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Hirschsprung's Disease - Review of Clinical Features, Diagnosis and Treatment

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Abstract:

Introduction and purpose: Hirschsprung's disease, also known as congenital aganglionic megacolon, is a rare congenital disorder that affects the large intestine. Due to the absence of ganglion cells, the affected segment of the colon becomes narrow and unable to relax. The disease is present from birth but may not always be immediately apparent. In this paper, we will attempt to present the current state of knowledge regarding the diagnosis and treatment of Hirschsprung's disease, based on the analysis of literature available on the PubMed platform.

Description of the state of knowledge: Hirschsprung's disease (HSCR), also known as congenital aganglionosis of the colon, involves abnormal migration, proliferation, and differentiation of neural crest cells, leading to the absence of autonomic nerve ganglia within the colon. HSCR is associated with mutations in several genes, with RET, GDNF, EDNRB and SOX10 being identified as the main causes of the disease. Mutations in the RET gene are associated with the hereditary form of Hirschsprung's disease. Symptoms of HSCR appear in newborns and may include bilious vomiting, diarrhea associated with enterocolitis, failure to pass meconium within the first 24 hours of life, impaired peristalsis, jaundice, feeding difficulties, and progressive abdominal distension.

Summary: Diagnosis is typically made based on clinical presentation, imaging studies, and biopsy. Treatment usually involves surgery to remove the affected segment of the colon and reconnect the healthy portions. Although postoperative complications are relatively common, long-term studies suggest that the majority of children with Hirschsprung's disease function well in society.

Key words: Hirschsprung's disease; Intestinal aganglionosis; HSCR; HAEC

Introduction:

Hirschsprung's disease (HSCR), named after the Danish physician Harald Hirschsprung, is also known as congenital aganglionic megacolon. It belongs to the group of neurocristopathies,[3] which are disorders caused by abnormal migration, proliferation, and differentiation of neural crest cells, leading to the absence of autonomic nerve plexuses within the colon segment.[1] It is the most common neurodevelopmental disorder of the gastrointestinal system (ENS), with a prevalence of 1 in 5,000 live births worldwide.[4] It is more frequently observed in boys.[5] The Latin name for Hirschsprung's disease is *megacolon congenitum*,[2] reflecting the characteristic dilation of the colon proximal to the affected segment. Disorders arising from the neural crest cell line lead to aganglionosis, which is the absence of nerve ganglia within the colon.[1] The classic form of Hirschsprung's disease involves the rectosigmoid region and occurs in over 80% of cases. In other cases, aganglionosis can extend even to the distal part of the small intestine. Total colonic aganglionosis is rare and associated with high mortality rates.[6] Symptoms of the disease appear in newborns. Hirschsprung's disease is often associated with other conditions such as Down syndrome, autosomal dominant nonsyndromic sensory-neural deafness, Waardenburg syndrome, neurofibromatosis, neuroblastoma, pheochromocytoma, and MEN 2B syndrome.[10] HSCR can be caused by gene mutations, and in particular, mutations in the RET, GDNF, EDNRB, and SOX10 genes have been identified as causes of HSCR. RET is a gene encoding a receptor for nerve growth factor, and mutations in this gene are associated with familial Hirschsprung's disease. The genes GDNF, EDNRB, and SOX10 are involved in various aspects of enteric nervous system cell development, and mutations in these genes are associated with sporadic HSCR.[16]

Symptoms:

The absence of nerve ganglia causes a constant narrowing of the affected segment of the large intestine. The most common symptoms of Hirschsprung's disease include disturbances in peristalsis, feeding difficulties, and progressive abdominal distension. These symptoms occur in 80% of patients in the first few months of life. Failure to pass meconium within the first 24 hours of life is present in up to 90% of newborns with HSCR. In older children, chronic progressive constipation, fecal impaction, developmental disorders, and malnutrition are the most common manifestations [7]. Other symptoms that may occur in newborns and older children with HSCR are presented in Table 1.

Symptoms of Hirschsprung's Disease:

In newborns:

- Bile vomiting
- Diarrhea associated with inflammation of the intestines
- Failure to pass meconium within the first 24 hours of life
- Disordered peristalsis, infrequent peristaltic movements
- Jaundice
- Feeding difficulties
- Progressive abdominal distension
- Tightly constricted anal sphincter with an empty rectal vault

U starszych dzieci:

- Lack of soiling
- Chronic progressive constipation
- Developmental disorders
- Fecal impaction
- Malnutrition
- Progressive abdominal distension

Table 1.[7],[8],[9]

Intestinal inflammation in Hirschsprung's disease:

In one-third of cases, instead of constipation, diarrhea associated with intestinal inflammation may occur in Hirschsprung's disease (HAEC). Both the small and large intestines can be affected by inflammation [8]. HAEC is also the most common serious postoperative complication in patients who have undergone a pull-through operation [11]. Approximately 30% of patients with HSCR will experience at least one episode of postoperative intestinal inflammation [11]. Table 2 presents the diagnostic criteria developed by Pastor et al. [12] to aid in the recognition of intestinal inflammation in HSCR.

HAEC score	Pts.
History:	
• Explosive diarrhea	2
• Diarrhea with foul-smelling stools	2
• Diarrhea with bloody stools	1
• Prior history of intestinal inflammation	1
Physical examination:	
• Explosive release of gas and stool during rectal examination	2
• Distended abdomen	1
• Decreased peripheral perfusion	1
• Lethargy and lack of energy	1
• Fever	1
Imaging studies:	
• Multiple air-fluid levels	1
• Dilated bowel loops	1
• “Sawtooth” appearance and irregular musoca	1
• “Cutoff sign” at the rectosigmoid region	1
• Pneumatosis intestinalis	1
Laboratory tests:	
• Leukocytosis	1
• Shift to the left	1
Table 2. [12] HAEC ≥ 10pts.	

Setting the cutoff point at ≥ 4 points, instead of the ≥ 10 points proposed by Pastor et al., appears to have higher sensitivity and clinical utility in detecting HAEC [11].

Classification:

Hirschsprung's disease is classified based on the length of the aganglionic segment.

• Classic short-segment form (S-HSCR) - the most common form of the disease, accounting for 75-80% of cases, affects the distal part of the sigmoid colon and rectum.

• Long-segment form (L-HSCR) - the aganglionic segment extends from the rectum to the splenic flexure, occurring in 10% of cases.

• Total colonic aganglionosis (TCA) - the rarest and most severe form of the disease, occurring in 5% of patients [14].

Diagnosis:

The diagnosis of Hirschsprung's disease should be made as early as possible, which is why the diagnostic process should begin in newborns. Early diagnosis allows for prompt initiation of appropriate treatment and helps prevent complications in later years. The diagnosis of Hirschsprung's disease (HSCR) is based on a combination of clinical, laboratory, imaging, and histological examinations.

Imaging studies are an important tool in diagnosing HSCR, although their sensitivity is only around 80% [13]. A single abdominal radiograph may reveal dilated bowel loops with fluid levels. However, a series of radiographs taken over several consecutive days after rectal contrast administration may reveal the characteristic feature of HSCR known as the "transition zone" [14].

The "transition zone" is the area where the normally innervated part of the large intestine (dilated) transitions into the aganglionic zone (narrowed). If the "transition zone" is not

visible, delayed passage of contrast material may raise suspicion of HSCR. This should be confirmed by performing an abdominal radiograph 24 hours after contrast administration [14].

Unfortunately, this type of imaging study often does not allow for the determination of the "transition zone" in newborns and infants [15]. Another diagnostic test is anorectal manometry. This test has a sensitivity of 90% in detecting HSCR, but it cannot be used in children younger than 12 months because the relaxation reflex of the internal anal sphincter may not yet be developed [14]. The most sensitive and reliable test for newborns is rectal biopsy, with a sensitivity of up to 95%. When combined with immunohistochemical studies, the sensitivity can reach nearly 100% [14,17]. There are several methods of performing different forms of biopsy to obtain tissue for examination, such as transmural, submucosal, and seromuscular biopsies. In most centers, suction biopsy is recommended as a simple, safe, fast, and cost-effective method. It does not require general anesthesia or surgical sutures [18]. Biopsies should be taken at least 2 cm above the dentate line to avoid the physiological aganglionic zone at the distal end of the rectum [19]. Suction biopsy has become the method of choice in the diagnosis of Hirschsprung's disease [18].

Treatment and prognosis:

Treatment of Hirschsprung's disease almost always requires surgical intervention. Prior to the surgical procedure, rectal irrigations are recommended to reduce the size of the intestine and prevent significant complications such as enterocolitis. In cases of uncomplicated S-HSCR, a one-stage pull-through operation can be performed. However, in the presence of HAEC or significant bowel distension, a staged reconstruction starting with a temporary decompressive colostomy is recommended [20].

The most commonly used surgical technique is laparoscopically assisted pull-through with a transanal approach [21]. The pull-through operation involves the removal of the aganglionic segment of the colon and restoration of intestinal continuity by mobilizing a healthy segment of the intestine and connecting it to the anus. Nowadays, two-stage surgery with colostomy formation is rarely performed since Hirschsprung's disease is diagnosed and treated at a young age before complications such as HAEC can develop. However, the two-stage procedure still has its application in cases of complications or total colonic aganglionosis [21].

Nearly 60% of children will experience postoperative complications. In the immediate postoperative period, up to 50% of patients may experience soiling and non-obstructive diarrhea. These symptoms often resolve within a few months [21]. Approximately 30% of patients will experience postoperative HAEC [11]. Long-term complications can be divided into those related to constipation and those related to fecal incontinence. In both cases, they significantly impact the physical and psychological well-being of the patients. Around 22%-33% of adults who have undergone surgery continue to struggle with constipation, while about 9%-19% of adults still experience fecal incontinence [22]. Postoperative care and long-term follow-up of patients are important. Over time, most children show significant improvement in terms of fecal incontinence, although this may not occur until late adolescence [23]. Despite the relatively common occurrence of postoperative problems such as symptoms of obstruction, HAEC, and fecal incontinence, long-term studies suggest that the majority of children with Hirschsprung's disease cope with these difficulties regardless of the surgical technique used [24].

Summary:

From the literature review, it is evident that Hirschsprung's disease, when diagnosed and treated early, can be well controlled. The characteristic symptoms aid in early diagnosis, which is crucial to avoid numerous complications, with Hirschsprung-associated enterocolitis (HAEC) being one of the most serious. Continuously improving surgical techniques allow for favorable treatment outcomes and minimize the need for reoperations. Patients with Hirschsprung's disease can lead normal lives and function properly in society.

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