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
restedsessionof disease [9]. Maternal fever int he first trimester of pregnancy may be a risk factor for HD [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 transition zone even when the contrast enema is uncertain. 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 transition zone even when the contrast enema is uncertain.
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 neurite 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 polyph 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-OBSTUCTION

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 tract 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, gastrosophageal reflux, abdominal pain, vomiting, abdominal distension, constipation or diarrhea, 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 multidisciplinary 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


