

## REVIEW ARTICLE

# CURRENT APPROACHES TO DIAGNOSIS AND TREATMENT OF HIRSCHSPRUNG DISEASE IN NEWBORNS AND INFANTS (LITERATURE REVIEW AND FIRST-HAND EXPERIENCE)

DOI: 10.36740/WLek20220420120

**Olga M. Gorbatyuk**

SHUPYK NATIONAL HEALTHCARE UNIVERSITY OF UKRAINE, KYIV, UKRAINE

**ABSTRACT**

**The aim:** To analyze the current state of the issue of Hirschsprung disease in newborns and infants on the basis of literature data and first-hand experience.

**Conclusions:** 1. Hirschsprung disease should be suspected in all newborns with late meconium passage. 2. The main methods of diagnosing Hirschsprung disease in newborns and infants are the assessment of anamnestic data, clinical manifestations and features of the clinical course of the pathology, contrast enema, morphological examination of rectal biopsies and immunohistochemistry for ACE. 3. The presence of enterocolitis in newborns and infants should raise suspicion of Hirschsprung disease. 4. Low intestinal obstruction, perforation of the cecum, ascending or terminal small intestine, and peritonitis in the first days of a child's life may be complications of Hirschsprung disease. 5. In newborns and infants, early diagnosis of Hirschsprung disease and timely surgical correction by one-stage surgery help improve treatment outcomes

**KEY WORDS:** Hirschsprung disease, newborns, diagnosis, transanal endorectal pull-through

Wiad Lek. 2022;75(4 p2):1026-1030

**INTRODUCTION**

Hirschsprung disease in newborns and infants is a complex problem of modern pediatric surgery. The improvement in the treatment of children with Hirschsprung disease in the last decade has been due to advances in understanding the etiology and pathogenesis of the disease, improving diagnostic methods and developing surgical methods of correction. Increased awareness of Hirschsprung disease and improved diagnosis have significantly reduced the age of detecting Hirschsprung disease in recent times, but there are often cases of late diagnosis of the disease in newborns. Thus, the issue of early diagnosis of this pathology and timely treatment of newborns and infants remains relevant today [1-3].

It is the late diagnosis of Hirschsprung disease in newborns that has necessitated a more in-depth study of this issue.

**THE AIM**

The aim is to analyze the current state of the issue of Hirschsprung disease in newborns and infants on the basis of literature data and first-hand experience.

**REVIEW AND DISCUSSION****CURRENT VIEWS OF THE ETIOPATHOGENESIS OF HIRSCHSPRUNG DISEASE IN NEWBORNS**

A review of the literature indicates that the issues of etiology and pathogenesis of Hirschsprung disease are no longer considered controversial. The etiology of Hirschsprung

disease is represented by cellular and molecular abnormalities in the enteric nervous system development and disorders of crest-derived cells migration to the intestinal tract. Neuroblasts first appear in the esophagus after the 5th week of gestation. These cells migrate in a craniocaudal direction into the intestine between 5 and 12 weeks of gestation. The form of Hirschsprung disease depends on the time and place of migrating neuroblast stop. An early delay in cell migration leads to an extensive aganglionosis [4, 5]. The pathogenesis of Hirschsprung disease is based on the obstruction of the narrow part of the large intestine, where peristaltic waves are not formed due to the absence of parasympathetic ganglion cells. Aganglionosis, cholinergic hyperinnervation, failure of nerve supply by nitric oxide synthase, disruption of interstitial cells of Cajal are all involved in the pathogenesis of Hirschsprung disease [4, 6]. There are many factors contributing to the development of Hirschsprung disease. These include extracellular matrix component damage, neurotrophic disorders, molecular damage to nerve cells, etc. [7]. Hirschsprung disease is a neurocristopathy, a tissue developmental anomaly due to defective migration of neural crest cells [5].

An increased risk of children being born with Hirschsprung disease among relatives of patients with this disease, association of Hirschsprung disease with other congenital anomalies (heart, central nervous system, genitourinary system), syndromes and chromosomal disorders (Waardenburg-Shah syndrome, Bardet-Biedl syndrome, Mowat-Wilson syndrome, Down syndrome) prove the presence of genetic factors in the etiopathogenesis of



Fig 1. Characteristic appearance of a newborn suspected of having Hirschsprung disease.

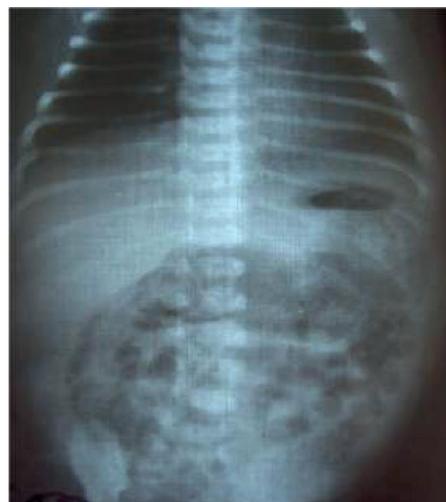


Fig 2. Toxic dilatation of the colon in Hirschsprung-associated enterocolitis in a newborn child.

the disease. We have the clinical case of the boy T. with Hirschsprung disease, whose mother had an operation for a similar disease in her childhood. Today it is known that mutations in 10 genes are associated with Hirschsprung disease, among which the RET protooncogene, the glial cell line-derived neurotrophic factor (GDNF) gene, the neurturin (NRTN) gene, the endothelin receptor type B (EDNRB) gene, and the endothelin 3 (EDN3) gene are the most studied [8, 9, 10]. The increased risk of children being born with Hirschsprung disease among relatives of patients with this disease, association of Hirschsprung disease with other congenital malformations, syndromes and chromosomal abnormalities prove the presence of genetic factors in the pathogenesis of the disease.

## CLINICAL FINDINGS

Hirschsprung disease in newborns is manifested by signs of low intestinal obstruction due to the presence of aganglionic segment of varying length of the distal colon: failure to pass meconium for 48 hours after birth, progressive bloating, vomiting bile, restlessness, enteral nutrition disorders, etc. [11]. Most newborns with Hirschsprung disease are usually full-term babies with delayed passage of meconium (more than 24 - 48 hours of life). The complicated course of Hirschsprung disease in newborns is manifested by enterocolitis and/or cecal perforation and peritonitis. Hirschsprung disease is often accompanied by loose stools, the presence of which indicates enterocolitis, which is the most common cause of mortality. The appearance of a newborn with Hirschsprung disease is shown in Figure 1.

Enterocolitis in Hirschsprung disease in newborns is a severe complication that can develop in the pre- and postoperative period. Approximately 5-42% of infants with Hirschsprung disease develop enterocolitis [12]. It is manifested by symptoms of fever, colic-like abdominal pain, intoxication, bloating, diarrhea, sometimes with blood. Despite numerous studies, there is still no complete

understanding of the etiology of enterocolitis. There are the following theories in this regard:

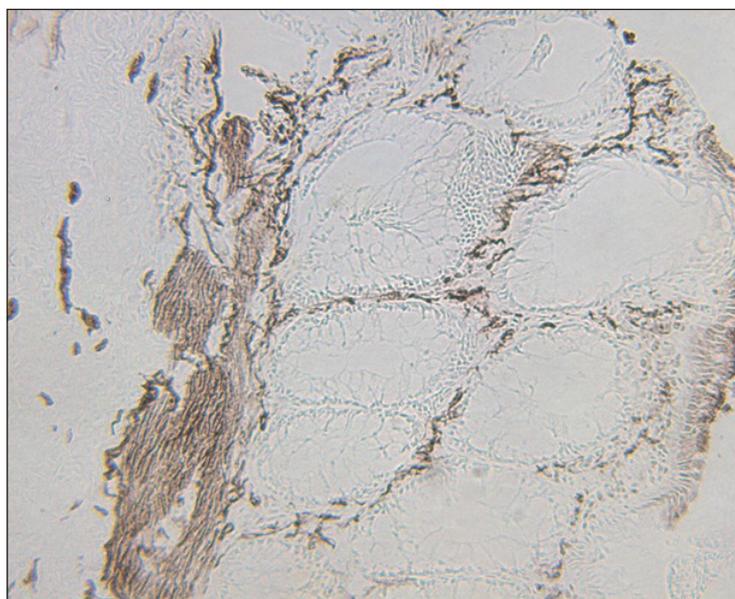
1. Proximal colon distention, which leads to intestinal stasis, and even greater distention in dynamics, mucosal ischemia and bacterial invasion. However, this theory does not explain the occurrence of enterocolitis in the distal from stoma part of the intestine, or the histological finding of enterocolitis even in the aganglionic segment
2. Long-segment aganglionosis, which is common in newborns and characterized by a more pronounced proximal obstruction with greater pressure, increasing bacterial stasis and proximal distention. However, numerous studies indicate a correlation between aganglionic segment length and the prevalence of enterocolitis
3. Mucin production is significantly reduced in newborns, which leads to the intestinal mucosal barrier damage and bacterial translocation
4. Reduced production of secretory immunoglobulin A, which provides an immunological barrier in the gastrointestinal tract of the child, resistance to bacteria and eliminates bacterial translocation, that is, immature mucosal immunity in newborns
5. An increase in the number and activity of macrophages during inflammation of the intestinal wall leads to disruption of the interstitial cells of Cajal responsible for the rhythmic contractions of the intestinal peristaltic activity.

## DIAGNOSIS

The diagnosis of Hirschsprung disease is based on X-ray examination of the colon, biopsy of the mucosa and submucosa of the rectum and colon, where aganglionosis, hypertrophied nerve fibers and hyperproduction of acetylcholinesterase (ACE) are detected. Microbiological study reveals *Clostridium difficile* in most cases [13]. Differential diagnostic search is performed with congenital



**Fig. 3.** Contrast enema radiograph in a newborn with Hirschsprung disease. Note the narrowed aganglionic segment – 1, transition zone – 2, and supragenetic dilatation of the colon – 3.



**Fig. 4.** Rectal mucosal biopsy sample shows the presence of numerous nerve fibers between crypts with high ACE activity, forming a dense network in some places. In the proper and muscular mucous plates there is also a dense network of thickened brightly colored tortuous cholinergic nerve fibers. Ganglia are absent.

malformations of the small intestine (atresia, malrotation, meconium ileus), congenital malformations of the colon (rectal malformations, small left colon syndrome), hypothyroidism, sepsis, metabolic disorders, etc.

Extensive intestinal pneumatosis, dilatation of the colon can be seen on the plain radiograph of a newborn child with Hirschsprung disease. In case of evident enterocolitis, the signs of toxic dilatation of the colon can be found (Figure 2). Complicated Hirschsprung disease can be characterized by signs of low intestinal obstruction or intestinal perforation with free gas in the abdominal cavity [14, 15].

The signs of Hirschsprung disease during contrast enema are pathological narrowing of the distal colon, funnel-shaped transition zone and distention of the proximal colon (Figure 3). In some newborns (approximately 10%), funnel-shaped transition zone and proximal colonic distention may be indistinct. By 1 month of age, the risk of false-positive and false-negative results increases almost 3 times [1, 11]. Contrast enema in newborns is performed using water-soluble contrast at a dilution of 1:3 in the volume of 20 ml/kg. Excess contrast use should be avoided. The anterior and lateral X-ray films should be necessarily taken when filling the intestine and after defecation. The contrast material should be injected into the large intestine in small portions to gradually fill all its segments. The intestine is examined in different projections. The aganglionic segment is more easily seen in the lateral projection.

Contrast enema is a highly informative method of diagnosing Hirschsprung disease in newborns. It is important not to perform colon lavage and digital rectal examination before contrast enema, as this may contribute to radiographic distortion and give false-negative data [William J.Cochran. MSD Manual. 2019. Professional Edition].

It is important to note that full-thickness biopsy in newborns is technically sophisticated to perform, while

rectal mucosal biopsy is a technically simple procedure. In addition, the absence of aganglionic cells in the distal section of the anal canal is a normal variant, thus a biopsy in newborns is performed 1 cm above the dentate line.

A classical morphological examination reveals the absence of ganglion cells in the nerve plexuses of the intermuscular and submucosal layers of the rectum when stained with hematoxylin-eosin.

Histochemical analysis of rectal mucosal biopsy reveals the presence of acetylene-positive hypertrophied nerve fibers, which confirms Hirschsprung disease (Fig. 3). Histochemical reaction to ACE for the diagnosis of Hirschsprung disease in newborns has a sensitivity of 91%, specificity of 100%, false-negative result is observed in 8% of cases.

Newborns, especially premature and not fully developed ones, can have reduced number of nerve fibers in the intestinal wall even in Hirschsprung disease, so a decrease in the level of ACE – positive fibers in newborns can lead to a false-negative result. However, despite these limitations, rectal biopsy is more sensitive and specific than contrast enema and anorectal manometry combined.

## TREATMENT

Confirmation of the diagnosis of Hirschsprung disease is an indication for surgical treatment. Success in anesthesia and resuscitation of newborns, successful developmental care have made it possible for pediatric surgeons to perform one-stage correction of Hirschsprung disease in an uncomplicated form of the disease and the absence of total aganglionosis. This involves pulling through the aganglionic segment, performing transanal resection and colorectal anastomosis, that is de la Torre procedure, which is today considered the gold standard in the surgical treat-



**Fig. 5.** Transanal mobilization of the rectum in Hirschsprung disease.



**Fig. 6.** Transrectal mobilization of the gut for resection.



**Fig. 7.** Direct colorectal anastomosis after transendorectal pull-through and colon resection in Hirschsprung disease.

ment of newborns and infants with Hirschsprung disease [16-18]. The main stages of the de la Torre procedure are presented in Figures 5, 6, 7.

Most medical institutions and centers today perform pull-through radical operation in the neonatal period with good results and a minimum number of complications. Since in newborns it is possible to quickly cope with the dilation of the colon by washing it, then during the operation the diameter of the pulled-through colon is almost normal, which makes it possible to apply an optimal anastomosis and promotes healing without dehiscence and infection. The main contraindications to primary transanal pull-through in newborns are the following:

- severe congenital anomalies;
- severe enterocolitis;
- severe dilatation of the proximal colon;
- serious general medical condition of a child,

Radical one-stage surgical treatment of Hirschsprung disease by de la Torre in newborns and infants is becoming more widespread and improves the results of treatment.

The postoperative period in newborns and infants is mostly without complications, provided that appropriate surgical approach is adhered.

## CONCLUSIONS

1. Hirschsprung disease should be suspected in all newborns with late meconium passage.
2. The main methods of diagnosing Hirschsprung disease in newborns and infants are the assessment of

anamnestic data, clinical manifestations and features of the clinical course of the pathology, contrast enema, morphological examination of rectal biopsies and immunohistochemistry for ACE.

3. The presence of enterocolitis in newborns and infants should raise suspicion of Hirschsprung disease.
4. Low intestinal obstruction, perforation of the cecum, ascending or terminal small intestine, and peritonitis in the first days of a child's life may be complications of Hirschsprung disease.
5. In newborns and infants, early diagnosis of Hirschsprung disease and timely surgical correction by one-stage surgery help improve treatment outcomes.

Directions for future research: immunohistochemical study of calretinin (calretinin is negative in Hirschsprung disease) and on the detection of nerve fibers containing nitric oxide (no nitric oxide in the aganglionic zone).

## REFERENCES

1. Holschneider A.M., Puri P. et al. Hirschsprung's disease and Allied Disorders. 3rd. ed. New York, NY: Springer. 2008, 414p.
2. Bradnock T.J., Walker G.M. Evolution in the management of Hirschsprung's disease in the UK and Ireland: a national survey of practice revisited. *Ann R. Coll Surg. Engl.* 2011; 93(1): 8-34.
3. Govoruhina O.A. Diagnostika i lechenie bolezni Girshprunga u detei na sovremennom etape [Diagnostics and treatment of Hirschsprung disease in children at the present time]. *Novosti hirurgii [Surgery News]*. 2017; 25(5): 510 – 517. (In Russian).
4. Gariepy C.E. Intestinal motility disorders and development of the enteric nervous system. *Pediatr Res.* 2001; 49(5): 605.

5. Butler Tjaden N.E., Trainor R.A. A development etiology and pathogenesis of Hirschsprung disease. *Transl. Res.* 2013; 13: 71 – 76.
6. Tam P.K., Garcia-Barcelo M. Molecular genetics of Hirschsprung's disease. *Semin Pediatr Surg.* 2004; 13 (4): 236.
7. Swenson O. Hirschsprung's disease: a review. *Pediatrics.* 2002; 109(5):914.
8. Orphanet: Hirschsprung disease. 2021. [https://www.orphanet.org/contributors/cgi-bin/OC\\_Exp.php?Lng=GB&Expert=389](https://www.orphanet.org/contributors/cgi-bin/OC_Exp.php?Lng=GB&Expert=389). [date access 14.01.2021]
9. Amiel J., Sproat-Emison E., Garcia-Barcelo M. et al. Hirschsprung disease Consortium. Hirschsprung disease, associated syndromes and genetics: a review. *J. Med.Genet.* 2008; 45(1): 1 – 14.
10. Kim J.H., Yoon K.O., Kim J.K. et al. Novel mutations of RET gene in Korean patients with sporadic Hirschsprung's disease. *J. Pediatr. Surg.* 2006; 41(7): 1250.
11. Dasgupta R., Langer J.C. Hirschsprung disease. *Curr Probl Surg.* 2004; 41(12): 942.
12. Demehri F.R. Hirschsprung- associated enterocolitis: pathogenesis, treatment and prevention. *Ped. Surg. Int.* 2013;29(9): 873 – 881.
13. Yan Z., Poroyko V., Gu S. et al. Characterization of the intestinal microbiome of Hirschsprung's disease with and without enterocolitis. *Biochem Biophys Res Commun.* 2014; 445(2): 269.
14. Diamond I.R., Casadiego G., Traubici J. et al. The contrast enema for Hirschsprung disease: predictors of a false-positive result. *J. Pediatr. Surg.* 2007;42(5):792-5. doi: 10.1016/j.jpedsurg.2006.12.031.
15. Diagnosis of Hirschsprung disease: a prospective, comparative accuracy study of common tests. *J. Pediatr.* 2005; 146(6): 787.
16. Spitz L., Coran A.G. et al. *Operative Pediatric Surgery*. 6th ed. London: Hodder Arnold. 2007, 1060p.
17. Nasr A., Langer J.C. Evolution of the technique in the transanal pull-through of Hirschsprung's disease: effect of outcome. *J.Pediatr.Surg.* 2007; 42(1): 9-36.
18. Somme S., Langer J.C. Primary versus staged pull-through for the treatment of Hirschsprung disease. *Semin Pediatr Surg.* 2004; 13(4): 249.
19. Puri P., Golvart M. *Atlas detskoi operativnoi hirurgii [Atlas of Pediatric Operative Surgery]*. M.: MEDpress-inform. 2009, 304p.

**ORCID and contributionship:**

*Olga M. Gorbatyuk*: 0000-0003-3970-8797 <sup>A,B,D-F</sup>

**Conflict of interest:**

*The Authors declare no conflict of interest.*

---

**CORRESPONDING AUTHOR**

**Olga M. Gorbatyuk**

Shupyk National Healthcare University of Ukraine

9 Dorogoshitska st., 04112 Kyiv, Ukraine

tel: +380503820641

e-mail: ol.gorbatyuk@gmail.com

**Received:** 23.11.2021

**Accepted:** 30.03.2022

---

**A** – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article