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*Review Article*

# Hirschsprung's Disease: Diagnosis and Management

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***Abstract***

*Hirschsprung's disease (HD) is a rare genetic congenital defect of intestine causing failure of migration of parasympathetic ganglionic cells in some definite part of intestine, resulting in functional intestinal obstruction. It commonly involves rectosigmoid region of colon but other parts of colon or total colon, even small intestine may be affected. Incidence is 1/5000 live births. It is one of the common pediatric surgical problems and 2nd most organic cause of constipation. Symptoms may be evident from 1st day of life. About 90% infants with Hirschprung's disease fail to pass meconium in 1st 24 hours of life. About 80% HD cases are diagnosed in early few months of life and present with abdominal distention, constipation, poor feeding, vomiting etc. HD enterocolitis is a devastating condition related to mortality. HD may be associated with some congenital anomalies and syndrome. High index of suspicion is the main key to diagnosis. Radiological investigation supports the diagnosis and rectal biopsy for histopathology is confirmatory. Although it is a surgical problem, physician can play a key role in early diagnosis and thus help to prevent HD enterocolitis-related mortality and restore near-normal life.*

***Key words****: Children; Enterocolitis; Hirschsprung's disease*

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## Introduction

Hirschsprung's disease (HD) or congenital intestinal aganglionosis is a birth defect characterized by complete absence of neuronal ganglion cells in the myenteric Auerbach's plexus, the deep submucosal Henle's plexus, and the submucosal Meissner's plexus from a portion of the intestinal tract. The aganglionic segment includes the distal rectum and a variable length of contiguous proximal intestine.[1-4]

Hirschsprung's disease was first described by Frederick Ruysch in 1691 as the phenomena of an extremely dilated colon.[5,6] First comprehensive description was given by Harold Hirschsprung, a pediatrician from Copenhagen, Denmark at the Society of Pediatrics in Berlin in 1886. Hirschsprung and his associate Mya first coined the term 'congenital megacolon'.[7-9]

## Epidemiology

Incidence is usually reported as 1 in 5,000 newborns. Recent large European study showed prevalence of 1.09 cases per 10,000 births.[10] It is about 3 times more common among Asian-Americans.[11,12] It is more common in boys than in girls (male-to-female ratio 4:1). It is the most common cause of lower intestinal obstruction in neonates. Approximately 50% of HD cases are diagnosed in neonates, with most of the remaining half of cases diagnosed in children younger than two years of age. HD is rarely diagnosed in older children or adults.[1-3,13-17]

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HD has previously been recognized as being rare or absent in premature babies. More recent reports indicate a rising prevalence in premature babies.[18,19] About 3 to 5 percent of male siblings and one percent of female siblings of children with short-segment disease also have the disease and the risk is substantially higher in siblings of children with total colonic involvement.[20, 21]

## Hirschsprung's disease and family history

Hirschsprung's disease has an overall recurrence risk in sibs of the proband (the individual through whom a family with a genetic disorder is ascertained) of 4%. According to the Carter paradox, the highest recurrence risk is for a male sib of a female proband long segment Hirschsprung disease.[1]About 3 to 5 percent of male siblings and 1 percent of female siblings of children with short-segment disease also have the disease and the risk is substantially higher in siblings of children with total colonic involvement.[20,21]

## Associated anomalies and syndromes

Hirschsprung's disease-associated congenital anomalies are around 21.1% and among them 12% are with associated chromosomal anomalies. Congenital anomalies are anomalies of the gastrointestinal tract (8.1%), genitourinary system (6.1%) and central nervous system (6.8%), musculoskeletal system (5.1%), cardiovascular system (5%), craniofacial area (3%), and skin (ectodermal dysplasia). Cardiac defects are mostly atrio- or ventriculoseptal defects. Genitourinary abnormalities include renal dysplasia or agenesis, hypospadias. Gastrointestinal malformations such as Meckel diverticulum, pyloric stenosis, single umbilical artery, inguinal hernia, or small bowel atresia are also found. Syndromic Hirschsprung's associations include Down syndrome, dominant sensorineural deafness, Waardenburg syndrome, neurofibromatosis, neuroblastoma, pheochromocytoma, the multiple endocrine neoplasia Type II syndromes, syndromes related to cholesterol and fat metabolism.[1,4]

## Pathophysiology

The cause of Hirschsprung's disease is multifactorial, and the disease can be familial or develop spontaneously.[4] The cause of the disease is the arrest of migration and differentiation of enteric neural crest-derived cells (ENCCs).[22] The enteric nervous system originates from neural crest-derived cells that undergo migration in the gut following the vagal pathways. Migration of neuroblasts in the vagal trunk begins in about week five of embryonic life and progresses down the gut and reaches the rectum by week 12.[23] The enteric nervous system (ENS) then develops into the complex interconnecting network of neurons and glial cells that regulate gastrointestinal tract motility, sensory response, secretion and blood flow.[24]

Hirschsprung's disease develops as a consequence of the premature arrest of the craniocaudal migration of the neural crest cells in the hindgut between the fifth and twelfth week of gestation to form the ENS.[25,26] Many transcription factors/genes have role in ENCCs migration and differentiation such as RET, PHOX2B GDNF, EDN3, BDNF, ZEB2, EDNRB etc. Absence or malfunction of these factors will cause arrest of migration or differentiation of ENCCs.[4, 27, 28]

Due to absence of parasympathetic ganglion cells in the distal colon there is lack of coordinated peristalsis and loss of involuntary relaxation of the internal anal sphincter, which leads to functional bowel obstruction. Aganglionic segment remains narrow and a proximal transitional zone progressing from a narrow to a ganglionic dilated lumen.[29]

## Types of HD

HD can be classified by the extension of the aganglionosis as follows: a) classic form (short segment) in 70–75% cases; limited to the rectum and sigmoid colon, b) long segment, or subtotal colonic

disease (10–15%) which generally involves the bowel up to the splenic flexure, c) total colonic aganglionosis (TCA) (3–6%) which may involve a variable amount of the short bowel, d) total intestinal aganglionosis and e) ultra short-segment variant involving the distal rectum below the pelvic floor and the anus.[1,9,14,30]

In ultra short-segmental variants of HD, the aganglionic segment is limited to the internal sphincter. Here child presents with feature of functional constipation. Ganglion cells are present in rectum, but the rectal motility is abnormal.[2,3,7,9]

## Presentation

HD usually presents in infancy, although some patients present later in life. Symptoms range from neonatal intestinal obstruction to chronic progressive constipation in older children (Table I).[20,21,31] In neonates classic symptom is failure to pass meconium in the 1st 24 hours of life (about 90%), and abdominal distention (Fig 1), poor feeding and vomiting.[20,32,33] But other causes of delayed passage of meconium also should be considered (Table II). Later in infancy or in adulthood children present with severe constipation, chronic abdominal distension, vomiting, and failure to thrive.[36] History of constipation with frequent rectal irrigation and foul smell feces are found in the older children.[32,37] There may be urinary incontinence, urinary tract infection and refractory vulvovaginitis. Digital rectal examination demonstrates a tight anal sphincter, often with the absence of stool in the rectal vault and on withdrawal of the finger explosive discharge of stool and gas.[29]

About one-third of patients with Hirschsprung's disease may present with enterocolitis-related diarrhea rather than constipation.[20] Hirschsprung's disease is the most common organic cause of constipation[38] and it must be differentiated from functional constipation (Table III).

## Differential diagnoses

In a newborn infant differential diagnoses are: 1) meconium ileus resulting from cystic fibrosis, (2) intestinal malformations such as lower ileal and colonic atresia, isolated or occasionally associated with HSCR, intestinal malrotation, or duplication, (3) ENS anomalies grouped together as chronic intestinal pseudo-obstruction syndromes, and (4) functional intestinal obstruction resulting from maternal infection, maternal intoxication, or congenital hypothyroidism.[1,31]

In older children, it must be differentiated from functional constipation (Table III). In addition, endocrine disorder, drug side effects, electrolyte imbalance, spinal cord anomalies should be kept in mind.

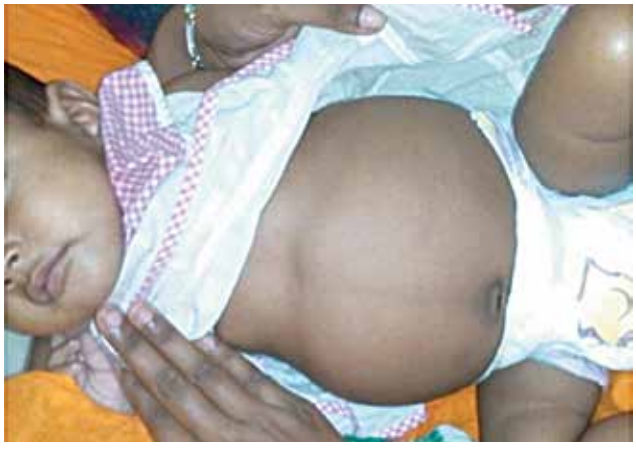

Fig 1. Distended abdomen of patients with Hirschsprung's disease

| Table I: Symptoms of Hirschsprung's disease[20,21,31] |
|---|
| *Neonates* |
| Failure to pass meconium in the first 24 hours of life |
| Abdominal distension that is relieved by rectal stimulation or enemas |
| Vomiting |
| Neonatal enterocolitis |
| *Infants* |
| Bilious vomiting |
| Enterocolitis-associated diarrhea |
| Infrequent, explosive bowel movements; difficult bowel movements |
| Jaundice |
| Poor feeding |
| Progressive abdominal distension |
| Tight anal sphincter with an empty rectum |
| *Older children* |
| Absence of soiling or overflow incontinence |
| Chronic progressive constipation, usually with onset in infancy |
| Failure to thrive |
| Fecal impaction |
| Malnutrition |
| Progressive abdominal distention |

## Hirschsprung's disease associated with enterocolitis

Hirschsprung's disease associated with enterocolitis can occur preoperatively in up to 50% cases or as a postoperative complication in up to 22% cases.[41,42]

| Table II: Differential diagnoses associated with a newborn's failure to pass meconium[1,4,34,35] |
|---|
| Hirschsprung's disease |
| Meconium plug syndrome |
| Cystic fibrosis–associated meconium ileus |
| Anorectal malformation |
| Small left colon syndrome |
| Hypoganglionosis |
| Neuronal intestinal dysplasia |
| Preterm newborn |

Patients present with fever, explosive diarrhea, foul-smelling feces, abdominal distension, vomiting, lethargy and shock (Table IV). This condition causes mortality in 1–10% in newborn Hirschsprung's disease.[43]

Fecal stasis from aganglionosis leads to bacterial overgrowth in the gut, followed by inflammation of the mucosa with fever and an elevated white blood cell count. If left untreated bowel perforation, septic shock and death can occur.

Table IV: Symptoms of Hirschsprung disease-associated enterocolitis[20,21,44]

| Early | Late |
|---|---|
| Abdominal distension | Fever |
| Poor feeding | Emesis |
| Foul-smelling, watery stool | Hematochezia |
| Lethargy | Shock or death |

Table III: Differences between functional constipation and Hirschsprung disease[39,40]

| Features | Functional constipation | Hirschsprung's disease |
|---|---|---|
| Delayed passage of meconium | None | Common |
| Onset | After 2 years | At birth |
| Fecal incontinence | Common | Very rare |
| History of fissure | Common | Rare |
| Failure to thrive | Uncommon | Possible |
| Enterocolitis | None | Possible |
| Forced bowel training | Usual | None |
| Abdominal distension | Rare | Common |
| Rectal examination | Stool | Empty but after removing finger gush of liquid stool comes out |
| Malnutrition | None | Possible |

## Associated anomalies and syndromes

Hirschsprung's disease with associated congenital anomalies is seen in around 21.1% cases. Among them 12% are with associated chromosomal anomalies. Congenital anomalies of the gastrointestinal tract (8.1%), genitourinary system (6.1%), central nervous system (6.8%), musculoskeletal system (5.1%), cardiovascular system (5%), craniofacial area (3%) and skin (ectodermal dysplasia) are found.

Syndromic Hirschsprung associations include Down syndrome, dominant sensorineural deafness, Waardenburg syndrome, neurofibromatosis, neuroblastoma, pheochromocytoma, the multiple endocrine neoplasia type II syndromes, syndromes related to cholesterol and fat metabolism.[4,45]

## Investigations

Imaging is very much helpful for diagnosis of suspected Hirschsprung's disease and evaluation should begin with abdominal radiography (diagnostic accuracy is 52%).[45]

*Plain radiography of abdomen*

Plain radiography of abdomen on in erect posture may show dilated loops of bowel, often with the absence of stool and gas in the rectum (Fig 2), air-fluid levels in the colon (if intestinal obstruction), pneumatosis intestinalis and free air in the abdomen (in enterocolitis with perforation).[46,47] Lateral view may occasionally demonstrate a narrow rectum (Fig 3). If small bowel obstruction is prominent, a longer aganglionic segment should be considered.[45]

*Contrast radiography*

Barium enema is commonly used for diagnosis of Hirschsprung's disease. Important finding is transitional zone (Fig 4), between normal and aganglionic bowel, most commonly in the recto-sigmoid colon. The transition zone represents the site where the narrow aganglionic bowel joins the dilated ganglionic bowel.[48]

Presence of contrast in the rectum after 24 hours on plain radiography is suggestive of diagnosis (Fig 5).[45] The recto-sigmoid index (the ratio of the diameter of the rectum to the diameter of the sigmoid colon) will be less than one.[49] Sensitivity and specificity of barium enema is 73% and 90% respectively. False negative results may be found after rectal washouts or digital rectal examinations, and false-positive results may be found in patients with meconium plugs.[50,51] In neonates contrast enema should be performed without rectal balloon. It is commonly normal in the first three months of life and indefinitely in TCA.[44] Contrast enemas should be avoided in patients with enterocolitis because of the risk of perforation.[21]

*Manometry*

Anorectal manometry is useful, especially in the older child to differentiate ultra short-segment HD from other causes of constipation. In HD, there is a characteristic absence of sphincter relaxation in response to rectal dilatation.[52] Contrast enema and anal manometry are similar in sensitivity and specificity.[44,51] Manometry is now considered unnecessary because the reflex also can be evaluated with a modified contrast enema.[52,53]

*Rectal biopsy and histopathology*

Rectal biopsy should be done for confirmation of HD, if these initial tests suggest the diagnosis of Hirschsprung's disease, or have a high index of suspicion. Gold standard for diagnosis of HD is full-thickness biopsy. Several samples of the rectal mucosa should be obtained 1 to 3 cm above the dentate line and should include the submucosa. Rectal suction biopsy collects only mucosa. Diagnostic pathological findings are absence of submucosal and myenteric ganglion cells with hypertrophied nerve trunk (Fig 6). Ultra short-segmental variants usually show normal mucosa. The sensitivity and specificity of rectal suction biopsy are 96.84% and 99.42% respectively. If no hypertrophic nerve trunks are found, then full-thickness biopsy may be indicated.[32,54,51]

*Antenatal diagnosis*

Antenatal ultrasound may show dilated loops of bowel and polyhydramnios; but the sensitivity and predictability of it are limited. Amniotic fluid disaccharidase activity in the amniotic fluid may be measured, but without much success.[55]

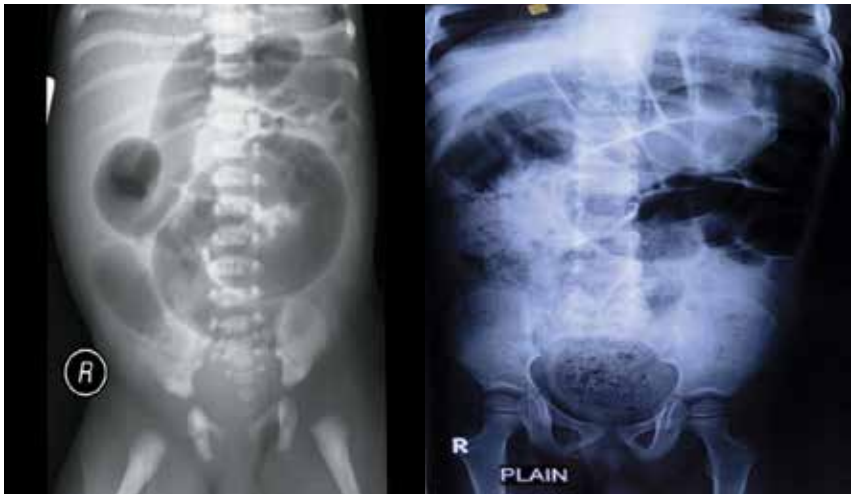


Fig 2. Dilated loops of bowel, often with the absence of stool and gas in the rectum[45]

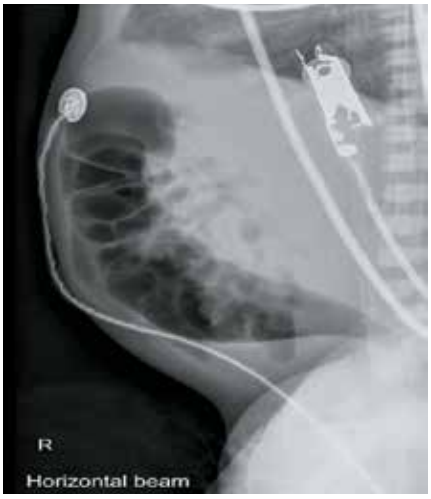


Fig 3. Narrow rectum on plain X-ray abdomen

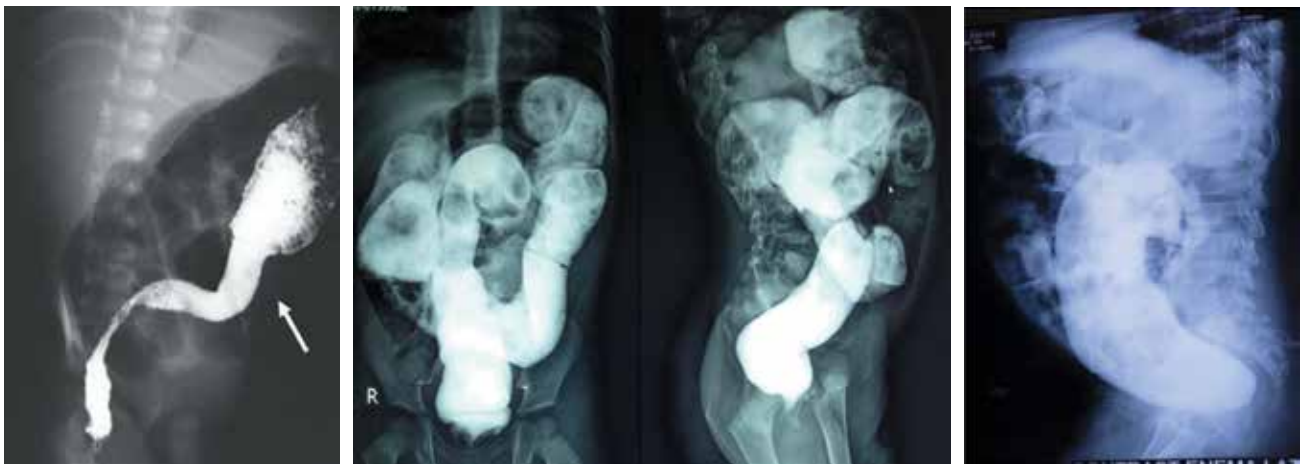


Fig 4. Barium enema showing transition zone with proximal dilatation of colon in short segment

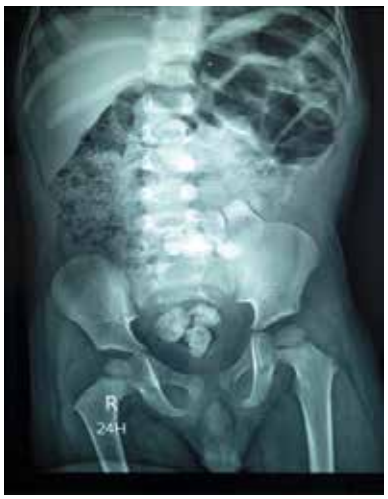


Fig 5. Presence of contrast in the gut after 24 hours

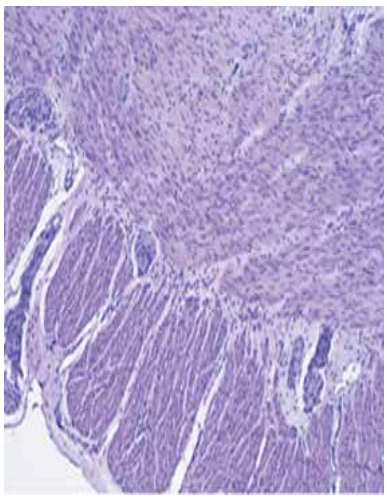

Fig 6. Histopatholgy of Hirschsprung's disease

## Treatment

Surgery is the mainstay of treatment in Hirschsprung's disease. Resection of aganglionic segment and anastomosis of normal ganglionated bowel to the rectum without injuring anal sphincter is done.[21,45]

## Preoperative management

Serial rectal irrigation is done to prevent enterocolitis and to reduce colonic distension.[21] Rectal irrigation with 10 to 20 mL/kg warm 0.9% sodium chloride solution facilitates passage of stool and keeps the rectum decompressed.[46]

## Definitive surgery

Three definitive surgical procedures commonly performed for HD: (a) Swenson procedure (removal of aganglionic portion of colon), (b) Duhamel procedure (retro-rectal anastomosis), and (c) Soave procedure (endorectal pull-through).[2,7,17]

All three techniques can be done with open abdominal incisions or laparoscopic-assisted procedure. They can be done as two-stage (with an initial diverting colostomy) or as single-stage. Transanal pull-through procedure can be performed in Swenson and Soave techniques.[29,45]

## Management of Hirschsprung's disease-associated enterocolitis

Treatment consists of antibiotic coverage for Gram-negative organisms and anaerobes, nasogastric suction, IV fluids and rectal irrigation 2–4 times per day until decompression. After decompression colostomy is placed for several months until the child recovers and waits for definitive surgery.[13]

## Prognosis

If patients are appropriately treated, growth and development are mostly within the normal population parameters and intellectual function approximates normal.[57] One possible cause of poor postoperative outcome is incomplete resection of affected bowel and pull-through only to the transition zone. Enterocolitis frequently occurs after surgical resection, which have mortality rates ranging from 6% to 30%. Constipation was observed in up to one-third of patients with long-term follow-up in surgically treated Hirschsprung's disease patients and it may response to conservative measures, such as chronic stool softeners and regular toileting habits. About 20–30% of patients may require anal myectomy or myotomy for relief of constipation.[58]

## Conclusion

Hirschsprung's disease is a surgically correctable condition. High index of suspicion is the key to diagnosis. Early diagnosis and treatment may be life-saving. After diagnosis physician must counsel the parents and communicate with pediatric surgeon for optimum management.

## Acknowledgement

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Table V: Complications of HD[13,45,56]

| If untreated | Postoperative | |
|---|---|---|
| Intestinal obstruction | Early complications | Late complications |
| Enterocolitis<br>Death | Anastomotic insufficiency<br>Rectal stenosis<br>Prolonged ileus<br>Intestinal adhesive obstruction<br>Neorectal retraction. Intrapelvic abscesses<br>Presacral abscesses, Metabolic derangements | Enterocolitis<br>Stricture<br>Resistant constipation<br>Fecal incontinence<br>Enuresis<br>Incontinence of urine<br>Dysuria<br>Impotence |

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