Hirschsprung's Disease in Newborns

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Contents

Abstract

Hirschsprung's disease, first described by Harald Hirschsprung in 1886, is one of the most common causes of intestinal obstruction in the newborn.

The disease occurs in roughly 1 in 5000 live births with a strong male preponderance and results as a consequence of abnormal migration of neural crest-derived neuroblasts that determines congenital absence of intestinal intramural ganglia within the enteric nervous system (ENS) with variable distal bowel involvement.

Symptoms range from neonatal intestinal obstruction to chronic progressive constipation in older children; a common severe complication presenting in many patients is enterocolitis.

The gold standard for the diagnosis of Hirschsprung is rectal suction biopsy.

The treatment is surgical and involves removing the aganglionic bowel and reconstructing the intestinal tract by bringing the normally innervated bowel down to the anus.

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85.1 Salient Points

- Hirschsprung's disease (HSCR) is one of the most common causes of intestinal obstruction in the newborn.

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- Mutations affecting the RET proto-oncogene on chromosome 10q11.2 were identified in HSCR patients.
- Hirschsprung-associated enterocolitis (HAEC) represents the most severe complication of the disease.
- The gold standard for the diagnosis of HSCR is rectal suction biopsy.
- Laparoscopic-assisted endorectal pull-through (Soave-Georgeson technique) is the procedure of choice both in newborns and infants with HSCR.

85.2 Introduction

Although sporadic reports of patients with suggestive clinical features are dated back to the seventeenth century, the first telling and concise description of the disease is that of Sir Harald Hirschsprung, a Danish pediatrician who reported the details of his series of two patients at the Society of Pediatrics in Berlin in 1886.

Hirschsprung's disease (HSCR) is one of the most common causes of intestinal obstruction in the newborn. The disease occurs as a consequence of abnormal migration/differentiation of the neural crest-derived neuroblasts into the developing gut; this determines absence of intestinal intramural ganglia. Synonyms of HSCR are congenital megacolon and intestinal aganglionosis that indicate severe bowel loops distension and absence of intramural ganglia, respectively. Most patients present in infancy, and early diagnosis is important to avoid complications. Overall prognosis is good. In fact, with proper treatment most patients live normal adult lives (Holschneider and Puri 2000).

85.3 Etiology and Pathogenesis

The disease is caused by the failure of the neural crest-derived neuroblasts to migrate cranio-caudally during weeks 5–12 of gestation. This abnormal migration determines congenital absence of intestinal intramural ganglia within the enteric nervous system (ENS) (myenteric and submucosal plexuses) with variable distal bowel involvement. This intrinsic innervation is named "gut mini brain" or enteric nervous system and coordinates movements, immune functions, and secretion of the gut. Subsequently, its abnormality determines functional bowel obstruction and facilitates the onset of severe infections known as Hirschsprung-associated enterocolitis (HAEC), which represents the most severe complication of the disease.

The pathogenesis is still unclear, but recent studies suggest that the intestinal microbiota contributes to the etiology of enterocolitis and may play an important role in the development of the disease (Frykman et al. 2015).

The diseased bowel begins at the pectinate line (anal canal shows physiologic aganglionosis) and extends proximally with variable distal bowel involvement. Aganglionosis extending up to the splenic flexure of the colon is named classic or rectosigmoid HSCR (most frequent, accounts for up to 80% of cases); the one extending beyond (confined within the large bowel) is named long HSCR (10%); whereas the one involving the whole large bowel (usually extending to at least 5–7 cm of terminal ileum) is defined total colonic aganglionosis (TCSA) or ultralong HSCR (10%). Total intestinal aganglionosis (TIA) is extremely rare and is nearly incompatible with life, even though the advent of parenteral nutrition, innovative surgical techniques, and small bowel transplantation have improved survival (Holschneider and Puri 2000; Coran and Teitelbaum 2000; Loening-Baucke and Kimura 1999; Ruttenstock and Puri 2009).

This is a complex genetic disease as suggested by the high proportion of sporadic cases, variable expressivity, incomplete sex-dependent penetrance, and variable risk of sibling recurrence. In 1994, mutations affecting the RET proto-oncogene on chromosome 10q11.2 were identified in HSCR patients, the same being also involved in different diseases such as multiple endocrine neoplasia type 2A and 2B and sporadic and familial medullary thyroid carcinoma. Since then, loss-of-function of RET tyrosine-kinase has been demonstrated in approximately 50% of familial and 10–15% of sporadic HSCR cases (Parisi and Kapur 2000; Stewart and von Allmen 2003; Eng 1996; Romeo et al. 1994). Eight other HSCR susceptibility genes

have been identified to date namely GDNF, EDN3, EDNRB, NRTN, ECE1, PHOX2B, SOX10, and ZFHX1B. Amongst these, GDNF belongs to the Ret signaling pathway.

Strong genetic background is also confirmed by the frequent presence of associated anomalies that can basically involve all systems and organs. Association can be either syndromic or not. Down syndrome (trisomy 21) is the most common chromosomal abnormality associated with the disease, accounting for approximately 10% of patients. Other syndromic associations are those with congenital central hypoventilation (Ondine's course), Waardenburg-Shah, Bardet-Biedl, Mowat-Wilson, Goldberg-Shprintzen, and others. Non-syndromic associations are those involving neurologic, cardiovascular, urogenital, gastrointestinal, and skeletal systems, metabolism, or pigmentation. Anomalies that have been encountered in HSCR patients include congenital deafness, refractive anomalies or visual impairment, hydrocephalus, bladder diverticulum, Meckel's diverticulum, imperforate anus, ventricular septal defect, renal agenesis, cryptorchidism, and neuroblastomas. Recent evidence suggested that the incidence of associated anomalies is somehow underestimated with true isolated HSCR being relatively rare (Amiel et al. 2008; Tomita et al. 2003; Pini Prato et al. 2009, 2013).

85.4 Clinical Aspects

HSCR is a congenital disease, which can be familial or sporadic. It occurs in roughly 1 in 5000 live births, but its incidence varies significantly among ethnic groups (1.5, 2.1, and 2.8 per 10,000 live births in Caucasians, African-Americans, and Asians, respectively). There is a strong male preponderance, with a male to female ratio of roughly 4:1. Familial cases are not infrequent. Approximately 3–5% of male siblings and 1% of female siblings of children with classic HSCR also have the disease. However, the risk is substantially higher (12.4–33%) in siblings of children with TCSA.

Symptoms range from neonatal intestinal obstruction to chronic progressive constipation in older children (Table 1). Although meconium delay has long been considered a characteristic feature of HSCR patients, in a review of more than one hundred patients, we demonstrated that "only" 64% percent of infants with Hirschsprung's disease fail to pass meconium in the first 24 h of life (Pini Prato et al. 2008a). More than 90% of HSCR patients had symptom onset before 1 year of age with difficult bowel movements, poor feeding, and progressive abdominal distention. Explosive bowel movements caused by functional colonic obstruction and hyperperistalsis are common in infants with Hirschsprung's disease. In fact, rectal examination may demonstrate a tight anal sphincter and explosive discharge of stool and gas. A small percentage of patients may not have symptoms until later in life. Common symptoms in older children include chronic progressive constipation, recurrent fecal impaction, failure to thrive, and malnutrition. One third of patients with Hirschsprung's disease present with the Hirschsprung associated enterocolitis rather than constipation. This severe and frightening complication is characterized by explosive smelly diarrhea, abdominal distension, and signs of impending septic or hypovolemic shock. HAEC still carries a significant morbidity (need for enterostomy) and mortality range between 5% and 50% (Khan et al. 2003; Hackam et al. 1998; Pini Prato et al. 2008b, 2011).

Table 1 Clinical features of patients with Hirschsprung's disease and incidence of symptoms

Symptoms of Hirschsprung's disease (series of 112 patients) (Pini Prato et al. 2008b)	Incidence (%)
Newborns and infants	
Abdominal distension	94
Difficult bowel movements	92
Failure to pass meconium	63
Intestinal obstruction	61
Failure to thrive	42
Enterocolitis	35
Older children	
Absence of soiling or overflow incontinence (Hackam et al. 1998)	96
Chronic constipation with onset before 1 year of age	96
Progressive abdominal distension	85
Fecal impaction	49
Failure to thrive	27

Though clinical features do not strictly correlate to length of aganglionosis, long HSCR and TCSA tend to have worse clinical features and outcome. Total bowel aganglionosis is extremely rare and is nearly incompatible with life (Pini Prato et al. 2008b, 2011; Menezes et al. 2008).

Based on typical clinical findings, HSCR can be suspected if the child is younger than 12 months at onset, complains of meconium delay, fails to thrive, does not experience overflow incontinence or soiling, and has a tight anal sphincter with empty rectum at physical examination. Symptoms may recur after previously resolving with enemas, laxatives, or feeding changes. Conditions that can mimic HSCR in the neonatal period include cystic fibrosis, meconium plug syndrome, small left colon syndrome, hindgut atresia, anorectal malformations, ENS immaturity of the preterm, hypothyroidism, intestinal neuronal dysplasia, and chronic intestinal pseudo-obstruction (Khan et al. 2003; Martucciello et al. 2005).

85.5 Diagnosis

The gold standard for the diagnosis of HSCR is rectal suction biopsy (RSB) (Pini-Prato et al. 2007). This is a safe and painless procedure that can be accomplished in an outpatient setting. The harvested specimens must be taken 1, 3 and 5 cm above the pectinate line and should contain enough submucosa to properly assess the ENS. It should be processed with histochemical and enzyme histochemical staining techniques including acetylcholinesterase, alpha-naftylesterase, NADPH-diaphorase, succinic and lactic dehydrogenases, and nitric oxide synthase for innervative assessment, and toluidine blue or hematoxylin and eosin for gross histology. The diagnostic features include absence of ganglia and thick parasympathetic nerve trunks in the submucosa and increased achetycholinesterase activity in the lamina propria (Bruder and Meier-Ruge 2010).

The diagnostic accuracy of RSB is close to 100% after 1 month of age but must be taken with care in the newborn or preterm who can only partially express all diagnostic features. In order to improve the diagnosis of HSCR, we implemented an innovative instrument to perform safe RSB at the bedside of both newborn and adult patients, which was named Solo-RBT. We reported a series of 389 biopsies performed with the instrument Solo-RBT with an incidence of complications (bleeding, perforation) lower than 1% (Martucciello et al. 2001; Pini Prato et al. 2001, 2006). Imaging can help diagnose Hirschsprung's disease. A plain abdominal radiograph may show a dilated small bowel or proximal colon. Contrast enema radiographs of the colon are commonly normal for the first few months of life and indefinitely in patients with total colonic disease. After the dilation process begins, the diseased portion of the colon will appear normal and the more proximal colon will be dilated. A "transition zone" (passage from aganglionic to normoganglionic bowel) may be visible on a contrast enema radiograph. However, the aganglionic colon will extend beyond this point in about 10% of patients (Proctor et al. 2003). Fig. 1 shows contrast enema radiographs of an infant with Hirschsprung's disease. Anal manometry (balloon distention of the rectum) demonstrates the absence of internal anal sphincter relaxation upon rectal distention. Contrast enema and anal manometry are similar in sensitivity and specificity and can only be used as adjunctive diagnostic tools with the diagnosis only being confirmed by histochemistry with a RSB (Fig. 2). The usefulness of barium enema relies in the possibility of predicting the length of aganglionosis and therefore plan surgical treatment accordingly.

85.6 Treatment

After HSCR is diagnosed, surgery is mandatory. Serial rectal irrigation helps decompress the bowel and prevent enterocolitis in the preoperative period. This treatment is essentially a temporary noninvasive colostomy to decompress the dilated colon. In otherwise healthy newborns with undistended colons and classic HSCR, radical surgery can be attempted primarily. If the child has HAEC, TCSA, or a significantly dilated colon, a decompressive enterostomy (either a colostomy or an ileostomy) can be placed for several months while the child

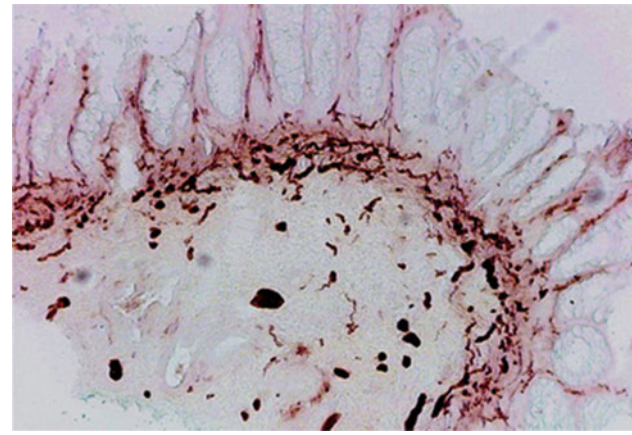

Fig. 1 Rectal suction biopsy of a neonatal Hirschsprung's disease. Acetylcholinesterase staining showing absence of ganglia, thick nerve trunks in the submucosal and increased acetylhcolinesterase activity in the lamina propria

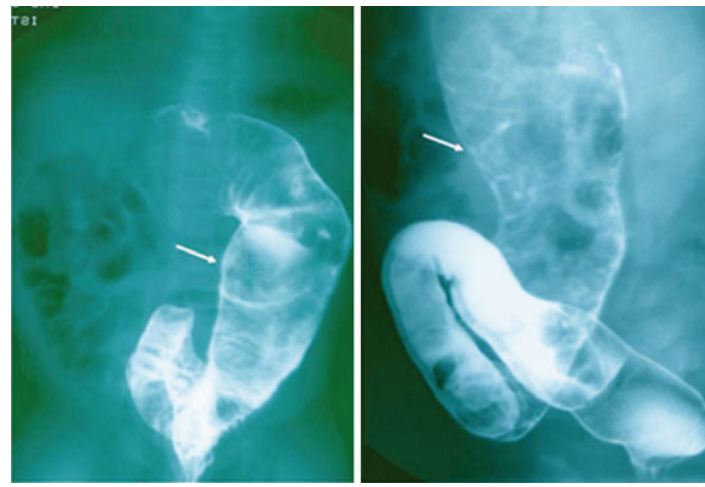

Fig. 2 Barium enema of a 2-month-old baby showing dilated descending colon (*white arrows*). These slides do not clarify the site extent of aganglionosis and the site of normoganglionic colon

recovers. There are several alternative surgical procedures to treat HSCR. All work well provided certain considerations are taken into account: (1) aganglionic bowel must be removed radically, including the rectum down to the sphincters, (2) the normoganglionic bowel must be identified with intraoperative seromuscular biopsies stained with histochemistry avoiding gross anatomical considerations and blind pull-through, (3) an experienced pathologist is required for intraoperative assessment in order to correctly identify the correct site of anastomosis as well as the possible presence of associated hypoganglionosis or intestinal neuronal dysplasia, and (4) surgeons must be well experienced to achieve better results and reduce the incidence of complications. The radical resection of the aganglionic bowel can be performed either with an endorectal, retrorectal, or perirectal approach (Soave, Duhamel, or Swenson procedure, respectively) depending on the surgeon's attitude. We have operated many patients since 1991, and we adopted either endorectal, retrorectal, or perirectal approaches with similar results (Pini Prato et al. 2008a). The advent of laparoscopy has modified the surgical approach and HSCR treatment changed accordingly (Mattioli et al. 2008; Langer et al. 2003; Ekema et al. 2003). The most frequently employed technique is, currently, the Soave-Georgeson technique, which embraces the advantages of the endorectal pull-through and those of the minimally invasive surgery (Figs. 3, 4, and 5) (Ekema et al. 2003).

We reviewed the results of a series of patients who underwent the Soave-Georgeson procedure

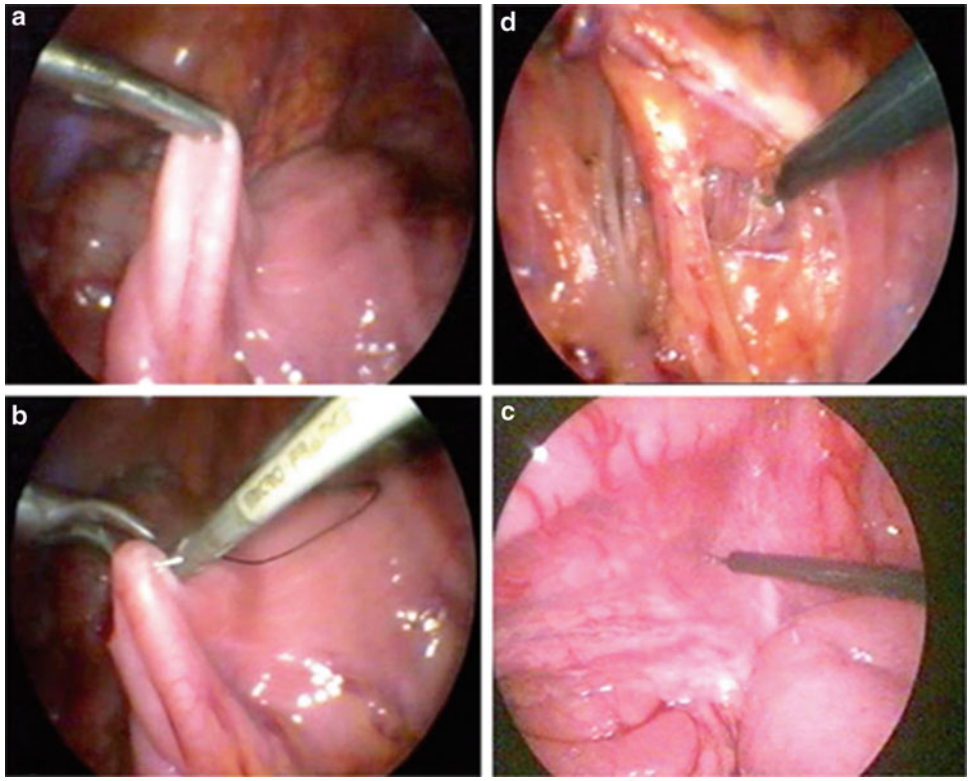

Fig. 3 Laparoscopic pictures of the intracorporeal steps of Soave-Georgeson technique. Anticlockwise: (**a**) Identification of the distended and hypertrophic colon, site of the seromuscular biopsy, (**b**) seromuscular biopsy to identify normoganglionic bowel, (**c**) commencing the preparation of the aganglionic rectum (newborn patients with virtually transparent mesentery), (**d**) nearly completed preparation of the mesentery before the perianal step of the procedure

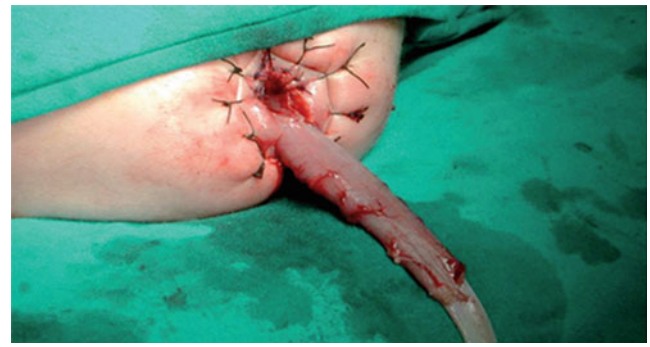

Fig. 4 Soave-Georgeson technique: transanorectal pull-through of the aganglionic bowel previously prepared during the laparoscopic step

and compared them with those of a matched series of patients who underwent a Soave-Boley procedure (conventional laparotomic procedure). We observed similar results (complications, functional outcome, fecal continence, etc.) but shorter hospitalization and better cosmetic scores.

Recently the robotic approach was introduced in the pediatric surgery but our results in HSCR treatment suggest that robot-assisted procedure may play a role only for older patients affected by the disease (Mattioli et al. 2017).

Basing on these considerations, we concluded that laparoscopic-assisted endorectal pull-through (Soave-Georgeson technique) is the procedure of choice both in newborns and infants with HSCR.

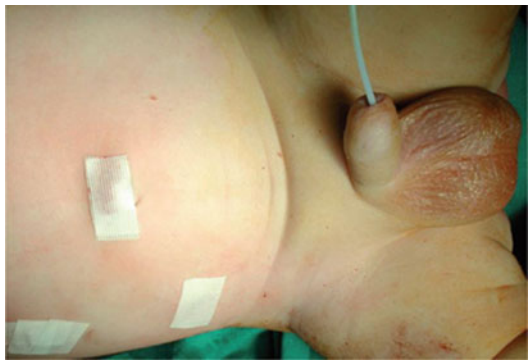

Fig. 5 Soave-Georgeson technique: final cosmetic appearance of the baby's belly

85.7 Prognosis

Mortality rate for HSCR is relatively low, being more frequent in the preoperative period as a result of severe HAEC occurrences (Pini Prato et al. 2011). Although mortality involves mainly newborns or young children, some reports described adult deaths due to septic complications secondary to severe enterocolitis. Postoperative results of the surgical treatment of HSCR appear to be satisfactory. However, despite good overall outcome, some authors showed a higher than expected incidence of problems in the long-term follow-up. Enterocolitis, constipation, failure to thrive, fecal soiling, and incontinence are the most frequent complaints regardless of the surgical technique adopted (Pini Prato et al. 2008a, b; Mattioli et al. 2008). In particular, various reports demonstrated that soiling and incontinence have an important impact on psychosocial functioning and parental criticism, and therefore on quality of life (Pini Prato et al. 2008a, b; Menezes et al. 2008).

There are many strategies for the treatment of these conditions (conservative management, pharmacological therapy, neuromodulation techniques, surgical intervention such as posterior sphincter myotomy or myectomy of the internal anal sphincter) (Ng et al. 2015). An alternative proposed management plan is the use of botulinum toxin (which is inoculated at the level of the internal anal sphincter), aiming for inducing a reversible relaxation of the internal anal sphincter (Han-Geurts et al. 2014).

Outcome of classic (rectosigmoid) HSCR can be hardly compared to that of ultralong HSCR (total colonic aganglionosis) as it is well known that the latter implies a significantly worse prognosis. Nonetheless, various reports demonstrated that overall outcome of HSCR improves with time and that this occurs during the whole childhood up to adolescence or adulthood.

In a series of 112 patients with HSCR, we observed a 15% incidence of complications (residual achalasia, stricture, adhesions, leakage, postoperative constipation, and enterocolitis) in the classic HSCR group and roughly 60% in the TCSA group. This confirmed that outcome is significantly interfered by extent of aganglionosis. With regard to long-term outcome, we observed overall good functional results. In particular, we observed 85% of excellent to good continence in the classic HSCR group of patients and 69% in the TCSA group. Psychological self-acceptance scored good to fair in 80% of classic HSCR and 55% of TCSA. Patients' perspectives were excellent to good in 98% and 100% of patients, respectively. Cosmetic results were excellent to good in 75% of classic HSCR and 18% of TCSA patients. Overall good expectations are reasonable but a number of patients with persistent issues can occur (Pini Prato et al. 2008a).

In the case of a redo operation, we can expect similar long-term results and outcome provided experienced surgeons and pathologists cooperate in the radical treatment. In our series, patients who underwent a redo pull-through for various reasons experienced results that do not significantly differ from those of a single pull-through. This allows optimistic expectations but suggests centralization of care in order to achieve the best for patients.

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