Hirschsprung's disease

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Abstract

Hirschsprung's disease (HSCR) is characterized by a lack of enteric nervous system ganglion cells (aganglionosis) in a variable extent of distal bowel. It is the most common congenital bowel motility disorder, and affected neonates usually present with distal intestinal obstruction in the first few days of life. Current treatment involves resection of the aganglionic bowel and a 'pull-through' procedure to bring the normally innervated bowel down to the anal margin. Despite advances in surgery, outcomes can be poor especially in long-segment HSCR in which a longer segment of bowel or the entire colon is aganglionic. Children are more prone to enterocolitis and up to 75% have problems with incontinence or constipation. Some children require a long-term colostomy. This review aims to provide an overview of Hirschsprung's disease, outlining the aetiology of HSCR and management of children with HSCR.

Keywords Aganglionosis; enteric nervous system; Hirschsprung's disease

Definition

Hirschsprung's disease (HSCR) is the most common congenital gut motility disorder and is characterized by the absence of ganglion cells (aganglionosis) in the myenteric and submucosal plexuses of the distal intestine. It is thought to arise from a failure of colonization of the distal gut by enteric nervous system (ENS) precursors during embryonic development.

Background

The first description of this condition dates back to the ancient Hindu surgeons in the Shushruta Samheta who described a disease analogous to HSCR named Baddha Gudodaram. In 1887, Dr Harald Hirschsprung, a Danish paediatrician, was first to describe HSCR in the medical literature following the demise of two children with intestinal obstruction. At this time, the pathological basis of HSCR was still unknown and the condition was conceived as 'congenital megacolon'. Treatment involved removal of the dilated segment which was thought to be abnormal. The absence of ganglion cells in the distal colon of a child with HSCR was first recognized by Tittel in 1901, but it was not until 1946 that Ehnpreis attributed to the cause of the intestinal obstruction in HSCR to aganglionosis within the non-dilated distal bowel segment.

Incidence and classification

The incidence of HSCR is approximately 1 in 5000 live births, although this does not account for interracial differences and the incidence can be significantly higher in populations with high consanguinity rates. Short-segment HSCR, in which the aganglionic segment is restricted to the rectosigmoid region, accounts for over 80% of cases. The aganglionosis is more extensive in long-segment (LS) HSCR and may affect the entire colon resulting in total colonic aganglionosis (TCA). On rare occasions the distal small bowel may also be affected and this is associated with significant associated morbidity and mortality. Males are two to four times more commonly affected by HSCR than females; however, this gender bias does not remain in children with more extensive aganglionosis.

Pathoembryology

ENS neurons and glia are derived from the vagal segment of the neural crest as demonstrated in neural crest ablation studies in chick-quail chimaera experiments. Vagally derived neural crest cells (NCCs) migrate along the course of the vagus nerves, enter the foregut mesenchyme and spread in a cranio-caudal direction throughout the GI tract. In humans, this process takes 7 weeks. Neural crest derivatives enter the foregut, distal ileum and mid-colon by 5, 7 and 8 weeks, respectively, infiltrating the myenteric plexus prior to the submucosal plexus. The colon is colonized by ENS derivatives by 12 weeks of gestation. It is thought that the slowing of rate of colonization of the distal gut is caused by elongating growth of the bowel rather than a reduction in velocity of migration. There is also an additional sacral contribution to the colonic ENS which follows vagal neural crest colonization.

Vagally sourced NCC's in the distal rectum migrate further than any other cells during embryogenesis. It is not surprising that factors affecting the proliferation, survival, migration or differentiation of NCCs may result in aganglionosis of the distal gut.

The critical role of the ENS is demonstrated by the obstruction that occurs in children with HSCR. The aganglionic segment remains in a tonic state and colonic movements are unable to propagate through the segment. Presence of faeces in the rectum fails to elicit relaxation in the aganglionic internal anal sphincter, which contributes to the obstructive picture seen clinically even after corrective surgery.

Genetics

A large number of genes have been identified as being involved in the development of HSCR through a combination of gene-mapping studies in humans and through targeted gene deletions in animals.

Associated malformations occur in up to 35% of cases (Table 1). Typically, these malformations occur in neural crest derived structures and HSCR is regarded as a *neurocristopathy*.

Up to 20% of cases of HSCR are familial. However, the pattern of inheritance is complex — often gene mutations exhibit

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Additional anomalies in Hirschsprung's disease

Anomaly	Example
Neural crest-related anomalies	• Congenital central hypoventilation syndrome • Isolated sensorineural deafness • Waardenburg syndrome • Di George syndrome • CRASH syndrome (X-linked aqueductal stenosis) • Congenital muscular dystrophy • Goldberg Shprintzen syndrome • Neurofibromatosis type 1 • Multiple endocrine neoplasia type 2A • Multiple endocrine neoplasia type 2B • Smith—Lemli—Opitz syndrome • Dysautonomias
Other anomalies	• Trisomy 21 • Microcephaly • Mental retardation • Inguinal hernia • Small bowel atresia • Duodenal atresia • Genital reproductive tract • Undescended testes
Regional anomalies	• Rectal stenosis • Anal stenosis • Imperforate anus • Colonic atresia

Table 1

autosomal dominant inheritance with variable penetrance. Mutations in any of the genes responsible for neural crest cell migration, proliferation, differentiation, survival or that alter the environment for NCC migration, can lead to failure of ENS development resulting in HSCR. The main gene that has been linked with HSCR is the Receptor tyrosine kinase (*Ret*) gene, a proto-oncogene on chromosome 10q11. Other genes that have been identified are outlined in Table 2.

Knowing which genes are involved is important with regards to genetic counselling and potential adverse associations, i.e. familial medullary thyroid carcinoma (FTMC) as part of multiple endocrine neoplasia syndrome type 2 B (MEN2B). Individuals with disease-causing mutations in *Ret* are offered prophylactic thyroidectomy before the FTMC has metastasized (typically <2 years of age). Trisomy 21 (Down's) is one of the most commonly associated malformations and carries 100 times the risk of HSCR than the normal population. However, due to the variable penetrance of known mutations, knowledge of presence/absence of mutations does not allow prediction of the risk of Hirschsprung's disease so at present widespread screening is not advocated. In addition, fetal environmental factors such as first trimester maternal pyrexia may play a role in determining the development of HSCR.

Presentation and examination

Neonates with HSCR usually present with distal intestinal obstruction (DIO) in the first few days of life. Any term baby who fails to pass meconium in the first 24—48 hours after birth should be assessed for HSCR. Signs of DIO include abdominal distension, failure to establish feeds, and non-bilious or bilious vomiting.

Hydration should be adequately assessed by examining the baby's fontanelles, central capillary refill time, peripheral temperature, mucous membranes, and skin turgor in addition to physiological parameters (i.e. heart rate, blood pressure, respiratory rate and oxygen saturations).

It is important to assess for dysmorphic features, in particular features of Down's syndrome, spinal abnormalities, and for normal placement of the anus to exclude an anorectal malformation. The abdomen is usually moderately distended with palpable intestinal loops. Alternative diagnoses are outlined in Table 3.

In some cases, presentation may be delayed and the neonate or infant may present with features of enterocolitis. These include foul-smelling stools or blood per rectum, pyrexia, and abdominal distension. The child may be irritable, look generally unwell or listless, or may be critically unwell with signs of septic shock. Key management includes early resuscitation and

Summary of genes involved in Hirschsprung's disease and associated conditions

Gene	Abbreviation	Associated conditions
Receptor tyrosine kinase	*Ret*	Multiple endocrine neoplasia type IIA (MEN2A) Multiple endocrine neoplasia type IIB (MEN2B) Medullary thyroid carcinoma
Glial cell-line derived neurotrophic factor	*GDNF*	
Neurturin	*NTN*	
Endothelin B receptor	*EDNRB*	Shah-Waardenburg syndrome (WS4)
Endothelin-3	*EDN3*	
Endothelin-converting enzyme	*ECE-1*	
SRY-related HMG-box 10	*Sox10*	
Pairedlike homoeobox 2 b	*Phox2b*	Neuroblastoma Central hypoventilation syndrome

Table 2

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