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 article 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. Dr Harald Hirschsprung, a Danish Paediatrician, was the first to describe HSCR in the medical literature in 1887 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; however, it was not until 1946 that aganglionosis within the non-dilated distal bowel segment was attributed to the cause of the intestinal obstruction in HSCR by Ehnpreis.

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. 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 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 in rectosigmoid disease; however, this gender bias does not remain in children with more extensive aganglionosis.

Neural crest origin of the enteric nervous system (ENS) and pathogenesis of Hirschsprung's disease

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 cranio-caudal direction through the gastrointestinal (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 completely 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 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.

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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 • SmitheLemlieOpitz 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

Associate 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 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 common associated malformations and carries one hundred times the risk of HSCR than the normal population. However, due to the variable penetrance of known mutations, at present, knowledge of presence/absence of mutations does not allow prediction of the risk of Hirschsprung's disease so 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, although about half of infants with HSCR will pass meconium within this time. Signs of DIO include abdominal distension, failure to establish feeds and non-bilious or bilious vomiting.

Hydration should be adequately assessed by examining the fontanelles, central capillary refill time, temperature of the peripheries, 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 listed in Table 3.

In some cases, presentation may be delayed and the neonate or infant may present with features of enterocolitis. Features of enterocolitis includes 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 administration of broad spectrum IV antibiotics in addition to bowel decompression. Enterocolitis can be fatal and should not be underestimated by the clinician.

Investigations and management

Following clinical examination, intravenous access should be sought and a fluid bolus of 20 ml/kg normal saline administered if the neonate demonstrates signs of dehydration or shock. A further fluid bolus may be required. Intravenous metronidazole or vancomycin should be administered to prevent enterocolitis and bacterial translocation.

A nasogastric tube aids decompression of the stomach and should be regularly aspirated. Rectal stimulation using a 10 or 12 French rectal tube may incite explosive stool per rectum and is highly suggestive of HSCR. Decompression of the colon is carried out via a rectal catheter inserted into the rectum using 10 ml/kg aliquots of warm normal saline up to a maximum of 20 ml/kg. This can be performed up to three to four times per day as necessary. Anal dilatations using Hegar dilators are a useful adjunct to rectal washout.

An abdominal radiograph will demonstrate dilated loops of bowel with a paucity of distal gas in keeping with lower intestinal obstruction. In more extensive forms of HSCR, the dilatation may be more marked.

A contrast enema is useful for excluding other conditions and providing a topographic map of rectosigmoid anatomy to aid in surgical planning (Figure 1). Often a transition zone between dilated ganglionic bowel and normal calibre aganglionic bowel can be visualized; however, this does not reliably correspond to

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

the true transition zone between ganglionic and aganglionic intestine. The only way to determine the extent of aganglionosis is by serial extramucosal biopsies and histopathological examination.

A stoma may be required in long-segment disease or when there is failure to decompress the colon through rectal washouts.

Rectal suction biopsy is the gold standard investigation to obtain a diagnosis of HSCR and should be carried out once the neonate has been sufficiently decompressed and re-established on oral feeds. Neonates should be above 2 kg and prior consent should be obtained from parents. The potential risks include perforation, bleeding and inadequate tissue sampling. At least two biopsies should be obtained from 2 cm to 4 cm above the anal verge.

Histopathology

Histological examination using hematoxylin and eosin staining confirms absence of ganglion cells in the submucosal and myenteric plexi and presence of hypertrophied nerve trunks. In addition, there is an abundance of acetylcholinesterase which is revealed during frozen section staining. Immunohistochemical staining using antibodies to neuronal markers such as calretinin and S100 are useful to confirm the diagnosis and they can be performed on fixed specimens. Thickened nerve trunks may be absent in cases of total colonic aganglionosis.

Alternative diagnoses in children with distal intestinal obstruction

- Anorectal malformation
- Small left colon syndrome
- Meconium ileus
- Colonic atresia
- Volvulus
- Pelvic mass/tumour
- Idiopathic constipation
- Hypercalcaemia
- Hypothyroidism

Table 3

Older children

Some children present at a much later stage with chronic constipation refractory to medical management. A thorough history and examination is pertinent to rule out alternative causes of constipation and investigations should include serum thyroid function and calcium levels prior to proceeding to rectal biopsy. In such cases, a strip rectal biopsy should be obtained. Only a very small proportion of children referred with chronic constipation have HSCR.

Surgery

Traditionally, surgery was carried out in two or three stages. This is less frequent currently and most surgeons perform a single-stage primary pull-through in the first few months of life. In the interim, the neonate may be nursed at home once the parents are confident in performing washouts. Parents should be informed about the signs and symptoms of enterocolitis and preoperative

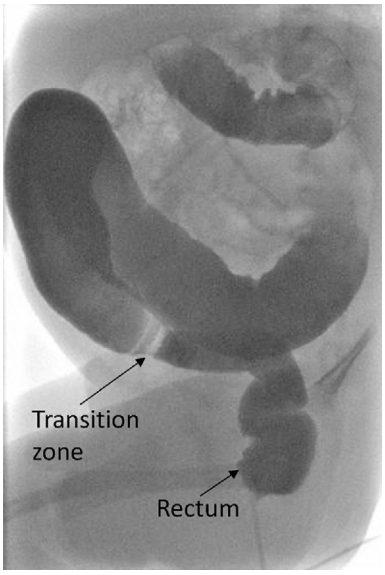

Figure 1 Contrast enema demonstrating the funnel-shaped transition zone within the sigmoid colon. The proximal colon appears dilated in contrast to distal narrowed sigmoid colon.

enterocolitis should be treated aggressively. A stoma is formed if decompression is not possible, if the child presents with severe enterocolitis or if a primary definitive procedure is complicated by extensive aganglionosis.

Definitive surgery for HSCR involves resection of the aganglionic bowel including transition zone and bringing the 'normal' ganglionic bowel down to the dentate line with preservation of sphincter function. There are two distinct steps during surgery:

1. **Intraoperative extramucosal biopsies followed by frozen section pathological examination** in order to assess the extent of aganglionosis and determine the demarcation of normal ganglionic bowel. Typically, the biopsies are obtained laparoscopically. This step allows the surgeon to know how much bowel needs to be resected and to plan the operation. The proximal resection margin should be 5 cm proximal to the most distal ganglionic biopsy to avoid a transition zone pull-through. We recommend sending the histopathologist a donut of tissue intraoperatively from the proximal resection margin to ensure that the bowel is appropriately ganglionic circumferentially.
2. **Completion of pull-through by bringing ganglionic bowel down to the dentate line**. There are three commonly performed procedures with various modifications. These are the Swenson, Soave and Duhamel pull-through procedures. The different techniques and complications associated with each technique are outlined in Figure 2 and Table 4. At present, there are no robust long-term comparative studies to establish which approach is associated with the lowest complication rate and best long-term outcomes.

Laparoscopy is useful for mobilizing the colon proximal to the rectosigmoid colon (i.e. splenic flexure) to enable a tension-free anastomosis. It is also useful for assessing the orientation of the pulled through segment to prevent obstruction secondary to twisting. When performing pull-through surgery, recognition and preservation of the dentate line is essential in preserving sensation and continence.

In cases of TCA, further techniques include using a colonic patch to aid water absorption following pull-through (Martin — left colon, Kimura — right colon) or creating an ileal J pouch. Despite these techniques outcomes remain poor for children with very extensive aganglionosis and some children may be considered to be candidates for bowel transplantation in the future is a significant proportion of their small bowel is affected.

Early complications following pull-through include enterocolitis, anastomotic leak or stricture, perianal excoriation and adhesional obstruction.

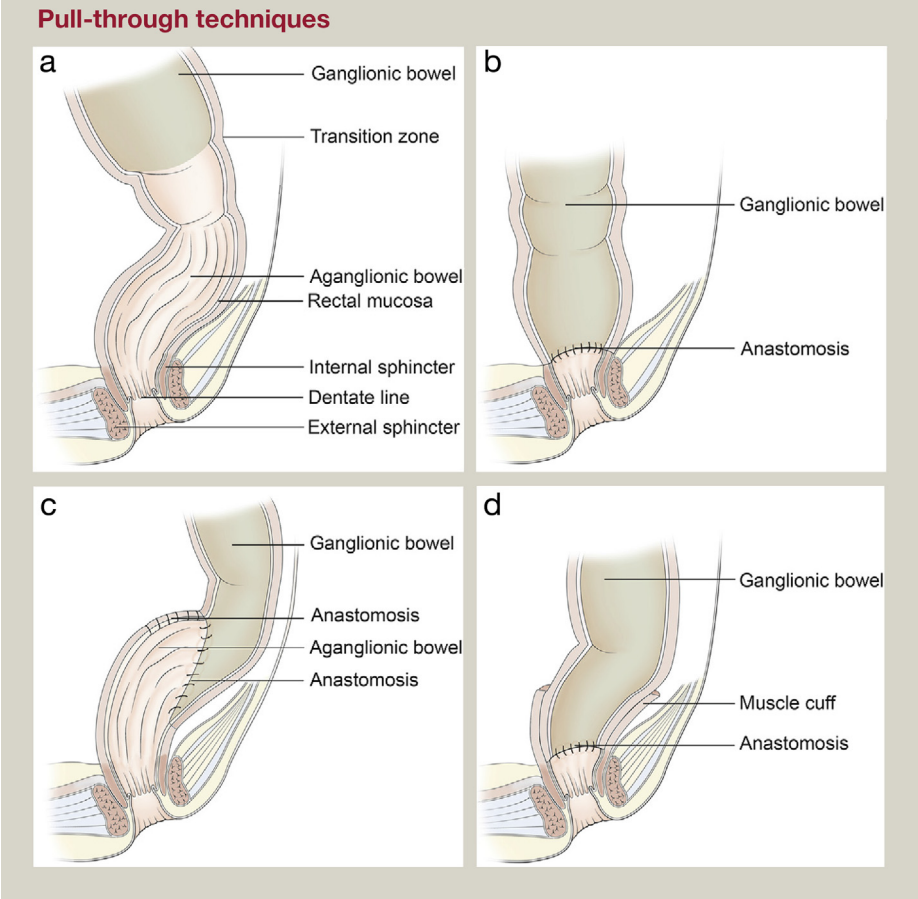

Figure 2 (a) The anatomy of recto-sigmoid Hirschsprung's disease. (b) Swenson pull-through: full-thickness dissection of rectum. The proximal ganglionated bowel is anastomosed to the anus (c) Duhamel procedure: ganglionic bowel is delivered through an incision in the posterior aspect of the aganglionic rectum and the septum is divided using a stapler. (d) Soave procedure: extramucosal dissection of the lower rectum and full thickness dissection superiorly, with pull-through of the ganglionated colon into an aganglionic muscle cuff.

Commonly performed pull-through procedures

Procedure	Technique	Complications
Swenson (1948)	• Full-thickness dissection above dentate line • Colo-anal anastomosis from outside	Pelvic nerve and anterior structure damage (incontinence, damage to vas/urethra/bladder/vagina)
Soave (1964)	• Colonic dissection in submucosal plane above dentate line • Ganglionic bowel pulled-through rectal muscle sleeve	Retained ganglionic muscle cuff may cause functional obstruction and constipation or sleeve abscess
Duhamel (1956)	• Dissection behind rectum to create a tunnel • Ganglionic bowel brought through and side to side anastomosis with GI stapler to aganglionic bowel	Anterior blind pouch can lead to faecaloma and recurrent obstruction

Table 4

Outcomes

Long-term problems are associated with ongoing obstructive symptoms, soiling and enterocolitis. Up to 10% of children may require a colostomy and a further 10% need further surgery to treat constipation/incontinence.

Constipation

Constipation can be due functional megacolon or to mechanical obstruction, i.e. stricture, retained spur in Duhamel operation, long muscular cuff in Soave or twist of pull-through bowel. Rectal examination and contrast enema are helpful to identify a mechanical cause. Other causes include recurrent or residual aganglionosis and internal anal sphincter achalasia.

A rectal biopsy should be obtained if residual aganglionosis is suspected as in some cases the anastomosis may have been performed at the transition zone and re-do surgery may be beneficial if a zone of aganglionosis is identified.

No currently described surgical procedure overcomes residual aganglionosis seen in the internal sphincter. Obstructive symptoms due to internal anal achalasia are often seen due to the lack of normal recto-inhibitory reflex of the internal anal sphincter. This can be confirmed by demonstrating a response to botulinum toxin which is also temporarily therapeutic.

Stool-holding behaviour is common in children and often best managed with a bowel management regime consisting of laxatives and behaviour modification strategies. Some children may require a caecostomy for antegrade enemas.

There may be altered motility in the remaining bowel following pull-through which can be demonstrated by a colonic transit study or colonic manometry.

Soiling

Soiling can be due to abnormal rectal sensation, abnormal sphincter function or 'pseudoincontinence'. Lack of sensation can be a consequence of the anastomosis being performed below the dentate line and if the internal anal sphincter is damaged during the pull-through procedure this too can lead to soiling. Unfortunately, these problems cannot be salvaged in retrospect and require a bowel management routine to enable the child to be continent for a majority of the time. In some cases, a long-term colostomy may be required.

Pseudoincontinence may be secondary to severe constipation with overflow or hyperperistalsis of the pull-through bowel and a transit study can be very useful in determining the cause of incontinence. Children with rapid transit may benefit from a constipating diet and anti-motility agents such as loperamide. Fructose, lactose and protein intolerances have been recognized in causing rapid transit and incontinence after HSCR surgery. Exclusion diets can be very effective if sensitivity is found on testing.

Enterocolitis

Enterocolitis is a potentially lethal sequelae of HSCR which can occur both before and after a pull-through procedure. The aetiology of HSCR-associated enterocolitis is unknown; however, stasis caused by functional obstruction may lead to bacterial overgrowth and secondary infection. Younger children, those with longer segment disease and trisomy 21 or other associated congenital malformations tend to be more prone to developing enterocolitis. Early identification of symptoms is paramount and as previously described, treatment consists of fluid resuscitation, administration of broad spectrum IV antibiotic, including Gram negative cover, and bowel decompression.

Long-term outcomes

The long-term outcomes of Hirschsprung's disease remain poorly described. Small cohort studies show minimal impact on quality of life but significant diarrhoea and incontinence persisting into adulthood. These outcomes will become increasingly well described over the next decade as the core outcome set is used to standardize the assessment of patients with HSCR.

Conclusion

Successful surgery for Hirschsprung's disease requires meticulous operative technique, thorough preoperative and perioperative planning and access to reliable experienced histopathology. Despite this, challenges remain in managing the long term complications of enterocolitis, incontinence and constipation. ◆

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