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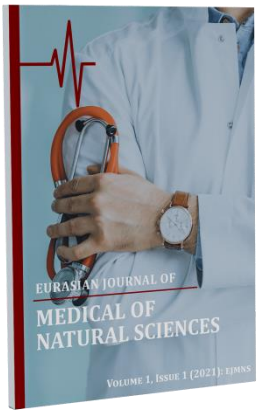

MODERN APPROACHES TO THE DIAGNOSIS AND TREATMENT OF HIRSCHSPRUNG'S DISEASE IN CHILDREN

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ABSTRACT

This review presents a systematic analysis of the literature reflecting current approaches to the study of Hirschsprung's disease in children, as well as modern methods of diagnosis and therapy of this disease. The results of the analysis showed that the issues of the pathogenesis of Hirschsprung's disease have already been studied well enough and do not cause significant disagreement, while the implementation of the latest diagnostic and surgical techniques remains a complex and controversial task. Radical one-stage operations using minimally invasive technologies are becoming increasingly popular in clinical practice. Progressive surgical approaches to the treatment of Hirschsprung's disease in newborns and young children can significantly reduce the mortality rate and improve long-term outcomes.

СОВРЕМЕННЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ И ЛЕЧЕНИИ БОЛЕЗНИ ГИРШПРУНГА У ДЕТЕЙ

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ABSTRACT

В данном обзоре представлен систематический анализ литературы, отражающей актуальные подходы к изучению болезни Гиршпрунга у детей, а также современные методы диагностики и терапии этого заболевания. Результаты анализа показали, что вопросы патогенеза болезни Гиршпрунга уже достаточно хорошо изучены и не вызывают значительных разногласий, в то время как внедрение новейших диагностических и хирургических методик остается сложной и противоречивой задачей. Радикальные одноэтапные операции с применением малоинвазивных технологий становятся все более

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популярными в клинической практике. Прогрессивные хирургические подходы к лечению болезни Гиршпрунга у новорожденных и детей младшего возраста позволяют значительно уменьшить уровень летальности и улучшить долгосрочные исходы.

БОЛАЛАРДА ГИРШПРУНГ КАСАЛЛИГИНИ ТАШХИС ҚЎЙИШ ВА ДАВОЛАШДА ЗАМОНАВИЙ ЁНДАШУВЛАР

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ABSTRACT

Мазкур шарҳда болаларда Гиршпрунг касаллигига оид илмий адабиётларнинг тизимли таҳлили, шунингдек, ушбу касалликни ўрганиш бўйича долзарб ёндашувлар, замонавий ташхислаш ва даволаш усуллари келтирилган. Таҳлил натижалари Гиршпрунг касаллиги патогенези масалалари етарлича яхши ўрганилганлиги ва жиддий ихтилофлар туғдирмаслиги, бироқ, янги ташхислаш ва жарроҳлик даволаш усулларини жорий қилиш мураккаб ва баҳсли вазифа бўлиб қолишига ишора қилади. Кам инвазив технологиялардан фойдаланган ҳолда радикал бир босқичли жарроҳлик амалиётлари клиник амалиётда тобора оммалашиб бормоқда. Чақалоқлар ва кичик ёшдаги болаларда Гиршпрунг касаллигига нисбатан прогрессив жарроҳлик ёндашувлари ўлим даражасини сезиларли даражада камайтиришга ва узоқ муддатли натижаларни яхшилашга имкон беради.

Introduction. Hirschsprung's disease is considered one of the most significant and challenging pathologies in pediatric surgery. Over the past decades, substantial progress has been made in understanding the mechanisms of its development, primarily due to advances in molecular genetics and new discoveries in the field of pathomorphology.

The new stage of advancing the diagnosis and treatment of Hirschsprung's disease is largely associated not only with a deeper understanding of the pathophysiology of the condition and the possibility of earlier detection but also with significant improvements in surgical techniques. Surgical interventions have evolved from multi-stage approaches to primarily radical operations [1, 2, 3]. In recent years, minimally invasive methods of radical correction have gained increasing popularity. For newborns and young children, these progressive treatment methods significantly reduce mortality rates and enhance the

effectiveness of therapy. An analysis of contemporary literature helps to better understand the current state of the problem.

Etiology. Hirschsprung's disease is associated with cellular and molecular disruptions in the formation of the enteric nervous system, as well as impaired migration of neural crest cells into the developing intestine. These pathological changes form the foundation of the disease's pathogenesis. The first neuroblasts appear in the esophagus of the fetus at the fifth week of gestation, and by the 12th week, their migration spans the entire intestine in a cranio-caudal direction. The clinical variability of the disease is caused by numerous possible abnormalities in the development of the intestinal nervous system, as well as differences in the timing of neuroblast migration arrest. When migration halts early, an extensive aganglionic segment is formed [2].

Additionally, factors such as extracellular matrix abnormalities, disturbances in neurotrophic factors, and various molecular damages to nerve cells can contribute to the development of the disease.

Genetic factors. The hereditary predisposition to Hirschsprung's disease is supported by an increased risk of occurrence among relatives of patients, gender predisposition, and the combination of this disease with other congenital malformations, syndromes, and chromosomal abnormalities. Genetic studies have identified mutations in ten different genes associated with the development of this pathology [4]. The most common mutations include those in the RET gene (7–35% of sporadic cases), the EDNRB gene (7%), and the END3 gene (less than 5%) [3, 4, 7]. Over 20 different mutations have been described in the RET proto-oncogene, some of which are linked to specific forms of Hirschsprung's disease [3, 5].

Even when Hirschsprung's disease presents as an isolated pathology, it is often associated with congenital anomalies or syndromes such as trisomy 21 (Down syndrome), septal heart defects, congenital central hypoventilation syndrome, multiple endocrine neoplasia type 2, neurofibromatosis, and Waardenburg syndrome in 5–32% of cases [4]. Hirschsprung's disease and trisomy 21 co-occur in approximately 7% of cases. The most common associated anomalies involve the gastrointestinal tract, central nervous system, and genitourinary system [4, 5].

Thus, genetic and molecular mechanisms play a key role in the development of Hirschsprung's disease, allowing for a better understanding of the pathogenesis and approaches to its treatment.

Pathophysiology. The pathogenesis of Hirschsprung's disease is rooted in the functional obstruction of a segment of the large intestine, caused by the absence of ganglion cells in the parasympathetic nervous system. This deficit prevents the normal formation of peristaltic waves. Despite significant research efforts, the exact cause of the persistent narrowing of the aganglionic intestinal segment remains unresolved. Factors implicated in the disease's development include the absence of ganglia, excessive cholinergic innervation, a deficiency of nitric oxide synthase in nerve cells, and abnormalities in the interstitial cells of Cajal. However, a comprehensive understanding of all the causal mechanisms of this pathology remains elusive [2, 6].

Classification. The classification of Hirschsprung's disease is based on the extent of aganglionosis, which progresses proximally from the internal anal sphincter. The following forms of the disease are distinguished:

- Rectosigmoid form: Involves the rectosigmoid region (74–80% of cases).
- Subtotal form (long segment): Aganglionosis extends to the splenic flexure or transverse colon (12–22% of cases).
- Total form: Involves the entire colon and the terminal ileum (4–13% of cases).
- Additionally, ultrashort and intestinal forms are recognized. The most severe but rare variant is total intestinal aganglionosis, in which ganglion cells are absent along the entire length of the intestine, from the duodenum to the rectum [7].

Based on clinical presentation, the disease is categorized into ***uncomplicated*** and ***complicated*** forms.

Clinical Presentation. The incidence of Hirschsprung's disease is approximately 1 case per 5,000 live births. The male-to-female ratio for the rectosigmoid form is 4:1, whereas for longer segments of aganglionosis, the ratio is 1:1 or 2:1.

Improved clinical awareness and advancements in diagnostic methods have significantly reduced the age at diagnosis, with most cases now identified during the neonatal period. Typical symptoms include delayed passage of meconium, abdominal distension, bilious vomiting, and feeding difficulties [8].

In neonates with Hirschsprung's disease, delayed meconium passage occurs in 70–90% of patients within the first 24–48 hours of life. Differential diagnosis requires ruling out other conditions, such as intestinal atresia, malrotation, volvulus, meconium obstruction in cystic fibrosis, and colonic abnormalities, including meconium plug syndrome, anorectal malformations, and small left colon syndrome. Other potential causes include exposure to narcotics, electrolyte disturbances, hypothyroidism, sepsis, and extremely low birth weight. Hirschsprung's disease should be considered in all neonates with delayed passage of meconium.

In the complicated form, the disease may present as intestinal obstruction, cecal perforation, or peritonitis during the first days of life, making diagnosis more challenging. Complications can also arise later, most commonly in the form of enterocolitis, which is an almost inevitable complication of the disease.

Enterocolitis in Hirschsprung's Disease. Enterocolitis is a serious complication of Hirschsprung's disease, occurring both in the preoperative and postoperative periods. Clinical manifestations include diarrhea, abdominal distension, fever, colicky pain, signs of intoxication, hypovolemia, and loose stools, which may contain blood.

Enterocolitis can develop at any age – from the neonatal period to adulthood – regardless of whether surgical intervention or medical treatment has been performed. Recurrences of enterocolitis can occur even in the presence of a diverting stoma [7, 8].

Despite extensive research, the causes of enterocolitis in Hirschsprung's disease remain poorly understood. Various hypotheses attempt to explain its pathogenesis: physical dilation of the proximal intestinal segment, alterations in intestinal contents, infections (e.g., rotavirus or Clostridia), increased activity of prostaglandin E1, immunological dysfunction of the

intestinal mucosa, and other factors. Some studies have identified the presence of localized or systemic immunodeficiency linked to lymphocyte dysfunction [9].

Partial mechanical obstruction may serve as a trigger for enterocolitis in Hirschsprung's disease by inducing dilation of the proximal intestinal segment. This results in stasis of intestinal contents, further dilation, mucosal ischemia, and bacterial translocation. However, this theory does not explain the occurrence of enterocolitis in the distal segment of the intestine beyond a stoma, its development in the postoperative period, or its histological identification within the aganglionic segment. While the length of the aganglionic segment may be considered a factor that increases the risk of enterocolitis, research data does not confirm a significant correlation between the length of the affected segment and the frequency of this complication.

Mucin production in patients with Hirschsprung's disease is significantly reduced, with mucus secretion abnormalities observed in both aganglionic and ganglionic segments of the intestine. This indicates a compromised protective mucosal barrier even in normal-appearing intestinal segments, increasing the risk of bacterial invasion and mucosal damage. Reduced mucin secretion makes the mucosa more vulnerable to infection and may promote microbial translocation across the intestinal wall.

Secretory immunoglobulin A (IgA) plays a critical role in intestinal immune defense, preventing bacterial penetration and protecting the mucosa from invasion. The first episode of enterocolitis can cause significant disruption to local immunity, leading to chronic changes in the intestinal mucosa and an increased risk of recurrent episodes. This may explain the recurrence of enterocolitis even after successful surgical interventions or the creation of a stoma [7, 9].

Macrophages in the intestinal muscular layer play a key role in inflammatory processes. Their activity during inflammation disrupts the function of the interstitial cells of Cajal, which are responsible for coordinating peristaltic movements in ganglionic segments of the intestine. This, in turn, exacerbates intestinal stasis, promotes bacterial overgrowth, and, combined with impaired mucus secretion, enhances microbial translocation [8].

Genetic factors also contribute to the development of enterocolitis in patients with Hirschsprung's disease. For example, children with Down syndrome have a nearly 50% risk of developing enterocolitis, with many experiencing multiple episodes [7, 8]. The presence of other congenital anomalies also increases the frequency of this complication.

Microbiological studies often identify *Clostridium difficile* as a pathogen in patients with enterocolitis associated with Hirschsprung's disease [7, 8, 9].

Diagnosis. In recent years, due to increased vigilance among pediatricians and pediatric surgeons, Hirschsprung's disease has been diagnosed as early as the neonatal period. The disease should be suspected in infants with delayed passage of meconium (beyond 24–48 hours after birth), abdominal distension, bilious vomiting, and feeding difficulties. Signs of enterocolitis in a neonate should also prompt an evaluation to exclude Hirschsprung's disease. Complicated cases of the disease may present as low intestinal obstruction with intact bowel integrity, cecal or ascending colon perforation, or peritonitis during the first days of life.

In older children, the clinical presentation often includes chronic constipation alternating with episodes of enterocolitis, abdominal distension, and delayed physical development.

Diagnostic methods include *contrast enema (irrigography), anorectal manometry, full-thickness rectal biopsy*, and *mucosal biopsy* of the rectum for histochemical or immunohistochemical analysis.

Radiographic Examination. A plain abdominal X-ray in a child with Hirschsprung's disease may show pronounced intestinal pneumatosis and dilation of segments of the colon proximal to a narrow distal segment involving the rectum and sigmoid colon. A transition zone between the narrowed and dilated segments is often visible. In cases of severe enterocolitis, signs of toxic megacolon may be evident on X-ray [10, 11].

In complicated forms of Hirschsprung's disease, radiographic findings may vary depending on the clinical stage. These may include low intestinal obstruction or perforation of a hollow organ, with the presence of free intraperitoneal gas.

Contrast Enema (Irrigography). In some medical centers, irrigography is the first diagnostic test performed when Hirschsprung's disease is suspected in children presenting with symptoms of intestinal obstruction. Radiographic signs of the disease on irrigography include:

- Pathological narrowing of the distal segments of the colon.
- A transition zone with funnel-shaped dilation proximal to the affected area.
- Signs of enterocolitis and an abnormal rectosigmoid index.

In older children, the sensitivity and specificity of irrigography are 70–83%. However, in neonates, these values are significantly lower because the transition zone may be indistinct, and the typical funnel-shaped dilation of the intestine may be absent.

In cases of concurrent enterocolitis, spasms in sections of the bowel can create a false appearance of narrowing, increasing the risk of both false-positive and false-negative results in the first months of life. Furthermore, the radiographic transition zone may not correspond to the affected segment identified through biopsy, particularly in children younger than one month [7, 8, 14].

Anorectal Manometry. Anorectal manometry can be used to diagnose Hirschsprung's disease in older children. However, it poses technical challenges in neonates and is less reliable in this population [11].

Morphological Examination of Intestinal Biopsies. Morphological analysis of intestinal biopsies employs various methods, such as light microscopy with hematoxylin and eosin staining of full-thickness rectal biopsies, as well as histochemical and immunohistochemical studies of rectal mucosa. Hematoxylin and eosin staining of full-thickness biopsies reveals the absence of ganglion cells, a key diagnostic criterion for Hirschsprung's disease. Histochemical analysis demonstrates hypertrophied acetylcholine-positive nerve fibers, which confirm the diagnosis. The use of histochemical acetylcholinesterase (AChE) staining has made morphological diagnosis simpler and more reliable [7, 8, 11].

Despite the technical difficulties of performing full-thickness biopsies in neonates, mucosal rectal biopsies are easier to perform. It is important to note that the absence of ganglion cells in the distal portion of the anal canal may represent a normal variant.

Other diagnostic methods, such as enzyme activity assays (lactate dehydrogenase, succinate dehydrogenase, NADPH-diaphorase), can also be utilized. The histochemical acetylcholinesterase reaction for diagnosing Hirschsprung's disease in neonates has a sensitivity of 91% and a specificity of 100%, though false-negative results occur in approximately 8% of cases. In neonates, especially preterm or functionally immature infants, a reduced number of nerve fibers in the intestinal wall may be observed even in the presence of Hirschsprung's disease, potentially leading to false-negative results. Nonetheless, rectal biopsy remains a more sensitive and specific diagnostic method compared to contrast enema or anorectal manometry, even without additional immunohistochemical studies.

Immunohistochemical Studies. Immunohistochemistry is an important morphological method based on specific antigen-antibody reactions. Major immunohistochemical methods include direct and indirect immunofluorescence, as well as direct and indirect enzyme immunohistochemistry. Various immunohistochemical markers and stains are widely used to diagnose Hirschsprung's disease and other intestinal disorders. The most commonly utilized marker is calretinin [7, 15, 16].

Calretinin. Calretinin is a calcium-binding protein that plays a crucial role in the organization and function of the enteric nervous system. It is involved in maintaining calcium homeostasis within the body. Ganglion cells and their derivatives secrete calretinin from the submucosal and myenteric plexuses in normal ganglionic intestines. However, calretinin is absent in aganglionic segments in Hirschsprung's disease. The absence of calretinin staining in nerve fibers also indicates its absence in corresponding nerve cells, making this a valuable diagnostic test for identifying aganglionic segments.

The advantage of this method is its ability to detect various innervation abnormalities by staining all existing nerve cells, including immature and small ones. However, diagnosing hypertrophy of nerve fibers requires additional markers and methods.

Treatment. The confirmation of a Hirschsprung's disease diagnosis is an indication for surgical treatment.

Advancements in neonatal resuscitation, anesthesia, and newborn care over the past decades have enabled pediatric surgeons to successfully perform single-stage corrective surgeries for Hirschsprung's disease in cases without complications or total aganglionosis. In most instances, the diagnosis is established during the neonatal period, and many medical centers employ single-stage corrections with excellent outcomes. The primary contraindications for primary transanal correction include severe congenital anomalies, significant enterocolitis, pronounced dilation of the proximal intestine, and serious systemic conditions.

During surgery, the affected aganglionic intestinal segment is mobilized transanally and resected 10 cm above the level of the transition zone. A coloanal anastomosis is then created between the ganglionic bowel and the anus [17, 18, 24, 25, 26].

In cases involving a long aganglionic segment, laparoscopic mobilization of the colon may be utilized, followed by transanal endorectal pull-through [19, 20].

For patients with enterocolitis, intensive treatment is administered, including correction of fluid and electrolyte imbalances and cleansing enemas [7, 8].

In the complicated form of Hirschsprung's disease (intestinal obstruction, necrotizing enterocolitis with toxic megacolon, perforation of the small intestine or other bowel segments), a stoma is created, and biopsies are performed at various levels of the colon, along with a rectal biopsy. Once the diagnosis is confirmed and the extent of the aganglionic zone is determined, an appropriate surgical approach is selected [9].

The most serious prognosis is observed in the intestinal form of aganglionosis. High ileostomies often lead to short bowel syndrome, which complicates postoperative care [20].

Outcomes and Complications. Careful adherence to surgical techniques, adequate hemostasis, ensuring sufficient blood supply, and preventing bowel twisting or tension help minimize complications during transanal endorectal pull-through procedures.

Enterocolitis is the primary cause of morbidity and mortality following radical surgeries for Hirschsprung's disease [7, 9]. The reported incidence of postoperative enterocolitis varies widely, ranging from 5% to 42%, depending on differences in diagnostic criteria and research methods [7]. Although significant progress has been made in the treatment of Hirschsprung's disease, the pathogenesis of enterocolitis remains incompletely understood. It is hypothesized that obstructive mechanisms lead to intestinal stasis, bacterial invasion of the mucosa, and inflammation. Risk factors for enterocolitis include young age, anastomotic strictures, and nutritional deficiencies. It has been suggested that a thinner muscular layer may reduce the frequency of enterocolitis by lowering the risk of spasms. Thus, intestinal stasis and an immature mucosal immune system may contribute to the development of enterocolitis in early childhood [17].

Scar stenosis following radical pull-through surgery is another serious complication. The incidence of stenosis ranges from 0% to 35%, depending on how the condition is defined [18, 19]. Risk factors include ischemia, anastomotic failure, and circular anastomosis. As previously mentioned, stenosis is a significant risk factor for postoperative enterocolitis. Most cases of stenosis are treated conservatively using dilation, although more aggressive surgical correction may be necessary in some cases. The use of an oblique anal anastomosis reduces the risk of developing stenosis.

Failure of the coloanal anastomosis, presenting as peritonitis, perianal phlegmon, or the formation of a pararectal fistula, requires the creation of a stoma until the inflammation resolves. Such complications are rare, as the anastomosis is protected by the walls of the anal canal. However, inflammation may occur in cases of ischemia at the anastomotic site or secondary infection of a hematoma. If bowel integrity is restored and there are no deformations at the anastomotic site, the stoma is closed with the creation of an end-to-end anastomosis. In cases where the bowel is compromised, a repeat pull-through procedure is performed, including resection of the affected segment and closure of the stoma.

The frequency of bowel movements after surgery is typically high (5–10 times per day), but within six months, it decreases to 1–4 times per day. Constipation may develop weeks or months after surgery and depends on the type of procedure performed, most commonly arising after techniques that preserve an aganglionic segment of the bowel (e.g., Duhamel or Rehbein procedures). Constipation is observed in 8% of children, although some sources report a frequency as high as 20% [18, 20, 21]. Recent studies show that 37% of children experience defecation disorders following surgery for Hirschsprung's disease [22, 23].

Functional constipation can be treated conservatively with enemas or laxatives. Persistent constipation caused by sphincter achalasia, strictures, incomplete resection of the aganglionic zone, or dysganglionic bowel may require additional diagnostic methods, such as contrast enema or biopsy. Based on diagnostic findings, treatment options may include active dilations, botulinum toxin (Botox) injections, myectomy, or repeat pull-through surgery [6, 7, 18].

Fecal incontinence is typically evaluated in children older than 4 years. According to large studies, fecal incontinence is absent following transanal pull-through procedures. However, some authors report cases of incontinence associated with altered stool consistency or liquid stools in children with long-segment aganglionosis. Approximately 44% of children require dietary management to prevent constipation or incontinence [21, 22, 23]. Evidence suggests that many aspects of stool retention and consistency improve over time [17, 18].

Enuresis is reported in 5–26% of cases and may be related to iatrogenic injury to pelvic nerves or neuropathy [7]. The use of laparoscopic techniques or transanal pull-through surgery helps reduce the incidence of iatrogenic injuries.

Defecation disorders, including constipation, fecal incontinence, and enuresis, significantly affect the quality of life for patients after surgery for Hirschsprung's disease. Resection of a long aganglionic segment often results in a shorter residual colon, which can lead to a reduced quality of life. Nevertheless, over time, patients often learn to manage their condition using techniques such as enemas and dietary adjustments.

The primary goal of the surgeon is to minimize complications through meticulous surgical technique and to ensure long-term follow-up care for these patients.

Conclusion. Significant progress has been made in the diagnosis and treatment of Hirschsprung's disease; however, functional outcomes remain suboptimal. The timing of surgery and the choice of surgical method tailored to each individual child play critical roles in achieving the best results.

A review of the literature indicates that, despite the lack of controversy surrounding the pathogenesis of the disease, the implementation of new diagnostic and therapeutic methods remains a complex and ambiguous process. Addressing these challenges will require the development of comprehensive diagnostic programs, consideration of all potential complications, and the selection of appropriate treatment strategies.

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