

Review Article

Hirschsprung's disease: a review

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ABSTRACT

Hirschsprung disease (HD) is a congenital condition that affects intestinal function due to the absence of ganglion cells in the myenteric and submucosal plexus of the colon. This absence causes difficulty in intestinal relaxation and, consequently, normal intestinal evacuation, resulting in severe constipation from birth or early childhood. At the genetic level, mutations have been identified in genes such as RET, involved in the migration and differentiation of neural crest cells. The diagnosis is based on rectal biopsies that show the absence of ganglion cells. The main treatment is surgical, with techniques such as rectosigmoidectomy or pull-through to restore intestinal function. Despite advances, patients can experience complications such as fecal incontinence. Multidisciplinary management is crucial to improve the patient's quality of life.

Keywords: HD, Treatment, Management, Ethioopathogenesis, Neural crest cells, Intestinal function

INTRODUCTION

Hirschsprung's disease (HD) was initially reported by the Danish pediatrician Harald Hirschsprung in 2 infant patients in 1886. He described it as colonic hypertrophy accompanied by symptoms such as severe constipation without any mechanical obstructive justification, which is why it is attributed the origin of the disease itself is colon hypertrophy. Sometime later it was shown that at the rectal level and ascending colon the plexus of Auerbach and Meissner lacked ganglion cells. Likewise, alterations in innervation were described at the level of the circular muscular and mucosal layer, which leads to greater difficulty in intestinal relaxation and, therefore, normal intestinal evacuation.¹

The disease usually manifests itself during the first years of life, usually in these patients it is reflected during the neonatal period as gastrointestinal symptoms among which are vomiting, abdominal distention, and even a delay in the passage of meconium, among others. Only around 500 total cases with presentation in adulthood have been reported. Furthermore, a more hidden clinical presentation has been found in these patients, this is explained by the way in which the body compensates for functional obstruction through more proximal hypertrophy.² HD belongs to a group of diseases called dysganglionosis, which includes different anomalies of genetic origin. It is known that the main etiology is due to a failure that occurs between the fifth and sixth week of gestation in which the ganglion cells must migrate from

the neural crest, and it is even believed that there could be a defect in the extracellular matrix of the intestinal wall, which would prevent adequate colonization by cells from the neural crest (Figure 1). Finally, it was shown that

accompanied by this pathology, patients generally present an altered mucosal barrier in the colon, making them prone to other diseases.³

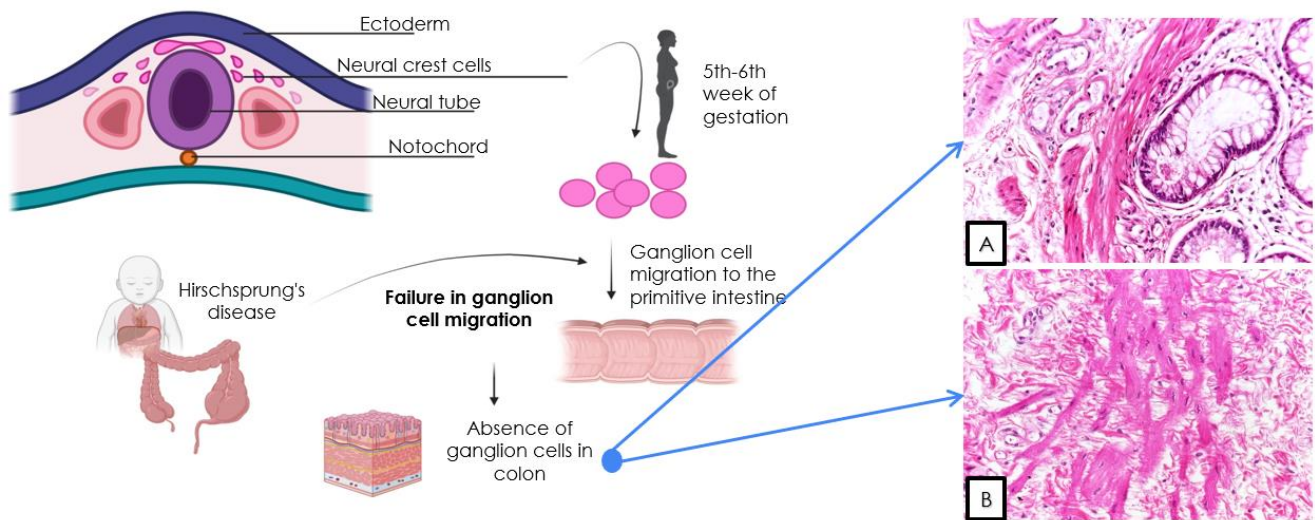


Figure 1 (A and B): Representation of neural crest cell migration in HD.

Embryogenesis of enteric ganglion cells, in the submucosal and myenteric plexuses. Absence of ganglion cells in submucosal plexus, seen with a 40× objective. Absence of ganglion cells in myenteric plexus, seen with a 40× objective.

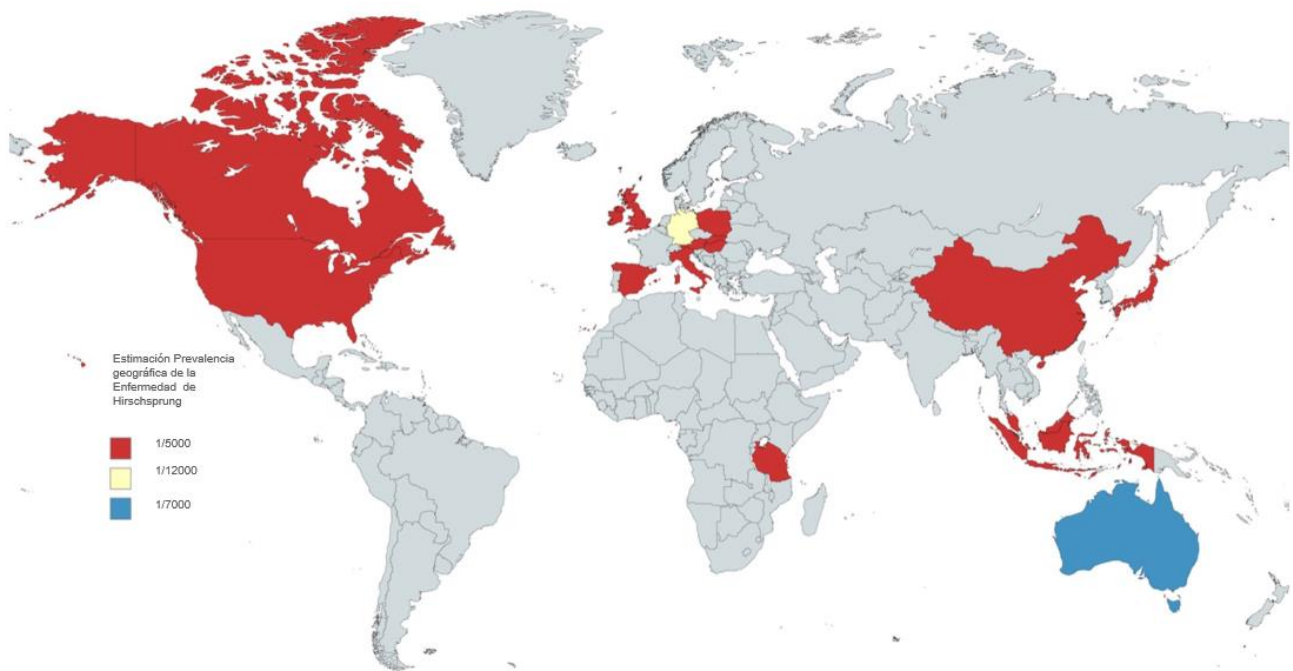


Figure 2: Geographic distribution of HD.

Collection of some epidemiological data on prevalence of HD.

The most common clinical presentation of HD is early-onset constipation, predominantly in newborns, especially those with full-term gestation. It also presents as intestinal obstruction in newborns and bloating. To make an initial approach, it is important to perform an anorectal manometry, colon by enema and finally confirmation is performed through a rectal biopsy.

Management in recent years has evolved significantly. Initially Swenson focused on performing a transanal dissection, in which he ultimately left patients with an ostomy. Over the years, the Georgeson technique appeared, which combined laparoscopic methods to perform a primary trans-anal descent. However, it has

been observed that at least 50% of these post-surgical patients are left with defecatory incontinence.⁴

Fecal incontinence is just one of the few complications resulting from HD. Management by an interdisciplinary team is of great importance to provide an adequate quality of life in adulthood for these patients, so follow-up by surgery, pediatrics and psychology should not be missing in the follow-up of these patients.⁵

EPIDEMIOLOGY

The presentation of HD has been reported in approximately 1 in 5000 live births. More frequently in patients born at term and of white race with a greater predominance of male patients with a ratio of 3-5:1.³ Around 95% of HD patients are diagnosed before the first year of life and in the neonatal stage. Different polymorphisms have been reported within the RET gene, which has been shown to be involved in the development of HD, the c135 polymorphism has been reported in different populations such as Spanish, German, Italian, Chinese, Polish and American, putting 11 times more at risk of suffering from HD in these populations. This possibly as a consequence of evolutionary migration from Africa to Asia and Europe.⁶ Unlike developed countries, only 20-40% of patients present as neonates and the average age of presentation is 24 months.⁷ A study carried out in Canada by Nasr et al. sought to determine the incidence of HD in Ontario, Canada, they found an incidence of HD in Canada, similar to that reported in Scotland, Germany, England, Denmark, United States, Japan, Oman which varied approximately between 1 in 5,000 live births (Figure 2).⁸

EPIGENETICS AND MOLECULAR BASES

Genetic alterations related to the appearance of HD have been found. Among which chromosomes 2, 10 and 13 stand out with the genes RET, GDNF, NTN, ENDR-B, EDN3, ECE1. One of the most studied genes is the RET gene, a gene with a receptor tyrosine kinase expressed in cells derived from the neural crest, located on chromosome 10q11.2, which has been found present in up to 50% of familial cases, in addition, mutations of this gene have been associated with Multiple Endocrine Neoplasias (MEN) 2A, MEN 2B and HD. In a study carried out by Emission et al in more than 690 Europeans and 192 patients of Chinese descent, in which it was demonstrated that susceptibility in the RET amplifier is generated as a result of a failure in SOX10, which is responsible for activating RET transcription. All of this is probably the product of a single mutation of a T allele, which is significantly elevated in HD. Historically, it is believed that as a result of population migration from Africa towards Asia and Europe, there are enough cases known to explain the difference and susceptibility of the disease between these populations. Furthermore, a greater number of cases was found in those T alleles with a greater common number of subtypes, in this case male

patients, unlike women where a lower common number of T allele subtypes was found. although with a higher risk of recurrence at the family level.⁹⁻¹¹

Additionally, Guevara et al carried out a study on the different genetic polymorphisms of the RET proto-oncogene that have been associated with HD in children from Ecuador. Among the results, the A45A polymorphism stands out, which was significantly associated with HD; in addition, the A432A polymorphism demonstrated a protective role against the disease. Therefore, it demonstrates the importance of polymorphisms in the RET proto-oncogene and its relationship with HD. Those patients who were shown to have the c135a variation in RET had a strong association with suffering from HD.⁶

Finally, it is known that more than 80% of patients with HD present a heritability factor, associated with different genetic variations that could also be related to other genetic alterations such as Down syndrome in 7.32% of individuals and in a 50% was found to be associated with congenital heart defects. Other congenital alterations that were found associated with HD are Waardenburg syndrome, congenital deafness, malrotation of the gastric diverticulum and intestinal atresia.¹²

CLINICAL MANIFESTATIONS

HD presents as an absence of involuntary relaxation of the internal anal sphincter, which is represented symptomatically in 70% of patients during the first days of life, such as constipation, delay in the elimination of meconium. In approximately 10% of patients, the disease occurs between 3 and 14 years of age (Figure 3). However, the age of presentation and its symptoms depend on the classification of disease, which will vary depending on the affected intestinal segments (Table 1).¹³

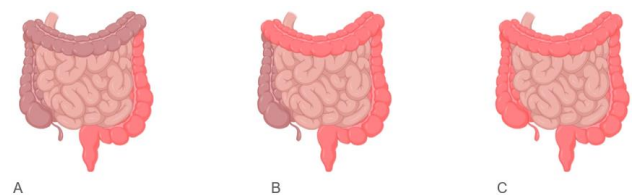


Figure 3: Anatomical representation of HD according to its types of presentation.

In bright red are the affected colony areas according to each type of presentation of HD; A: EH in short segment. B: EH in long segment. C: Total colonic HE.

Patients with chronic constipation, nutritional and growth disorders are commonly observed. Upon rectal examination, these patients present hypertonia of the anal sphincter, and the rectal ampulla is empty. It is frequently found as a case of enterocolitis that has symptoms of fever, abdominal distension, diarrhea, this because of the dilation of the loops which generates an increase in intraluminal pressure which ends up reducing blood flow,

creating an environment for bacterial stagnation and growth. Enterocolitis represents 30% of mortality in patients with HD, due to the high risk of intestinal perforation and sepsis.³

Table 1: Types and characteristics in HD.

Segment affected by HD	Characteristic
Short segment disease	Absence of ganglion cells at the rectal level and even the lower part of the sigmoid colon.
Long segment disease	Absence of ganglion cells at the rectal level and in greater quantities at the colonic level compared to short segment disease, but at least nerve cells are found in one segment of the colon.
Total colonic disease	Absence of ganglion cells in the rectum and entire colon, but they are present in the tip of the small intestine.

DIAGNOSIS

The gold standard for the diagnosis of HD is the rectal biopsy, with a sensitivity of 93% and a specificity of 98%. This biopsy should ideally be taken at a distance of 3 cm from the dentate line and in which it will be possible to observe. Through hematoxylin-eosin staining and histopathological studies, the absence of ganglion cells, the presence of hypertrophic nerve fibers, an increase in Acetylcholinesterase activity and the absence of calretinin-positive fibers in the lamina propria confirmed the diagnosis.² However, to reach this diagnosis through biopsy, generally when other possible pathologies are suspected, other diagnostic tests are performed initially, among these is anorectal manometry which has a sensitivity of 91% and a specificity of 94%. Anorectal manometry, although it could guide towards the diagnosis of HD, is considered more as a screening test, which is why it does not confirm the diagnosis. It is a non-invasive test through the introduction of a balloon catheter that will distend upon entry, this will evaluate the function of the internal anal sphincter. If an absence of the inhibitory anal reflex is found, it would guide a diagnosis of HD. The use of colon enema is also useful in guiding the diagnosis of HD. It provides, through images, the morphological characterization of the presentation and generally demarcates what is known as the transition zone of the disease; However, this transition zone does not always correspond to the histopathologically studied transition zone, especially in those patients with a clinical presentation of HD in the sigmoid rectum.⁵

TREATMENT

The management of HD is mainly surgical in nature which seeks to extract the affected colonic segment with

a subsequent anastomosis. It is important to perform decompression of the intestinal loops once the diagnosis is made in order to be able to perform the surgical intervention as soon as possible and to avoid the appearance of complications of the disease such as necrotizing enterocolitis. Decompression is achieved through Rectal irrigations at least 3 times a day, if they are not successful, an ostomy will be used. According to recommendations, the safest empirical form of ostomy for these patients is the ileostomy. Other scenarios have been described in which the use of the ostomy is resorted to, such as those patients where HD affects the entire colon or if they have complications such as necrotizing enterocolitis, megacolon or suffer from intestinal perforation.^{14,15} Depending on the age of presentation, it will be decided to perform the surgery in one or two stages. Generally, older patients undergo a one-time surgical intervention and newborns and younger infants' resort to first performing a procedure to leave a discharge ostomy and, in the same intervention, taking biopsies after waiting about 6 months. perform definitive surgical correction. Currently, 3 surgical methods have been described, among which rectosigmoidectomy, trans-anal recto-rectal pull-through, and endorectal pull-through stand out. To these surgical processes are added the use of new creations such as the use of mechanical sutures or intraluminal intestinal staplers, since they facilitate the possibility of performing a faster, safer and more successful surgical approach, through the reaction of good anastomoses. and safe. In those patients who present necrotizing enterocolitis or significant loop dilation, ostomies are recommended, generating decompression while waiting for intestinal recovery.^{3,16} A study carried out by Oyanía et al sought to determine the safety of closing an ostomy in the same surgical process as pull-through corrective surgery and found that it was a safe intervention that avoided performing management in 3 surgical moments, a process which generates greater morbidity and a decrease in the quality of life. However, they say more studies are needed to understand the impact on patients.¹⁷ Despite the advanced methods currently used for the surgical approach to HD, some post-surgical complications have been reported in 8 to 10%, such as mainly necrotizing enterocolitis, followed by perianal leakage of fecal matter, stenosis. Anal or rectal, surgical site infection or abscess formation, urinary incontinence and could even continue with persistent constipation. Other possible complications are the formation of adhesions with subsequent involvement of intestinal obstruction. The management of these complications depends on their level and severity, which will vary from antibiotic management, drainage or return to the operating room for surgical correction.^{18,19}

CONCLUSION

Hirschsprung disease is a congenital condition that affects intestinal function due to the absence of ganglion cells in the myenteric and submucosal plexus of the colon. This absence leads to abnormal contraction of the

colon, resulting in severe constipation from birth or early childhood. At the genetic level, mutations have been identified in several genes, including RET and others related to the migration and differentiation of neural crest cells. The diagnosis is made by rectal biopsy, which reveals the absence of ganglion cells. The main treatment is surgical, with techniques such as rectosigmoidectomy or various types of pull-through to remove the affected portion of the colon and restore adequate intestinal function. Despite advances in surgical management, patients may experience complications such as fecal incontinence. Multidisciplinary management is crucial to optimize the quality of life of patients, addressing medical, surgical and psychological aspects. Although the disease is more common in white, full-term newborns, cases have been reported in adults, highlighting the importance of continued surveillance and long-term follow-up. Hirschsprung disease represents a significant clinical challenge that requires a comprehensive and personalized approach for each patient, with the goal of minimizing complications and improving long-term outcomes.

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