.e. delay pass meconium, abdominal distention, feeding difficulties, and bilious or non-bilious vomiting. Up to 90% of newborns with HD fail to passage meconium within the first 48 hours of life, but passage of meconium during the first day of life does not exclude the disease [11]. In some cases, the infant may present life-threatening enterocolitis with fever, vomiting, diarrhoea, rectal bleeding, abdominal distension, and signs of septic shock. Other patients in whom the disease is diagnosed later complain of chronic, refractory constipation with lack of improvement after therapy, failure to thrive, or physical development delay [2].

The diagnosis requires considerable experience. Rectal biopsy is a gold standard, but it should be preceded by noninvasive tests. Contrast enema, performed without stool cleanout, is useful in showing rectosigmoid topography, excluding other diagnoses, and planning surgery. The transition zone between the aganglionic and ganglionic segment is pathognomonic of HD but does not always correspond with its true location [12]. Plain abdominal radiographs may show dilated bowel loops and decreased air in the rectum. In some cases, it may reveal the transition zone even when the contrast enema is uncertain [13]. Anorectal manometry (ARM) may also help with the diagnosis, especially for patients with USSHD. Absence of internal anal sphincter relaxation with balloon rectal distension has a high positive predictive value [14]. The diagnosis of HD is established by rectal suction biopsy and histopathological examination. Samples of rectal mucosa and submucosa should be taken 2 cm above the

level of the dentate line, and a second biopsy should be taken proximal to the first one [15]. The routine histological method is haematoxylin and eosin (H&E) staining to confirm lack of ganglion cells in the submucosal and myenteric plexi, and nerve trunk hypertrophy. Staining for acetylcholinesterase (AChE), conducted on fresh frozen specimens, demonstrates hypertrophied cholinergic nerve fibres in submucosa. However, in the case of newborns with an immature enzyme system, positive AChE may not be detected. Due to disadvantages of this method, more specific neural markers are required. Calretinin, a general marker of peripheral nervous system, is carried out as an adjunct to routine H&E methods, and its staining pattern is simple and positive in each case with ganglion cells [16]. Another useful diagnostic tool is S100, a common marker of neural tissue [2, 15].

The treatment of choice in HD is resection of the affected segment of the colon and anastomosis of the proximal bowel to the anus. Previously the operation involved two or three steps, but nowadays in most cases it consists of just one stage. Several surgical procedures, including the transabdominal approach (TAB) and transanal endorectal pull-through (TERPT), have been performed. The most common are TERPT procedures, with or without laparoscopy [17]. In systemic review and metanalysis in which totally transanal endorectal pull-through (TTERPT) and pull-through with any form of laparoscopic assistance (LAPT) were compared, differences were not found in the incidence of enterocolitis, incontinence, and chronic constipation [18]. An important problem is incomplete resection of the transition zone. In one study the occurrence of the transition zone extended up to 5 cm from the aganglionic part [19]. On the other hand, in some patients with USSHD, sufficient treatment may be diet, stool softeners, and laxatives, and if this is not sufficient, surgery should be performed [20].

Complications following pull-through include soiling, obstructive symptoms, and enterocolitis. The risk of complications increases with the length of the aganglionic intestine and is the highest in TCA [21]. Constipation after surgery, caused by stricture, persistent or acquired aganglionosis, internal anal sphincter achalasia, disordered motility in the proximal colon, or functional colonic dysmotility, affects 10–30% of patients. The diagnostic management consists of inter alia rectal examination, radiographic contrast study, and rectal biopsy [22]. Soiling may be a consequence of reduced surface of water absorption, damage of anal sphincter, lack of rectal sensation, or pseudo-incontinence secondary to constipation [2]. Regression of symptoms and improvement of bowel function are noticed with age [23]. Hirschsprung-associated enterocolitis (HAEC) may present as a fulminant, fatal disease. HAEC aetiology is not well understood, although intestinal stasis and bacterial overgrowth may play a role in development of this complication. HAEC is more likely to develop in younger children, with Down syndrome, and with long-segment disease, especially TCA. The treatment includes bowel decompression, intravenous fluid, and antibiotic therapy [2]. Historically, after surgery of HD urologic and sexual complications, specifically urinary incontinence and erectile dysfunction have been noticed. Due to new surgical techniques, more research should be carried out to evaluate urological and sexual outcomes [24].

HYPOGANGLIONOSIS

Isolated HG is a rare disorder. Usually it is detected in the transitional zone proximal to the aganglionosis [25]. The disorder is caused by hypoplasia of parasympathetic myenteric plexus and its diagnostic criteria are poorly determined [26]. Two types of disease are distinguished: congenital and acquired, which differ in histological examination. In the first case, both the density of myenteric ganglia cells and the cell size are reduced. With increasing age, the size of the cells may enlarge, in contrast to their number. Specific to acquired type is degeneration of ganglion cells and gliosis. Clinical presentation and radiological evaluation are similar to HD [27]. In comparison with HD, delay pass meconium is not reported as a characteristic symptom. In patients with HG ARM may reveal elevated anal canal pressure; however, unlike HD, rectoanal reflex inhibition is present [28]. Suction rectal biopsy is insufficient in HG diagnostics due to the presence of ganglion cells within the deeper layers of the gut wall. The disease can affect different parts of the intestine, i.e. the small intestine or colon, isolated to the left colon or rectosigmoid [29]. The diagnosis is made on the basis of multiple, full thickness biopsies of the colon. Characteristic microscopic features are small ganglia composed of one or two ganglion cells with significantly reduced neuropil number. H&E-stained sections are sufficient to make a diagnosis; only in exceptional cases are silver-stained preparations of en face thick sections or enzyme histochemistry used [26]. Management comprises the resection of the affected segment with colostomy or ileostomy formation. In severe cases, jejunostomy or bowel transplant may be required. Enterocolitis and constipation, requiring redo of pull-through procedures for residual disease, are the most frequent complications reported after HG surgery. Studies show that outcomes depend on the length of the affected bowel, time of use of total parenteral nutrition, and associated infections [30, 31].

INTESTINAL NEURONAL DYSPLASIA

IND is an uncommon cause of bowel obstruction in neonates and infants. The IND classification includes: very rare with immature or absent sympathetic innervation type A, and more frequent with submucosal hyperganglionosis in the colon – type B. Due to the clinical relevance, only IND type B will be described (> 95% of

IND cases). Similarly to HG, IND may be detected in the transitional zone proximal to the aganglionic segment in HD [16]. IND usually presents with chronic constipation in childhood [32]. The criterion for the diagnosis of IND is the presence of giant ganglia (containing > 8 ganglion cells per ganglion) in more than 20% of at least 25 ganglia assessed enzyme–histochemically stained (lactate dehydrogenase) in 15 μm-thick frozen sections [33]. The diagnosis should be made only below the age of one year, due to the normal occurrence of giant ganglia in infants. Treatment of IND is primarily conservative, but in some cases, surgery might be required, including sphincterotomy, diverting colostomy, or colectomy [34].

GANGLIONEUROMATOSIS

Ganglioneuromatosis is an extraordinary disorder of the enteric nervous system and refers to the diagnosis of hamartomatous polyposis in children and hyperplasia of the myenteric plexus and the enteric nerve fibres in adults [35]. Several genetic syndromes are associated with ganglioneuromatosis, including neurofibromatosis-1 (NF1), Cowden syndrome (CS), and most frequently multiple endocrine neoplasia type 2B (MEN 2B). The disease is characterised by constipation or diarrhoea and sporadic chronic intestinal pseudo-obstruction; however, patients may remain asymptomatic for decades. The polypoid form may be solitary with a single polyp or with multiple lesion in the terminal ileum and colon. In diffuse form, the clinical findings are bowel wall thickening, submucosal nodularities, and strictures [36]. A histological finding of ganglioneuromatosis is hyperplasia of the submucous plexus with development of giant ganglia and a high AChE activity in contrast to IND type B [32]. The diagnosis of ganglioneuromatosis requires appropriate treatment. Surgical resection of the affected parts is necessary in symptomatic cases. Syndromes associated with the disease require special oncological and endocrine attentions [26].

CHRONIC INTESTINAL PSEUDO-OBSTRUCTION

CIPO is a syndrome characterised by the presence of recurrent episodes of clinical derangement intestine propulsive motility in the lack of obstructive lesions. The disease is rare; for instance, the incidence in Japan is estimated to be 3.7 per 1 million individuals. In childhood, symptoms often occur during the neonatal period [37]. Classification of CIPO includes the cause, areas of gastrointestinal track involvement, and histology. Due to microscopic features, CIPO is classified into the following: myopathy, neuropathy, combined myopathy and neuropathy, abnormalities of interstitial cells of Cajal, or connective tissue disorders. However, the majority of cases are classified as idiopathic because of the lack of histological abnormalities. Congenital forms are mostly sporadic, but familiar cases are also described. CIPO may be a manifestation of a variety of inheritance neuropathies and myopathies. The main causes of secondary CIPO are drug, toxins, viral infections, autoimmune, oncological, endocrine, and metabolic disorders [38]. Sufferers may reveal a broad spectrum of intestinal problems depending on the location and the degree of involvement of the gastrointestinal tract. Patients suffer from dysphagia, gastroesophageal reflux, abdominal pain, vomiting, abdominal distension, constipation or diarrhoea, and involuntary weight loss [38, 39]. Diagnosis of CIPO is based on imaging studies and manometry evaluation, and occasionally, full-thickness bowel biopsies. Dilated stomach and bowel with air-fluid level are common radiographic signs. Contrast studies are necessary to exclude the anatomical obstruction. Manometry studies may reveal abnormal strength and coordination of contractions. Full-thickness biopsies are not always performed but may be helpful in identifying abnormalities [40]. Treatment of CIPO remains extremely challenging and obligates multi-disciplinary management including pharmacological therapy (non-opioid analgesics, antibiotics, and prokinetics), nutritional support with enteral nutrition or parenteral nutrition, and in exceptional circumstances surgery. In secondary forms, if possible, causal treatment should be included [19]. Intestinal failure, small intestinal bacterial overgrowth (SIBO), central line-associated bloodstream infections, and sepsis are the most common complications affecting these patients.

CONCLUSIONS

Gastrointestinal motility disorders in children are a group of various diseases with serious prognosis. Diagnosis and treatment require the cooperation of doctors of many specialties: paediatricians, gastroenterologists, surgeons, and pathologists. A greater awareness of these clinical conditions would help to improve the patients' care. Nevertheless, further research is needed in this field.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Schärli AF. Standardization of terminology of intestinal innervation disorders. Pediatr Surg Int 1995; 10: 440.
2. Chhabra S, Kenny SE. Hirschsprung's disease. Surgery 2016; 34: 628-632.
3. Godbole K. Many faces of Hirschsprung's disease. Indian Pediatr 2004; 41: 1115-1123.
4. Teerlink CC, Bernhisel R, Cannon-Albright LA, et al. A population-based description of familial clustering of Hirschsprung disease. J Pediatr Surg 2018; 53: 1355-1359.
5. Sribudiani Y, Chauhan RK, Alves MM, et al. Identification of Variants in RET and IHH Pathway Members in a Large Family With

History of Hirschsprung Disease. Gastroenterology 2018; 155: 118-129.
6. Butler Tjaden NE, Trainor PA. The developmental etiology and pathogenesis of Hirschsprung disease. Transl Res 2013; 162: 1-15.
7. Shin JG, Seo JY, Seo JM, et al. Association analysis of NOX5 polymorphisms with Hirschsprung disease. J Pediatr Surg 2019; 54: 1815-1819.
8. Shen Q, Zhang H, Su Y, et al. Identification of two novel PCDHA9 mutations associated with Hirschsprung's disease. Gene 2018; 658: 96-104.
9. Jaroy EG, Acosta-Jimenez L, Hotta R, et al. "Too much guts and not enough brains": (epi)genetic mechanisms and future therapies of Hirschsprung disease – a review. Clin Epigenetics 2019; 11: 135.
10. McKeown SJ, Stamp L, Hao MM, et al. Hirschsprung disease: a developmental disorder of the enteric nervous system. Wiley Interdiscip Rev Dev Biol 2013; 2: 113-129.
11. Bradnock TJ, Knight M, Kenny S, et al. Hirschsprung's disease in the UK and Ireland: incidence and anomalies. Arch Dis Child 2017; 102: 722-727.
12. Stranzinger E, DiPietro MA, Teitelbaum DH, et al. Imaging of total colonic Hirschsprung disease. Pediatr Radiol 2008; 38: 1162-1170.
13. Pratap A, Gupta DK, Tiwari A, et al. Application of a plain abdominal radiograph transition zone (PARTZ) in Hirschsprung's disease. BMC Pediatr 2007; 7: 5.
14. Meinds RJ, Trzpis M, Broens PMA. Anorectal manometry may reduce the number of rectal suction biopsy procedures needed to diagnose Hirschsprung disease. J Pediatr Gastroenterol Nutr 2018; 67: 322-327.
15. Muise ED, Cowles RA. Rectal biopsy for Hirschsprung's disease: a review of techniques, pathology, and complications. World J Pediatr 2016; 12: 135-141.
16. Szymańska S, Markiewicz-Kijewska M, Pyzlak M, et al. Pathogenesis of chronic constipation in a Polish group of paediatric patients – an attempt to create the optimal histopathological diagnostic protocol. Gastroenterology Rev 2019; 14: 109-111.
17. Westfal ML, Goldstein AM. Pediatric enteric neuropathies: diagnosis and current management. Curr Opin Pediatr 2017; 29: 347-353.
18. Thomson D, Allin B, Long AM, et al. Laparoscopic assistance for primary transanal pull-through in Hirschsprung's disease: a systematic review and meta-analysis. BMJ Open 2015; 5: e006063.
19. Kapur RP. Histology of the Transition Zone in Hirschsprung Disease. Am J Surg Pathol 2016; 40: 1637-1646.
20. Hong SM, Hong J, Kang G, et al. Ultrashort-segment Hirschsprung's disease complicated by megarectum: A case report. J Pediatr Surg Case Rep 2014; 2; 385-387.
21. Laughlin DM, Friedmacher F, Puri P. Total colonic aganglionosis: a systematic review and meta-analysis of long-term clinical outcome. Pediatr Surg Int 2012; 28: 773-779.
22. Langer JC, Rollins MD, Levitt M, et al. Guidelines for the management of postoperative obstructive symptoms in children with Hirschsprung disease. Pediatr Surg Int 2017; 33: 523-526.
23. Yanchar NL, Soucy P. Long-term outcome after Hirschsprung's disease: patients' perspectives. J Pediatr Surg 1999; 34: 1152-1160.
24. Versteegh HP, Johal NS, de Blaauw I, et al. Urological and sexual outcome in patients with Hirschsprung disease: A systematic review. J Pediatr Urol 2016; 12: 352-360.
25. Gfroerer S, Rolle U. Pediatric intestinal motility disorders. World J Gastroenterol 2015; 21: 9683-9687.
26. Kapur RP. Pathology of Intestinal Motor Disorders in Children. Surg Pathol Clin 2010: 3: 711-741.
27. Taguchi T, Masumoto K, Ieiri S, et al. New classification of hypoganglionosis: congenital and acquired hypoganglionosis. J Pediatr Surg 2006; 41: 2046-2051.
28. Markiewicz-Kijewska M. Organiczne przyczyny zaparcia stolca. In: Gastroenterologia dziecięca – podręcznik do specjalizacji, Socha P, Lebensztejn D, Kamińska D. Media-Press, Warszawa 2016; 67-77.
29. Sreedher G, Garrison A, Novak R, et al. Congenital intestinal hypoganglionosis: A radiologic mimic of Hirschsprung's disease. Radiol Case Rep 2018; 14: 171-174.
30. Schäppi MG, Staiano A, Milla PJ, et al. A practical guide for the diagnosis of primary enteric nervous system disorders. J Pediatr Gastroenterol Nutr 2013; 57: 677-686.
31. Dingemann J, Puri P. Isolated hypoganglionosis: systematic review of a rare intestinal innervation defect. Pediatr Surg Int 2010; 26: 1111-1115.
32. Feichter S, Meier-Ruge WA, Bruder E. The histopathology of gastrointestinal motility disorders in children. Semin Pediatr Surg 2009; 18: 206-211.
33. Knowles CH, Farrugia G. Gastrointestinal neuromuscular pathology in chronic constipation. Best Pract Res Clin Gastroenterol 2011; 25: 43-57.
34. Toledo de Arruda Lourenção PL, Terra SA, Ortolan EV, et al. Intestinal neuronal dysplasia type B: A still little known diagnosis for organic causes of intestinal chronic constipation. World J Gastrointest Pharmacol Ther 2016; 7: 397-405.
35. Chambonnière ML, Porcheron J, Scoazec JY, et al. Intestinal ganglioneuromatosis diagnosed in adult patients. Gastroenterol Clin Biol 2003; 27: 219-224.
36. Charagundla SR, Levine MS, Torigian DA, et al. Diffuse intestinal ganglioneuromatosis mimicking Crohn's disease. AJR Am J Roentgenol 2004; 182: 1166-1168.
37. Muto M, Matsufuji H, Tomomasa T, et al. Pediatric chronic intestinal pseudo-obstruction is a rare, serious, and intractable disease: a report of a nationwide survey in Japan. J Pediatr Surg 2014; 49: 1799-1803.
38. El-Chammas K, Sood MR. Chronic Intestinal Pseudo-obstruction. Clin Colon Rectal Surg 2018; 31: 99-107.
39. Pérez de Arce E, Landskron G, Hirsch S, et al. Chronic Intestinal Pseudo-obstruction: Clinical and Manometric Characteristics in the Chilean Population. J Neurogastroenterol Motil 2017; 23: 273-280.
40. Antonucci A, Fronzoni L, Cogliandro L, et al. Chronic intestinal pseudo-obstruction. World J Gastroenterol 2008; 14: 2953-2961.