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HIRSCHPRUNG'S DISEASE- A REVIEW ARTICLE

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ABSTRACT

Hirschprung's disease is a congenital disorder characterized by the absence of myenteric and meissner plexuses in the distal colon. It should be considered in a new born who has failed to pass mechonium within 24-48 hours.Accurate diagnosis is a key element for further treatment. Rectal suction biopsy along with H & E staining and acetylcholinesterase and calretenin histochemistry offers a high diagnostic accuracy.

INTRODUCTION

Hirschsprung's disease (HD) is a congenital condition of intestine innervations leading to a lack of ganglion cells in the area of the Auerbach plexus and Meissner plexus in the distal section of the large intestine leading to functional obstruction.

The disease prevalence is estimated at the level of 1: 5000 live births. The disease more often afflicts male than female patients at a ratio of around 4: 1 [1,2].

Most cases of Hirschsprung disease are diagnosed in the newborn period. Hirschsprung disease should be considered in any newborn that fails to pass meconium within 24-48 hours of birth.

HISTORICAL ASPECTS

This condition was first described by Ruysch in 1691 and popularized by Hirschsprung in 1886. Whitehouse and Kioernohan in 20th century reported aganglionosis of the distal colon as the cause of obstruction in a case series.

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PATHOPHYSIOLOGY

Three nerve plexuses innervate the intestine: the submucosal (Meissner) plexus, the myenteric (Auerbach) plexus, and the smaller mucosal plexus. All of these

plexuses are finely integrated and involved in all aspects of bowel function, including absorption, secretion, motility, and blood-flow regulation.

Normal motility is primarily under the control of intrinsic neurons. In the absence of extrinsic signals, bowel function remains adequate. Intrinsic activation causes muscle relaxation, mediated by nitric oxide and other enteric neurotransmitters. Extrinsic neural afferents to the ENS contain cholinergic and adrenergic fibers. The cholinergic fibers generally cause contraction, whereas the adrenergic fibres mainly cause inhibition.

In patients with HD both myenteric and submucosal plexuses are absent.

PATHOGENESIS

Various hypothesis are assumed, the most popular of these assumes that neuroblasts migration from the primary neutral tube's neural crest in the intrathecal direction during embryonic development between the 4th

and 12th week of pregnancy causes agangliosis of part or whole of intestine [3].

Alternatively, although normal cell migration may occur, neuroblasts may be subject to apoptosis, failure of proliferation, or improper differentiation within the affected distal intestinal segment [4].

Fibronectin, laminin, neural cell adhesion molecule (NCAM), and neurotrophic factors present in the intestinal stroma are necessary for normal enteric ganglion development, whereas their absence or dysfunction may also have a role in the etiology of Hirschsprung disease [5]. HD in most cases is not a genetic disease. Nowadays, there are eight identified genes that are probably related to the disease.

The RET protooncogene has been implicated in several studies of Hirschsprung pathogenesis.

In 2011, So and colleagues discovered that rare variants of RET were associated with more severe phenotypes among Chinese Hirschsprung patients. Leon and colleagues in 2012 determined that sporadic RET coding sequence mutations in Hirschsprung patients resulted in protein truncations that would deter cell membrane translocation and anchoring [6].

In 2013, Qin and colleagues performed microarray analyses of aganglionic colon and normal tissue. They discovered 622 genes with anomalous expression in the aganglionic tissue, and myenteric HAND2 expression was significantly attenuated [7].

In a comparison of gene expression among normal and aganglionic colon, Chen and colleagues determined that overexpression of DVL1 and DVL3 genes was associated with the Hirschsprung phenotype [8].

In a 2013 review, Butler Tjaden and colleagues report that mutations in the genes, RET, GDNF, GFRα1, NRTN, EDNRB, ET3, ZFHX1B, PHOX2b, SOX10, and SHH are present in approximately 50% of Hirschsprung disease patients [9].

These studies indicate the complexity of Hirschsprung pathogenesis.

Hirschsprung disease is confined to the rectosigmoid region in about 75% of cases. Approximately 60% of infants with Hirschsprung disease have an associated condition, ranging from subtle to severe. Ophthalmologic problems affect 43% of infants, 20% have congenital anomalies of the genitourinary tract, 5% have congenital heart disease, 5% have hearing impairment, and 2% have central nervous system anomalies [10].

Hirschsprung disease is associated with chromosomal abnormalities or syndromes in approximately 9% of cases. It may be associated with the following syndromes:
Down syndrome,
Neurocristopathy syndromes,
Waardenburg-Shah syndrome,
Yemenite deaf-blind syndrome,
Piebaldism,
Multiple endocrine neoplasia type II (MEN2),
Congenital central hypoventilation syndrome (CCHS) [11].

CLASSIFICATION

AGANGLIONICSECTION

Hirschsprung's disease is classified according to the length of aganglionicsection.

A. Short aganglionic segment (S-HSCR) 75-80%. The aganglionic segment is present in the distal part of the sigmoid colon and rectum.

B. Long aganglionic segment (L-HSCR) 10% cases and can be observed extending from the rectum, sigmoid colon, and colon up to the splenic flexure.

C. Total colonic aganglionosis (TCA) observed in 5% patients.

D.Ultra short segment (HSCR) in which the aganglionic section is very short in the anal canal above the pectinate line [12].

PRESENTATION

Hirschsprung disease should be considered in any newborn with delayed passage of meconium or in any child with a history of chronic constipation since birth.

Other symptoms include bowel obstruction with bilious vomiting, abdominal distension, poor feeding, and failure to thrive.

Older presentation is more common in breastfed infants who will typically develop constipation around the time of weaning.

COMPLICATIONS

Enterocolitis, chronic obstruction, incontinence, constipation, and late mortality may occur late after surgery for Hirschsprung disease [13].

Enterocolitis accounts for significant morbidity and mortality in patients with Hirschsprung disease. Enterocolitis is characterized by inflammation of the colon, the intestinal lumen fills with a fibrinous exudate, and the risk of perforation increases. Approximately 10-30% of patients with Hirschsprung disease develop enterocolitis. Long-segment disease is associated with an increased incidence of enterocolitis. The risk of enterocolitis does not decrease with surgical correction.

Complications of surgery include anastomotic leak (5%), anastomotic stricture (5-10%), intestinal obstruction (5%), pelvic abscess (5%), and wound infection (10%) [13].

Patients with a syndromic association and those with long-segment disease have poorer outcomes.

MORTALITY AND MORBIDITY

Untreated aganglionic megacolon in infancy may result in a mortality rate as high as 80%. In cases of treated Hirschsprung disease, the mortality rate may approach 30% as a result of severe enterocolitis [13].

DIFFERENTIAL DIAGNOSIS

- Acute or chronic megacolon
- Constipation
- Hypothyroidism
- Intestinal motility disorders
- Irritable bowel syndrome
- Toxic megacolon.

DIAGNOSIS

The diagnosis of HD is based on combination of clinical features, radiological appearance of bowel and histological features on suction renal biopsy that is agangliosis and abnormally large nerves.

An abdominal radiograph can show intestinal loop distention with fluid levels.

The major disadvantage of imaging techniques is their inadequacy in children under 3 months of age and risk of perforation during contrast administration in patients with acute enteritis [14].

Anorectal manometry detects the relaxation reflex of the internal sphincter after distension of the rectal lumen. This normal inhibitory reflex is presumed absent in patients with Hirschsprung disease.

The test demonstrates 90% sensitivity. Unfortunately, it can only be carried out in patients at least 12 months old because the relax reflex of the anal internal sphincter may not be developed in infants. Manometry is useful for screening in case of constipation in older children [15].

Recently, anal biopsy has been considered as the important diagnostic tool, with 95% accuracy in HD diagnosis.

Moreover, when additional immunohistochemical studies were carried out, the correct diagnosis was shown to have very high sensitivity, up to 99.7% [16].

Accurate diagnosis depends on the site of biopsy, the representativeness of the samples taken, the number of specimens, and finally the pathologist's skill. If all the criteria are met, diagnostic sensitivity can even reach 100%.

As far as histology is concerned, the basic criterion of HD diagnosis is the lack of ganglion cells in the submucosal or intramuscular nerve plexus of the intestinal wall and the presence of hypertrophic nerve fibres and trunks.

There are numerous ways of carrying out various forms of biopsy to obtain materials for tests, e.g. transmural, submucosal, and serosal-muscular. Suction biopsy is recommended in most centres, which is believed to be a simple, safe, fast, and inexpensive method [17].

The key point of the biopsy is the place from which the material was obtained. In children such material must be obtained at least 2 cm above the pectinate line [14].

If the material is not obtained accurately, in the his- topathological examination a pathologist can observe the presence of the so-called "anal transition zone" with epithelium different than that from the large intestine, showing characteristics of squamous epithelial cells (morphology resembling uroepithelium) in the proximity of the pectinate line. The presence of this area should be described in detail in the histopathological report to avoid false positive HD diagnosis.

Suction biopsies are more difficult to interpret than conventional biopsies because they show only the surface submucosal nerve plexus.

H + E staining remain the method of choice for identification of ganglion cells (Figure 3 A). Regular biopsies for H + E slides studies require "only" fixation of material in buffered formalin and then standard processing. Standard histology obtained from rectal suction biopsies that sample mucosa and underlying submucosa, demonstrating rectal aganglionosis, requires the analysis of 100 or more histological sections to ensure good specificity, and is therefore time consuming.

Moreover, difficulties in analysis may arise in several situations: (1) when the site of biopsy is too distal, because of the physiological paucity of ganglion cells; (2) when the sample is too superficial with not enough submucosa; and (3) when there is difficulty in identifying gang- lion cells with confidence, particularly in neonates. For these reasons, standard histology is frequently supplemented with acetylcholinesterase histochemistry.

This technique, showing staining of extrinsic nerve fibers, provides quick results but requires frozen tissue samples.

False-negative results are primarily related to the young age of patients, to short or long segments of aganglionosis and to HD associated with Down's syndrome.

Furthermore, besides typical abnormal staining, several subtle abnormal patterns of acetylcholinesterase staining have been described. Thus, acetylcholinesterase staining can be difficult to carry out and interpret even for pathologists experienced in diagnosing HD [18].

In practice, these difficulties may lead to sequential rectal biopsies and delay in surgical treatment.

Several immunohistochemical markers such as S-100 protein, neuron-specific enolase14 or glial fibrillar acid15 have been tried in the past years, but none have been demonstrated to be superior to acetylcholinesterase [19].

Calretinin is a vitamin D-dependent calcium-binding protein involved in calcium signaling, which has an important role in the organization and functioning of the central nervous system. Calretinin immunohistochemistry holds several ad-vantages, such as: it is carried out on a formol embedded superficial rectal biopsy and its staining pattern is simple and not doubtful; and it is either positive or negative.

In the submucosal nerve plexus, a strong nuclear staining highlights the ganglion cells usually accompanied by a positivity of Schwann cells .On the basis of calretinin immunohistochemistry results, non-HD diagnosis was made when specific calretinin staining was present and HD was diagnosed when there was no staining.

Calretinin immunohistochemistry overcomes most of the difficulties encountered using the combination of histology and acetylcholinesterase staining, and detects almost all cases of HD with confidence, with no false positives. Thus, we demonstrate that calretinin is superior to acetylcholinesterase to complete histology and could advantageously substitute for acetylcholinesterase [20].

DIAGNOSTIC SCHEME:

Figure 1. Classification Of Hirschsprung's Disease According To The Length Of Aganglionicsection

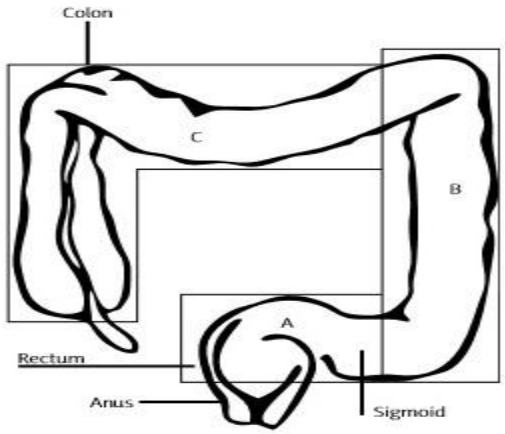


Figure 2. Rectal anatomical structure- The place of obtaining materials – at least 2 cm above the pectinate line

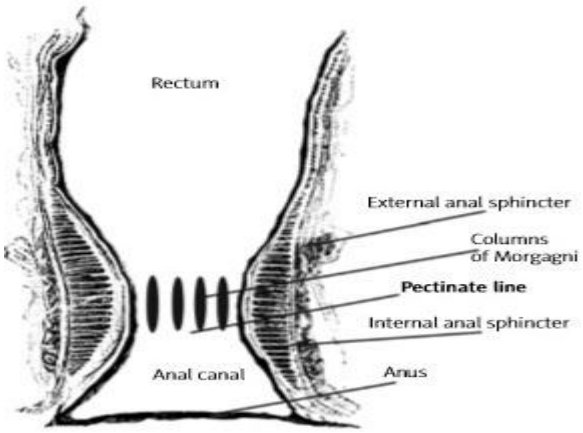
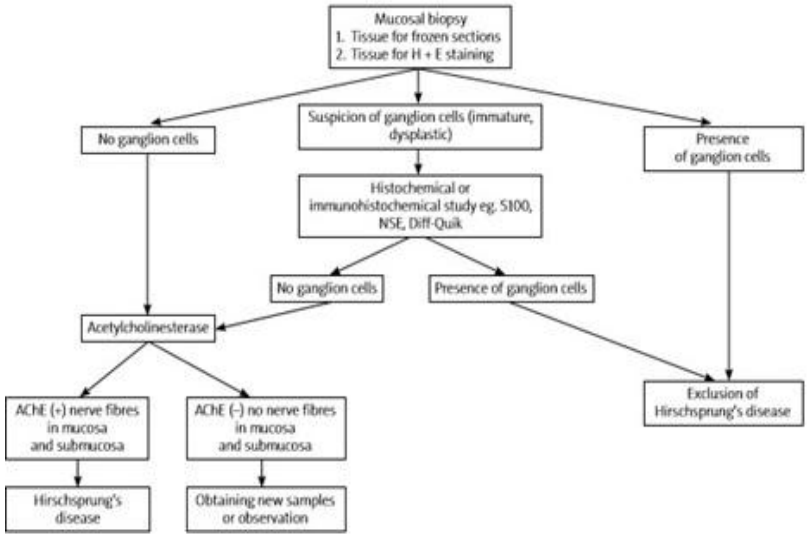


Figure 3. Diagnostic Scheme



CONCLUSION

Hirschsprung's disease diagnostics requires close cooperation between clinicians and pathologists. On the one hand, accurate diagnosis depends on the site of biopsy, the representativeness of the samples taken, the number of specimens, and finally the pathologist's skill. If all the criteria are met, diagnostic sensitivity can even reach 100%.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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