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HIRSCHSPRUNG'S DISEASE- DIAGNOSIS, TREATMENT AND NEW THERAPEUTIC STRATEGIES

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ABSTRACT

Hirschsprung's disease (HD, HSCR) is a congenital disorder of intestinal motility characterized by aganglionosis. It is the absence of ganglion cells in the nerve plexuses of the large intestine. It leads to peristalsis disorders and functional obstruction. The disease most often manifests itself in the neonatal period as delayed meconium passage, abdominal distension, vomiting, and symptoms of obstruction. Confirmation of the diagnosis requires a rectal biopsy with histopathological evaluation. Treatment consists of surgical removal of the aganglionic segment of the intestine and restoration of the continuity of the gastrointestinal tract. The choice of surgical method depends mainly on the surgeon's preference and the experience of the center. A common complication is Hirschsprung-associated enterocolitis (HAEC), which may occur before or after surgery. Research is currently underway on the use of cell therapy in the treatment of HD. The review presents the epidemiology, pathogenesis, diagnosis, and current therapeutic strategies for Hirschsprung's disease, with particular emphasis on recent reports from the scientific literature. We highlight also new directions in research and therapeutic perspectives.

Aim of this study: The objective of this study is to summarise the latest information on Hirschsprung's disease, including research on cell therapies and treatments aimed at tissue regeneration.

Materials and methods: A literature review was conducted using the professional PubMed database. Articles published between 2018 and 2025 were included. The searches included combinations of the keywords: “Hirschsprung's disease,” “pediatric surgery,” “aganglionosis,” and “stem cell therapy”.

KEYWORDS

Hirschsprung Disease, Pediatric Surgery, Aganglionosis, Stem Cell Therapy

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Introduction

Hirschsprung's disease (HD, HSCR) is a congenital malformation of the large intestine characterized by the absence of ganglion cells in the nerve plexuses of the intestinal wall, leading to motor disorders, functional obstruction, and secondary dilation of the intestine proximal to the aganglionic segment. The main role in the pathogenesis of this disease is played by the abnormal development of the enteric nervous system (ENS) originating from the neural crest cells [1]. In Hirschsprung's disease, intestinal neurons do not migrate properly during embryonic development, leading to a lack of nerve ganglia in the Auerbach and Meissner plexuses in the terminal segment of the large intestine. This segment remains in constant spasm, causing local functional obstruction [2].

HD is most commonly diagnosed in the neonatal period and early childhood. The standard treatment is surgical removal of the aganglionic segment of the intestine and connection of the healthy intestine to the anus (pull-through procedure). This procedure is considered the treatment of choice for most patients [3]. Postoperative complications remain a common problem. Research is currently underway on the use of cell therapies in the treatment of HD and tissue regeneration [4].

Pathogenesis

The pathogenesis of HD is based on impaired migration of enteric neural crest cells (ENCCs) during the embryonic period. ENCCs migrate from the cervical spine toward the distal intestine. Failure of this migration leads to aganglionosis of the terminal intestine [5].

The RET proto-oncogene is a key gene in ENS development. It encodes a tyrosine kinase receptor that reacts with ligands from the neurotrophin family, including GDNF (glial cell line-derived neurotrophic factor). RET mutations are the most common cause of HD and lead to signaling defects that prevent the normal proliferation, migration, and differentiation of ENCCs. Studies have shown that some mutations inhibit RET protein function even in the presence of a normal copy of the gene [6].

Other genes and pathways are also involved in the pathogenesis of HD. The endothelin B receptor and its ligand endothelin 3 (EDNRB/EDN3) are important in the development of ENS. Interactions with RET affect the positioning and survival of ENCCs. Signal deficiencies in this system may exacerbate aganglionosis [7]. Studies have shown that mutations in common transcription regulators (SOX10, GATA2) and disorders in the common RET–EDNRB regulatory network also contribute to signaling pathway differentiation and the risk of developing HD [8]. Some cases without coding mutations are explained by variability in RET regulatory regions (e.g., rs2435357), which is strongly associated with susceptibility to HD [9].

In addition to genetic factors determining the mechanisms of ENCC migration and differentiation, epigenetic modifications (DNA methylation, miRNA regulation) and cellular interactions in the intestinal microenvironment modulate the expression of genes important for ENS development and may influence the pathogenesis of Hirschsprung's disease. The absence of neurons in aganglionic segments causes an inability to relax the muscles and pass intestinal contents, resulting in proximal dilation and secondary peristaltic disorders. Clinically, this manifests as delayed meconium passage, constipation, abdominal pain, and symptoms of obstruction [1].

Epidemiology

The incidence of Hirschsprung's disease is approximately 1 case per 5,000 live births worldwide. Local differences between regions and populations are possible. One of the most recent epidemiological studies from France showed that the average incidence of HSCR in that country was 17.26 cases per 100,000 live births between 2012 and 2023, which corresponds to approximately 1.7/10,000 live births. HD is more common in boys and is often associated with genetic syndromes such as Down syndrome [2].

HSCR is a disease diagnosed mainly in the neonatal period and early childhood, as confirmed by clinical studies and medical records. In a French study, the median age of diagnosis was approximately 3 months and most cases were diagnosed before the age of 3 months, more frequently in boys (approximately 4:1) [10].

Symptoms

Symptoms Hirschsprung's disease usually manifests itself in the first days of life. The classic triad of symptoms includes delayed meconium passage (no first meconium more than 24–48 hours after birth), abdominal distension, and vomiting. If the disease is not diagnosed immediately after birth, the predominant symptoms in infants and young children are chronic constipation, weight gain disorders, lack of appetite, and periodic episodes of bloating and abdominal pain [11].

The most serious complication of Hirschsprung's disease is Hirschsprung-associated enterocolitis (HAEC). It is an inflammatory bowel disease associated with dysmotility and disturbances in the intestinal microbiota and intestinal barrier. Symptoms of HAEC include fever, abdominal distension, diarrhea, bloody stools, vomiting, general deterioration of health, lethargy, and dehydration [12].

A meta-analysis of the clinical presentation of HD in premature infants found abdominal distension in 83% of cases, vomiting in 61%, bilious vomiting in 54%, delayed meconium passage in 48%, constipation in 44%, and enterocolitis in 13%. This reflects the diverse spectrum of symptoms in patients with HD [13].

Diagnosis

The diagnosis of Hirschsprung's disease requires histopathological confirmation of aganglionosis. A rectal biopsy is the gold standard in the diagnosis of HD. It shows a lack of ganglion cells in the Meissner and Auerbach plexuses and often accompanying changes, such as excessive cholinergic innervation. We distinguish between suction rectal biopsy (SRB) and full-thickness biopsy. SRB is the most commonly used diagnostic technique with high specificity and sensitivity when interpreted correctly [14].

Research indicates that digital histopathological analysis supported by machine learning can improve the precision of identifying changes such as cholinergic hyperinnervation, which may further increase the accuracy of HD diagnosis [14].

Delayed diagnosis of HD, defined as diagnosis after 12 months of age, may lead to poorer clinical outcomes, an increased number of surgical procedures and a more complicated clinical picture [15].

Surgical treatment methods

The most important element of Hirschsprung's disease treatment is surgical removal of the aganglionic segment and pull-through, i.e., connecting the healthy intestine to the anus or rectum, which restores intestinal patency and normalizes motor functions [16].

The development of surgical techniques aims to reduce the invasiveness of procedures, improve functional outcomes and reduce complications. Standard methods include the Swenson, Soave and Duhamel techniques. The Swenson method involves complete resection of the aganglionic segment with end-to-end anastomosis. The Soave method is an endorectal resection of the mucosa, leaving a muscular “cuff.” The Duhamel method involves preserving part of the aganglionic rectum and performing an anastomosis with simple double lumen formation. The choice of technique depends on the length of the diseased segment of the intestine, the patient's age, and the surgeon's experience and preferences [3].

Laparoscopy

In recent years, laparoscopic and transanal approaches have been used more and more frequently. A common minimally invasive method for patients with a short aganglionic segment is transanal endorectal pull-through (TEPT). It is a minimally invasive method with good safety and efficacy results, although it is associated with the risk of complications such as enterocolitis or the need for additional procedures. It allows for single-stage treatment via transanal access without laparotomy. Retrospective studies involving a large group of patients have shown that TEPT is an effective method with a low complication rate, although there are still reports of the risk of enterocolitis and the need for reoperation due to residual obstruction [17].

A popular technique with less surgical trauma and shorter recovery time is laparoscopic pull-through [18]. Robotic surgical techniques are increasingly being explored in patients with Hirschsprung's disease, especially where surgical precision is critical (e.g., in cases of late diagnosis or requiring reoperation). Data indicate that robot-assisted procedures may reduce operative blood loss, although the clinical advantage over laparoscopy has not been conclusively confirmed [19].

Modern comparative analyses evaluated both conventional and minimally invasive techniques. A meta-analysis comparing the open Duhamel (OD) method, laparoscopic-assisted Duhamel (LD), TEPT and laparoscopic-assisted endorectal resection (LEPT) showed differences in bleeding, operating time and complications, suggesting the importance of choosing the right surgical technique. It was shown that the smallest intraoperative blood loss occurred during LEPT. The shortest operating time was associated with the TEPT method. Intestinal obstruction was also least common with TEPT. The time to recovery of gastrointestinal function and length of hospital stay were the shortest with LEPT. The lowest incidence of complications was associated with the LEPT method. The incidence of anastomotic strictures was lower in patients undergoing LEPT compared to TEPT. Anastomotic leakage and infection were least common in the

LEPT group. However, LEPT has certain disadvantages in clinical practice, such as the weak abdominal walls of children and the high skill requirements for surgeons [20].

Modern minimally invasive techniques, such as laparoscopy and robotic surgery, are becoming increasingly popular in the treatment of HD. A systematic review from 2025 showed that robotic pull-through procedures are a safe alternative to laparoscopic techniques, especially in cases of late diagnosis, although their superiority in standard infant cases has not been conclusively proven [19].

In addition to the surgical procedure itself, a proper pre-, peri-, and postoperative care plan is crucial. Bowel management before surgery, patient preparation and postoperative care are important factors that influence the speed of recovery and minimize complications. Perioperative care includes bowel preparation, including rectal irrigation. Postoperative support can affect surgical outcomes by shortening recovery time [21].

Postoperative complications

Despite advances in surgical techniques, postoperative complications remain a significant clinical problem, affecting patients' quality of life and long-term treatment outcomes.

Hirschsprung-associated enterocolitis (HAEC) is one of the most common and serious postoperative complications. In a retrospective analysis of 304 patients, approximately 29.9% experienced HAEC in the postoperative period, and early episodes (<3 months) were associated with poorer nutritional status, defecation disorders, and reduced quality of life. The risk of recurrent episodes was associated with a long aganglionic segment and a high complication class in the first 30 days after surgery [22].

Treatment of HAEC involves intensive medical care, hydration, antibiotic therapy, and, if necessary, surgical interventions or mechanical maneuvers in the case of anatomical complications. In some cases, botulinum toxin is used to relieve sphincter tension and reduce recurrent obstructive symptoms [23,24]. Hirschsprung-associated enterocolitis is described in more detail later in this review.

Studies have shown that postoperative complications have a significant impact on bowel function after pull-through. A prospective study from 2025 showed that both mild and severe postoperative complications correlate with poorer bowel function outcomes as assessed by the Bowel Function Score (BFS). A longer aganglionic segment of the intestine and formula feeding rather than breastfeeding were independently associated with poorer functional outcomes [25].

In addition to HAEC and functional disorders, other common complications are also described. Constipation is common after surgery and is often associated with the surgical technique and the length of the aganglionic segment [26]. The occurrence of obstruction or obstructive symptoms is due to tight anastomosis or motor disorders [23]. In many large cohorts, fecal incontinence and sphincter control disorders associated with anatomical or neuromotor problems are observed [27].

Risk factors for postoperative complications

Retrospective analyses show that late surgery (>1 year) increases the risk of unplanned reoperations, while early surgery is associated with a higher risk of late stenosis [27]. In addition, the length of the aganglionic segment significantly predisposes to HAEC complications and bowel dysfunction [22].

Malnutrition prior to surgery and low albumin concentration are associated with a higher risk of early complications and a more severe course of HAEC after surgery [22]. Appropriate optimization of nutritional status prior to surgery may improve prognosis.

Patients should be regularly monitored for symptoms of constipation, HAEC, fecal incontinence, and obstruction after surgery. Clinical symptoms, laboratory and imaging tests, as well as functional bowel tests are evaluated.

Hirschsprung-associated enterocolitis (HAEC)

Hirschsprung-associated enterocolitis is the most common and most serious complication of HSCR, which can occur both pre- and postoperatively [28]. The incidence of HAEC varies and depends on the diagnostic criteria and the population studied [29].

Risk factors for HAEC include a longer segment of intestine without nerve ganglia, previous episodes of enterocolitis, preoperative malnutrition, respiratory infections, and Down syndrome [30].

The pathogenesis of HAEC is multifactorial and involves intestinal motility disorders associated with a lack of innervation, leading to intestinal stasis and microbial dysbiosis. In addition, mucosal barrier impairment and abnormal immune response promote the development of inflammation [31].

Symptoms of HAEC include fever, abdominal distension, diarrhea, vomiting, abdominal pain, and septic symptoms. The presentation of these symptoms varies, which often delays diagnosis. Diagnosis is primarily based on the clinical picture, but imaging and laboratory methods may also be used to rule out other causes of enteritis [28].

HAEC is treated with fluid resuscitation and correction of electrolyte imbalances, broad-spectrum antibiotic therapy, enemas and bowel irrigation, and in more severe cases, treatment in an intensive care unit. There are no clear, widely accepted standards for the treatment of HAEC, which indicates the need for further clinical research [28].

Retrospective studies suggest that interventions such as rectal botulinum toxin, consistent postoperative irrigation, or careful monitoring of bowel patency may reduce the frequency of HAEC episodes [32].

Despite numerous publications, the etiopathogenesis of HAEC is not fully understood. Current models point to a complex interaction between ENS dysfunction, microbiota, intestinal barrier, and immune response. The lack of clear therapeutic recommendations highlights the need for further research [12].

Long-term results

Long-term outcomes in patients with HSCR include bowel function (fecal incontinence, constipation), quality of life, urological and sexual function, and psychosocial complications. Approximately 10–20% of patients experience persistent intestinal motor problems even many years after surgery, which affects their daily lives and mental health [33].

Systematic studies show that patients with HSCR aged > 10 years often experience fecal incontinence and constipation at a significantly higher rate than the general population. A 2020 meta-analysis found that approximately 20% of patients have fecal incontinence, approximately 14% experience chronic constipation, and there are also problems with bladder function [34].

The results of a cohort study (35-year follow-up) showed that bowel function improves with age—older patients had better stool control than younger patients. However, some patients still experience symptoms such as soiling and reduced awareness of the need to defecate [33].

Different surgical techniques (Duhamel, Soave, TEPT) may affect bowel function. The TEPT technique tends to yield good BFS (Bowel Function Score) results, but these may vary between centers and types of HSCR [35].

Quality of life (QoL) in adulthood after HSCR treatment is determined by both bowel function and psychosocial aspects. Studies have shown that patients with HSCR have lower GIQLI (Gastrointestinal Quality of Life Index) scores than healthy individuals. It has been observed that women and patients with longer aganglionic segments have poorer QoL scores [36].

A systematic review from 2025 analyzing outcomes ≥ 16 years after treatment showed that patients have a significantly higher risk of constipation and soiling compared to the control population. Longer disease duration and repeat surgeries correlated with poorer BFS outcomes. Differences in quality of life outcomes were dependent on gender and clinical characteristics [36].

In addition to bowel dysfunction and quality of life impairment, long-term complications include lower urinary tract dysfunction, sexual problems in adults, psychological and social consequences of chronic illness, and internal inflammatory bowel disease. An interdisciplinary approach is crucial in the care of patients many years after treatment [37].

New directions and therapeutic prospects

One of the most promising areas of current research is cell therapy, which aims to restore the function of missing intestinal neurons through the transplantation of neural progenitor cells or stem cells. Preclinical studies and conceptual reviews indicate that various cell sources, such as enteric nervous system (ENS) progenitors, induced pluripotent stem cells (iPSCs), and mesenchymal stem cells, have the potential to integrate and reproduce ENS elements [4].

The 2025 review suggests that future treatments for HSCR may include more precise diagnostic techniques and treatments focused on tissue regeneration. Research on the use of neural progenitor cells or ENS cells is gaining empirical ground in animal and in vitro models. This research represents the future of therapy, potentially allowing for neural reorganization in aganglionic areas of the intestine [3].

Currently, surgical treatment remains the standard of care. There has been an optimization of the timing of surgical intervention and a multidisciplinary approach combining gastroenterology, dietetics, and rehabilitation support, which may improve functional outcomes and quality of life for patients [38].

A growing number of studies also emphasize the need for long-term assessment of adult patients after HSCR surgery, including assessment of quality of life, intestinal, urological, and sexual dysfunction, indicating a continued need for therapeutic support during adulthood [36].

Many problems remain unresolved. Translating cell therapies into clinical practice requires overcoming technical, immunological, and ethical barriers. Standardization of treatment and diagnostic protocols is needed, particularly in the area of research into the long-term effects of postoperative treatment. A deeper understanding of the molecular mechanisms of the disease will enable the development of genetically or molecularly targeted therapies. Multiscale clinical trials are crucial for further progress, especially in the context of regenerative and immunological therapies.

Conclusions

Hirschsprung's disease (HSCR, HD) is a congenital disorder of the gastrointestinal tract characterized by the absence of ganglion cells in the distal intestine, leading to impaired peristalsis and intestinal obstruction [2].

This is a complex developmental disorder resulting from impaired migration, proliferation, and differentiation of neural crest cells in the intestine, leading to a lack of ganglion cells in the distal intestine. The main molecular determinants of the disease are mutations and polymorphisms in the RET gene and in elements of signaling pathways associated with it, such as EDNRB/EDN3 and transcription regulators. Genetic and epigenetic interactions of the network influence the final phenotype of the disease, making HD a disorder with a complex pathogenesis [6,9].

Data from studies published between 2018 and 2025 confirm that Hirschsprung's disease is a rare but significant congenital malformation of the gastrointestinal tract, with an incidence of approximately 1–1.7 cases per 10,000 live births, with a predominance in boys and a predominance of diagnoses in infancy. Further studies in populations from different regions remain crucial to better understand the epidemiology of this disease [10].

Typical symptoms of HSCR include delayed meconium passage, abdominal distension, vomiting, chronic constipation and episodes of enterocolitis. Early diagnosis is crucial to prevent complications, particularly HAEC, which can lead to severe systemic illness and life-threatening conditions [12,13].

The diagnosis of Hirschsprung's disease is a multi-step process involving clinical evaluation, functional tests, imaging and, most importantly, histopathological biopsy of the rectum as the gold standard for diagnosis. Advances in digital pathology and molecular diagnostics techniques may contribute to greater accuracy and earlier detection of the disease, which is crucial for effective treatment and improved quality of life for patients [14].

Surgical treatment of Hirschsprung's disease has undergone significant development in recent years, ranging from classic pull-through resections to advanced minimally invasive and robotic approaches. The choice of surgical technique should take into account the characteristics of the disease, the patient's age, and the experience of the center. Despite these advances, the management of postoperative complications and long-term care remain key challenges. High-quality clinical trials and meta-analyses are essential for the further improvement of surgical treatment of HD [3,19].

Postoperative complications following treatment of Hirschsprung's disease remain a common problem that affects bowel function, the frequency of inflammatory bowel disease recurrence, and the patient's quality of life. The most common complications are HAEC and bowel dysfunction, which are related to the length of the aganglionic segment, age at surgery, and nutritional status. Early identification of risk factors, preoperative optimization, and long-term monitoring are key to improving treatment outcomes [22,25].

HAEC is a serious clinical problem in the care of patients with HSCR. Further research is needed on the standardization of diagnosis and treatment and the search for targeted prevention strategies [12].

The long-term results of HSCR treatment remain the subject of research. Systematic analysis has shown that patients who have undergone surgical treatment may experience constipation, fecal incontinence, and reduced quality of life in adulthood, which highlights the need for ongoing care and monitoring [34]. Factors such as age at the time of surgery, the skills of the center performing the procedurę and the specifics of the surgical technique used are important. Studies suggest that early surgical intervention may reduce the risk of HAEC, although it does not clearly affect long-term functional outcomes [38].

Hirschsprung's disease remains one of the most clinically important congenital disorders of the digestive system. In recent years, scientific research has focused on an interdisciplinary approach, combining genomics, cell therapies, and digital tools in diagnosis and treatment. The development of regenerative therapies and precise diagnostic tools offers hope for more effective and less invasive treatment methods in the future [4].

Research is ongoing into therapeutic strategies such as cell therapies and tissue regeneration-targeted treatments. Surgical treatment remains the standard of care for Hirschsprung's disease [3].

Disclosure

Author's Contribution

Conceptualization: Agnieszka Bajkacz and Izabela Polakowska; Methodology: Agnieszka Bajkacz, Izabela Polakowska and Wiktoria Marzec; Formal analysis: Agnieszka Bajkacz and Wiktoria Marzec; Resources: Agnieszka Bajkacz, Izabela Polakowska and Wiktoria Marzec; Writing- original Draft Preparation, Agnieszka Bajkacz, Izabela Polakowska, Wiktoria Marzec; Writing-Review and Editing, Agnieszka Bajkacz Izabela Polakowska and Wiktoria Marzec; Visualization: Agnieszka Bajkacz, Izabela Polakowska and Wiktoria Marzec; Supervision: Agnieszka Bajkacz;

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