Hirschsprung's Disease and Variants

46

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Contents

46.1 Introduction Including Definition and Incidence

Hirschsprung's disease (HD) is characterised by an absence of ganglion cells in the distal bowel and extending proximally for varying distances. The pathophysiology of Hirschsprung's disease is not fully understood. There is no clear explanation for the occurrence of spastic or tonically contracted aganglionic segment of bowel.

The aganglionosis is confined to rectosigmoid in 75% of patients, sigmoid, splenic flexure or transverse colon in 17% and total colon along with a short segment of terminal ileum in 8%. The incidence of HD is estimated to be 1 in 5,000 live births. The disease is more common in boys with a male-to-female ration of 4:1. The male preponderance is less evident in long-segment HD, where the male-to-female ratio is 1.5–2:1.

46.2 Etiology

In the human fetus, neural crest-derived neuroblasts first appear in the developing esophagus at 5 weeks, and then migrate down to the anal canal in a craniocaudal direction during the fifth to 12th weeks of gestation. The absence of ganglion cells in HD has been attributed to a failure of migration of neural crest cells. The earlier the arrest of migration, the longer the aganglionic segment.

Genetic factors have been implicated in the etiology of HD. HD is known to occur in families. The reported incidence of familial cases varied from 3.6% to 7.8% in different series. A familial incidence of 15–21% has been reported in total colonic aganglionosis and 50% in the rare total intestinal aganglionosis. Several genes and

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signalling molecules have been identified which control morphogenesis and differentiation of the enteric nervous (ENS) system. These genes, when mutated or deleted, interfere with ENS development. One of these genes, RET with tyrosine kinase activity is involved in the development of enteric ganglia derived from vagal-neural crest cells. Mutations of RET gene account for 50% of familial and 15–20% of sporadic cases of HD.

The relationship with Down syndrome also tends to suggest a probable genetic component in the etiology of HD. Down syndrome is the most common chromosomal abnormality associated with aganglionosis and had been reported to occur in 4.5–16% of all cases of HD. Other chromosomal abnormalities that have been described in association with HD include: interstitial deletion of distal 13q, partial deletion of 2p and reciprocal translocation, and trisomy 18 mosiac. A number of unusual hereditary syndromes have been reported in patients with HD. These include: Waardenburg syndrome, Von Recklinghausen's syndrome, type D brachydactyly and Smith-Lemli-Optiz syndrome.

46.3 Pathology

The characteristic gross pathological feature in HD is dilation and hypertrophy of the proximal colon with abrupt or gradual transition to narrow distal bowel (Fig. 46.1). Although the degree of dilation and hypertrophy increases with age, the cone-shaped transitional zone from dilated to narrow bowel is usually evident in the newborn.

Histologically, HD is characterized by the absence of ganglionic cells in the myenteric and submucous plexuses and the presence of hypertrophied non-myelinated nerve trunks in the space normally occupied by the ganglionic cells. The aganglionic segment of bowel is followed proximally by a hypoganglionic segment of varying length. This hypoganglionic zone is characterized by a reduced number of ganglion cells and nerve fibers in myenteric and submucous plexuses.

46.4 Diagnosis

The diagnosis of HD is usually based on clinical history, radiological studies, anorectal manometry and in particular on histological examination of the rectal wall biopsy specimens.

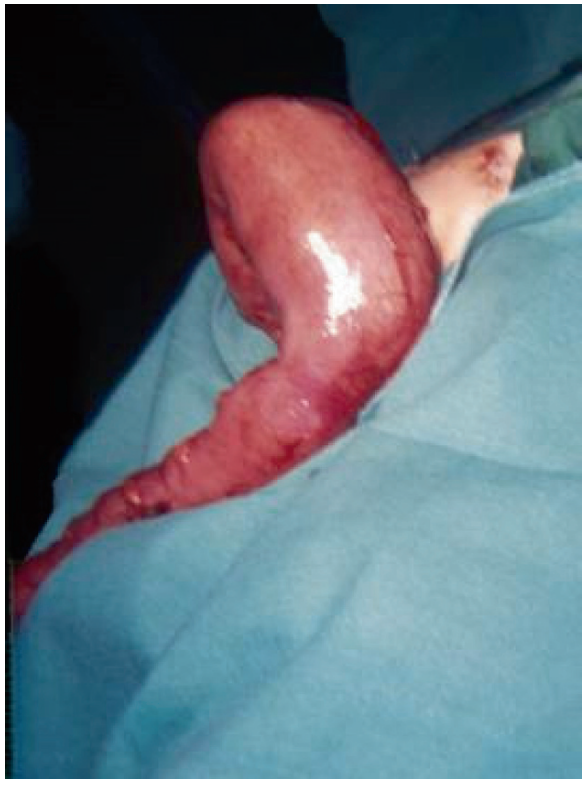

Fig. 46.1 Typical gross pathology in Hirschsprung's disease with transitional zone at rectosigmoid level

46.4.1 Clinical Features

Of all cases of HD, 80–90% produce clinical symptoms and are diagnosed during the neonatal period. Delayed passage of meconium is the cardinal symptom in neonates with HD. Over 90% of affected patients fail to pass meconium in the first 24 h of life. The usual presentation of HD in the neonatal period is with constipation, abdominal distension and vomiting during the first few days of life (Fig. 46.2). About one third of the babies with HD present with diarrhoea. Diarrhoea in HD is always a symptom of enterocolitis, which remains the commonest cause of death. Enterocolitis may resolve with adequate therapy or it may develop into a life-threatening condition, the toxic megacolon, characterised by the sudden onset of marked abdominal distension, bile stained vomiting, fever and signs of dehydration, sepsis and shock. Rectal examination or introduction of a rectal tube results in the explosive evacuation of gas and foul-smelling stools. In older children the main

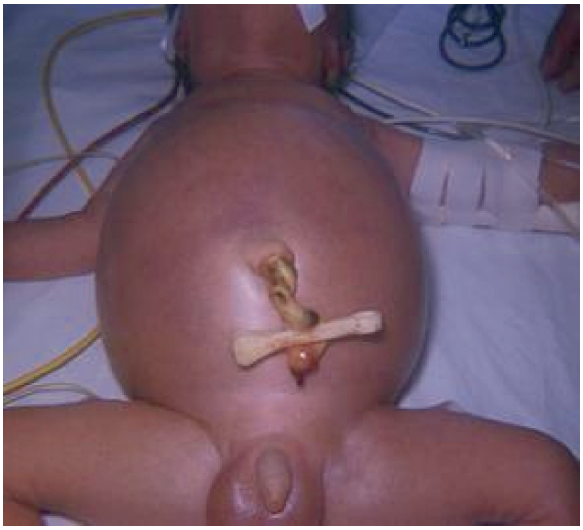

Fig. 46.2 A 2-day-old infant with abdominal distension and failure to pass meconium. Suction rectal biopsy confirmed Hirschsprung's disease

symptom is persistent constipation and chronic abdominal distension.

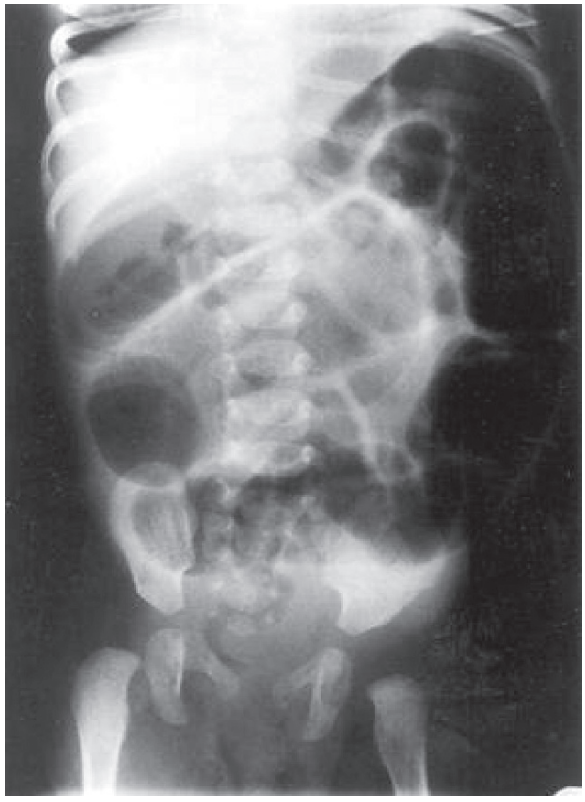

Fig. 46.3 Abdominal x-ray in a neonate showing marked dilatation of large and small bowel loops. Note gas in the undilated rectum. Rectal biopsy confirmed Hirschsprung's disease in this infant

46.4.2 Radiological Diagnosis

Plain abdominal films in a neonate with HD will show dilated loops of bowel with fluid levels and airless pelvis. Occasionally, one may be able to see a small amount of air in the undistended rectum and dilated colon above it raising the suspicion of HD (Fig. 46.3). Plain abdominal radiographs obtained from patients with total colonic aganglionosis (TCA) may show characteristic signs of ileal obstruction with air fluid levels or simple gaseous distension of small intestinal loops.

In patients with enterocolitis complicating HD, plain abdominal radiography may show thickening of the bowel wall with mucosal irregularity or a grossly dilated colon loop, indicating toxic megacolon. Pneumoperitoneum may be found in those with perforation. Spontaneous perforation of the intestinal tract has been reported in 3% of patients with HD.

Barium enema performed by an experienced radiologist, using careful technique should achieve a high degree of reliability in diagnosing HD in the newborn. It is important that the infant should not have rectal washouts or even digital examinations prior to barium enema, as such interference may distort the transitional zone appearance and give a false-negative diagnosis. A soft rubber catheter is inserted into the lower rectum and held in position with firm strapping across the buttocks. A balloon catheter should not be used due to the risk of perforation and the possibility of distorting a transitional zone by distension. The barium should be injected slowly in small amounts under fluoroscopic control with the baby in the lateral position. A typical case of HD will demonstrate flow of barium from the undilated rectum through a cone-shaped transitional zone into dilated colon (Fig. 46.4). Some cases may show an abrupt transition between the dilated proximal colon and the distal aganglionic segment, leaving the diagnosis in little doubt.

In some cases, the findings on the barium enema are uncertain and a delayed film at 24 h may confirm the diagnosis by demonstrating the retained barium and often accentuating the appearance of the transitional zone (Fig. 46.5).

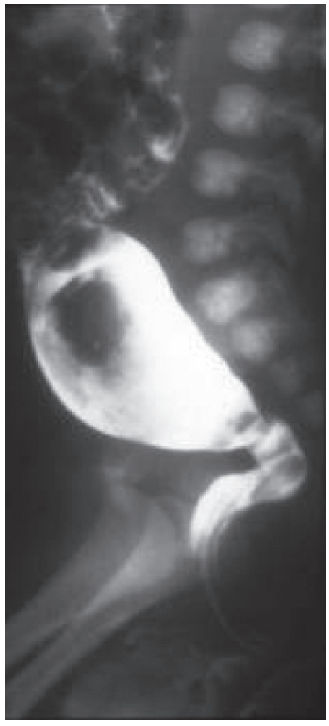

Fig. 46.4 Barium enema reveals Hirschsprung's disease with transitional zone at rectosigmoid

In total colonic aganglianosis (TCA), the contrast enema is not pathognomic and may not provide a definitive diagnosis. The colon in TCA is of normal calibre in 25–77% of cases.

46.4.3 Anorectal Manometry

In the normally innervated bowel, distension of the rectum produces relaxation of the internal sphincter rectosphincteric reflex. In normal persons, upon distending the rectal balloon with air, the rectum immediately responds with a transient rise in pressure lasting 15–20 s; at the same time the internal sphincter rhythmic activity is depressed or abolished and its pressure falls by 15–20 cm, the duration of relaxation coinciding with the rectal wave.

In patients with HD, the rectum often shows spontaneous waves of varying amplitude and frequency in the resting phase. The internal sphincter rhythmic activity is more pronounced. On rectal distension, with an increment of air, there is complete absence of internal sphincter relaxation (Fig. 46.6a, b). Failure to detect the rectosphincteric reflex in premature and term infants is believed to be due to technical difficulties and not to immaturity of ganglion cells. Light sedation particularly in infants and small children may overcome technical difficulties encountered in this age group.

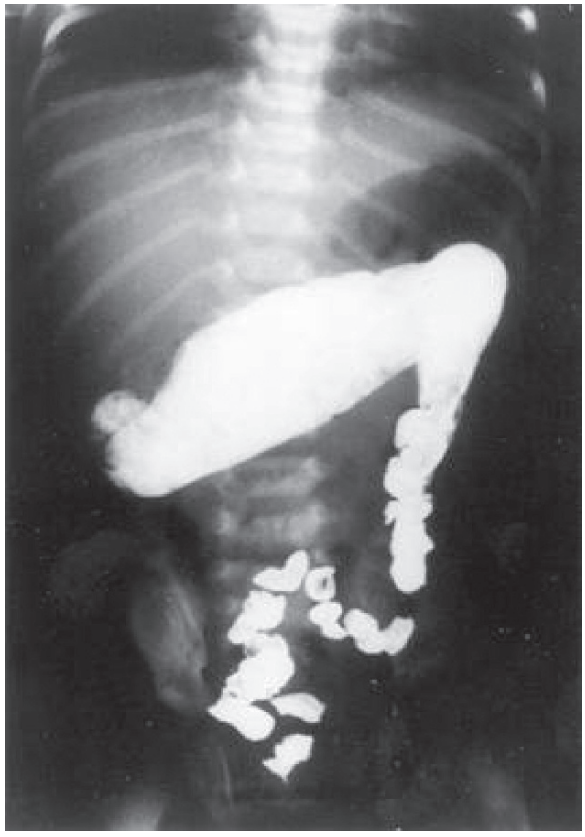

Fig. 46.5 Delayed 24 h film showing barium retention with transition zone at splenic flexure in a 10-day-old infant

46.4.4 Rectal Biopsy

The diagnosis of HD is confirmed on examination of rectal biopsy specimens. The introduction of histochemical staining technique for the detection of acetylcholinesterase (AChE) activity in suction rectal biopsy has resulted in a reliable and simple method for the diagnosis of HD. Full thickness rectal biopsy is rarely indicated for the diagnosis of HD except in total colonic aganglionosis. In normal persons, barely detectable acetylcholinesterase activity is observed within the lamina propria and muscularis mucosa, and submucosal ganglion cells stain strongly for acetylcholinesterase. In HD, there is a marked increase in acetylcholinesterase activity in lamina propria and muscularis which is evident as coarse, discrete cholinergic nerve fibers stained brown to black (Fig 46.7a, b).

In total, colonic aganglionosis (TCA), AChE activity in suction rectal biopsies presents an atypical pattern,

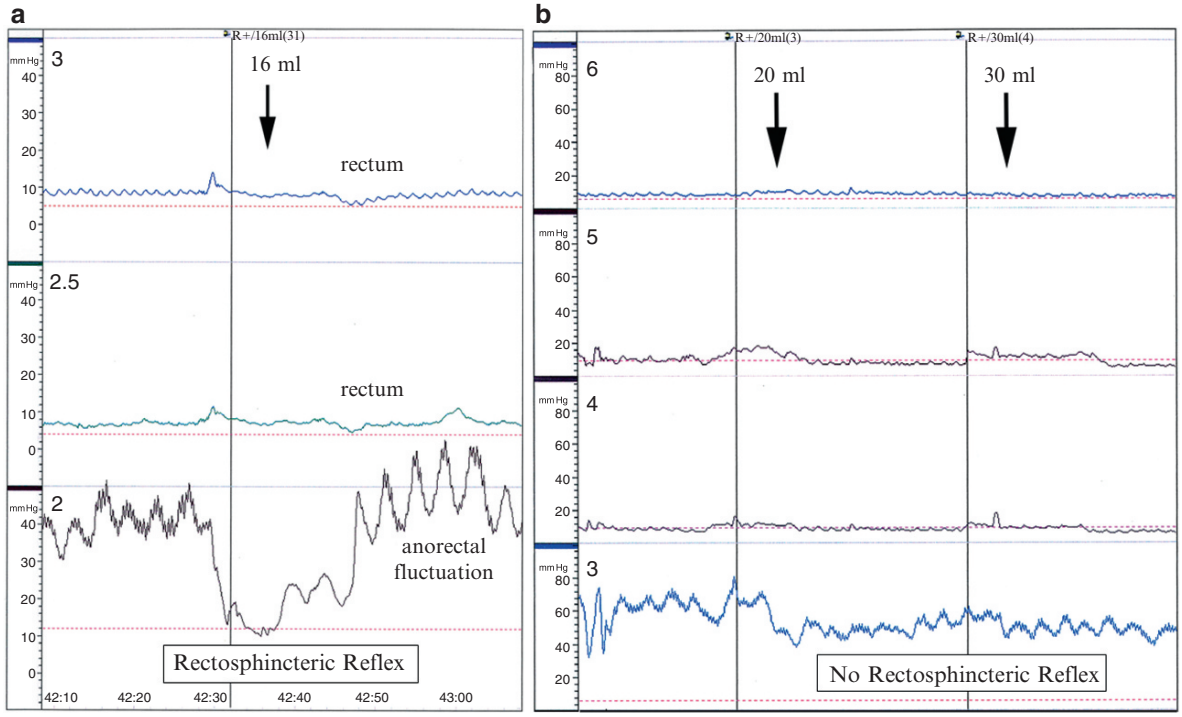

Fig. 46.6 Anorectal manometry (**a**) Normal rectosphincteric reflex on rectal balloon inflation. (**b**) Absence of rectosphincteric reflex and marked internal sphincter rhythmic activity in a patient with Hirschsprung's disease

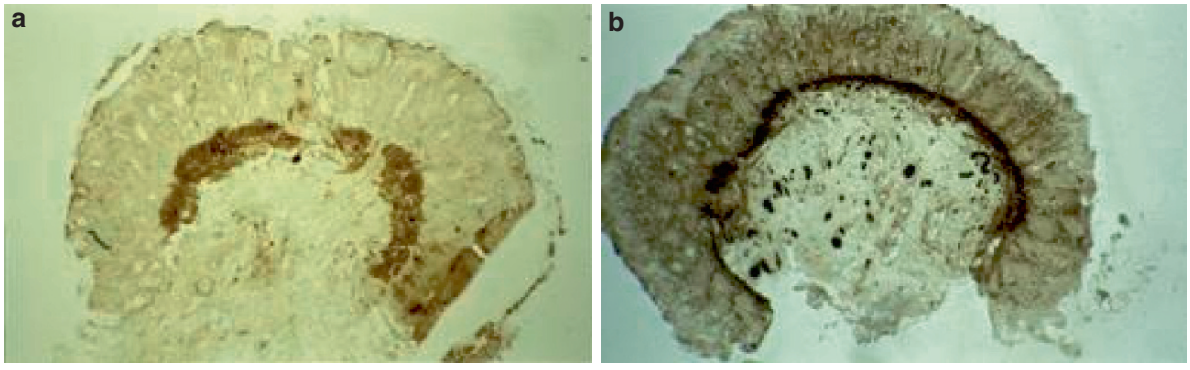

Fig. 46.7 Acetylcholinesterase (ache) staining of suction rectal biopsy. (**a**) Normal rectum showing minimal acetylcholinesterase staining of lamina propria and a ganglia in the submucosa. (**b**) Hirschsprung's disease characterized by marked increase in acetylcholinesterase positive fibers in the lamina propria and hypertrophic nerve trunks in the submucosa

different from the classic one. Positive AChE fibers can be found in the lamina propria as well as the muscularis mucosae. However, cholinergic fibers present a lower density than in classical HD.

46.5 Differential Diagnosis

Several conditions must be considered where an infant is being evaluated for Hirschsprung's disease. Table 46.1 gives the list of common differential diagnoses. Colonic atresia gives similar plain film findings to Hirschsprung's disease but is readily excluded with barium enema showing complete mechanical obstruction. Distal small bowel atresia shows gross distension of the bowel loop immediately proximal to the obstruction with the widest fluid level in it.

In meconium ileus the typical mottled thick meconium may be seen. Also clear, sharp fluid levels are not a feature in erect or lateral decubitus views. However,

Table 46.1 Differential diagnosis of Hirschsprung's disease

Neonatal bowel obstruction
Colonic atresia
Meconium ileus
Meconium plug syndrome
Small left colon syndrome
Malrotation
Low anorectal malformation
Intestinal motility disorders/pseudo-obstruction
Necrotizing enterocolitis
Medical causes: sepsis, electrolyte abnormalities, drugs, hypothyroidism, etc.
Chronic constipation
Functional megacolon
Intestinal motility disorders/pseudo-obstruction
Medical causes: electrolyte abnormalities, drugs, hypothyroidism, etc.

Hirschsprung's disease can sometimes simulate meconium ileus in plain films and may give equivocal findings on Gastrografin or barium enema.

Meconium plugs obstructing the colon can present as Hirschsprung's disease with strongly suggestive history and plain films. Small left colon syndrome with marked distension proximal to narrowed descending colon also simulates Hirschsprung's disease at the left colonic flexure (Fig. 46.8). These two conditions usually resolve with Gastrografin enema but a minority of these cases will actually have Hirschsprung's which should be excluded clinically.

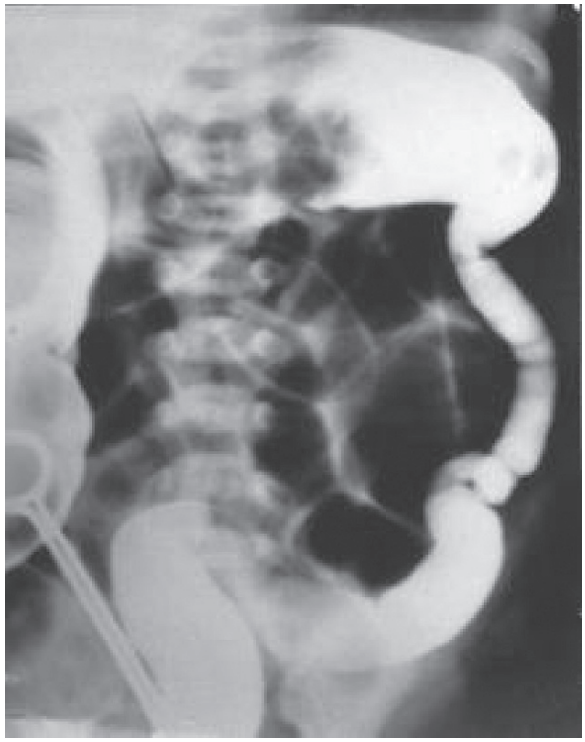

Fig. 46.8 The Small Left Colon Syndrome. The clinical and radiological features in this infant were indistinguishable from those in Hirshsprung's disease. Barium enema showed narrow descending colon with transition zone at splenic flexure. Suction rectal biopsy was ganglionic in this infant

46.6 Management

Once the diagnosis of HD has been confirmed by rectal biopsy examination, the infant should be prepared for surgery. If the newborn has enterocolitis complicating HD, correction of dehydration and electrolyte imbalance by infusion of appropriate fluids will be required. It is essential to decompress the bowel as early as possible in these babies. Deflation of the intestine may be carried out by rectal irrigations but some babies may require colostomy.

In recent years, the vast majority of cases of HD are diagnosed in the neonatal period. Many centres are now performing one-stage pull-through operations in the newborn with minimal morbidity rates and encouraging results. The advantages of operating on the newborn are that the colonic dilation can be quickly controlled by washouts and at operation the calibre of the pull-through bowel is near normal, allowing for an accurate anastomosis that minimizes leakage and cuff infection. A number of different operations have been described for the treatment of HD. The four most commonly used operations are the rectosigmoidectomy developed by Swenson and Bill, the retrorectal approach developed by Duhamel, the endorectal procedure developed by Soave and deep anterior colorectal anastomosis developed by Rehbein. The basic principle in all these procedures is to bring the ganglionic bowel down to the anus. The long-term results of any of these operations are satisfactory if they are performed correctly. Recently, a number of investigators have described and advocated a variety of one-stage pull-through procedures in the newborn using minimally invasive laparoscopic techniques. More recently, a transanal endorectal pull-through operation performed

without opening the abdomen has been used with excellent results in rectosigmoid HD.

46.7 Complications

Early postoperative complications which can occur after any type of pull-through operation include wound infections, anastomotic leak, anastomotic stricture, retraction or necrosis of the neorectum, intestinal adhesions, and ileus. Late complications include constipation, enterocolitis, incontinence, anastomotic problems, adhesive bowel obstruction and urogenital complications.

46.7.1 Anastomotic Leak

The most dangerous early post-operative complication following the definitive abdominoperineal pull-through procedure is leakage at the anastomotic suture line. Factors which are responsible for anastomotic leak include ischemia of the distal end of the colonic pull-through segment, tension on the anastomosis, incomplete anastomotic suture lines and inadvertent rectal manipulation. If a leak is recognized in a patient without a colostomy, it is imperative to perform a diverting colostomy promptly, to administer intravenous antibiotics and to irrigate the rectum with antibiotic solution a few times daily. Delay in establishing fecal diversion is likely to result in an extensive pelvic abscess which may require laparotomy and transabdominal drainage.

46.7.2 Retraction of Pullthrough

Retraction of a portion, or all of the colonic segment from the anastomosis can occur and is usually seen within 3 weeks of the operation. Evaluation under general anaesthesia is generally necessary. In occasional patients, resuturing the anastomosis may be feasible transanally. For those with separation of less than 50% of the anastomosis but with adequate vascularity of the colon, a diverting colostomy for approximately 3 months is necessary. For patients with wide separation at the anastomosis, early transabdominal reconstruction of the pull-through is recommended.

46.7.3 Perianal Excoriation

Perianal excoriation occurs in nearly half of the patients undergoing pull-through procedure, but generally resolves within 3 months with local therapy and resolution of diarrhoea. It is helpful to begin placing a barrier cream on the perianal skin promptly after the operation and to continue after each movement for the first few weeks. Resolution of diarrhoea will often hasten the clearance of perianal skin irration.

46.7.4 Enterocolitis

Hirschsprung's associated enterocolitis (HAEC) is a significant complication of HD both in the pre-and post-operative periods. HAEC can occur at any time from the neonatal period onwards to adulthood and can be independent of the medical management and surgical procedure performed. The incidence of enterocolitis ranges from 20% to 58%. Fortunately the mortality rate has declined over the last 30 years from 30% to 1%. This decrease in mortality is related to earlier diagnosis of HD and enterocolitis, rectal decompression, appropriate vigorous resuscitation and antibiotic therapy. It has been reported that routine post-operative rectal washouts decrease both the incidence and the severity of the episodes of enterocolitis following definitive surgery. In episodes of recurrent enterocolitis, which can develop in up to 56% of patients, anal dilatations have been recommended. However, prior to commencing a treatment regime, a contrast enema should be performed to rule out a mechanical obstruction. Patients with a normal rectal biopsy may require a sphincterotomy.

46.7.5 Constipation

Constipation is common after definitive repair of Hirschsprung's disease and can be due to residual aganglionosis and high anal tone. Repeated and forceful anal dilations or Botulin Toxin injection into the sphincter

under general anaesthesia may resolve the problem. In some patients internal sphincter myectomy may be needed. In patients with scarring, stricture or intestinal neuronal dysplasia proximal to aganglionic segment, treatment consists of underlying cause.

46.7.6 Soiling

Soiling is fairly common after all types of pull-through operations, its precise incidence primarily dependent on how assiduously the investigator looks for it. The reported incidence of soiling ranges from 10% to 30%. The attainment of normal postoperative defaecation is clearly dependent on intensity of bowel training, social background and respective intelligence of the patients. Mental handicap, including Down's syndrome, is invariably associated with long-term incontinence. Those patients with preoperative enterocolitis would also seem to have a marginally higher long-term risk of incontinence. In some patients in whom soiling is intractable and a social problem, a Malone procedure may be needed to stay clean.

46.8 Variant Hirschsprung's Disease

Variant Hirschsprung's Disease includes conditions that clinically resemble HD despite the presence of ganglion cells on suction rectal biopsy results. These conditions can be diagnosed by providing an adequate biopsy and employing a variety of histological techniques. The motility disorders which comprise Variant Hirschsprung's Disease are intestinal neuronal dysplasia, hypoganglionosis, internal sphincter achalasia and smooth muscle disorders.

46.8.1 Intestinal Neuronal Dysplasia

Intestinal neuronal dysplasia (IND) is a clinical condition that resembles Hirschsprung's disease. IND has been described proximal to the aganglionic segment and less frequently as an isolated condition. IND is classified into two clinically and histologically distinct subtypes. Type A occurs in less than 5% of cases, is characterized by congenital aplasia or hypoplasia of the sympathetic innervation, and presents acutely in the neonatal period with episodes of intestinal obstruction, diarrhoea and bloody stools. The clinical picture of Type B resembles HD and is characterized by malformation of the parasympathetic submucous and myenteric plexuses. IND occurring in association with HD is of Type B. The characteristic histologic features of IND Type B include hyperganglionosis of the submucous and myenteric plexuses, giant ganglia, ectopic ganglion cells and increased acetylcholinesterase (AChE) activity in the lamina propria and around submucosal blood vessels (Fig. 46.9).

Current treatment of IND Type B is in the first instance conservative, consisting of laxatives and enemas. In the majority of patients the clinical problem resolves or is manageable in this way. If bowel symptoms persist after at least 6 months of treatment, internal sphincter myectomy should be considered.

46.8.2 Hypoganglionosis

Hypoganglionosis as an isolated condition is rare. Failure to pass meconium may be the first symptom in the neonatal period, whereas infants and older children present with chronic constipation. The diagnosis of hypoganglionosis by means of suction rectal biopsy is difficult. Suction rectal biopsy in these patients demonstrates absence of submucosal ganglion cells with no or extremely low acetyl-cholinesterase activity in lamina propria or mucosal mucosae. Full thickness biopsy is usually required for the reliable diagnosis of hypoganglionosis. Characteristic histological features of hypoganglionosis include sparse and small myenteric ganglia, absence of or low AChE activity in the lamina propria and hypertrophy of muscularis mucosa and circular muscle.

The treatment of hypoganglionosis is similar to HD involving resection of the affected segment and pull-through operation.

46.8.3 Internal Sphincter Achalasia

Internal anal sphincter achalasia (IASA) is a clinical condition with presentation similar to Hirschsprung's disease but with the presence of ganglion cells on suction rectal biopsy. The diagnosis of IASA is made on anorectal

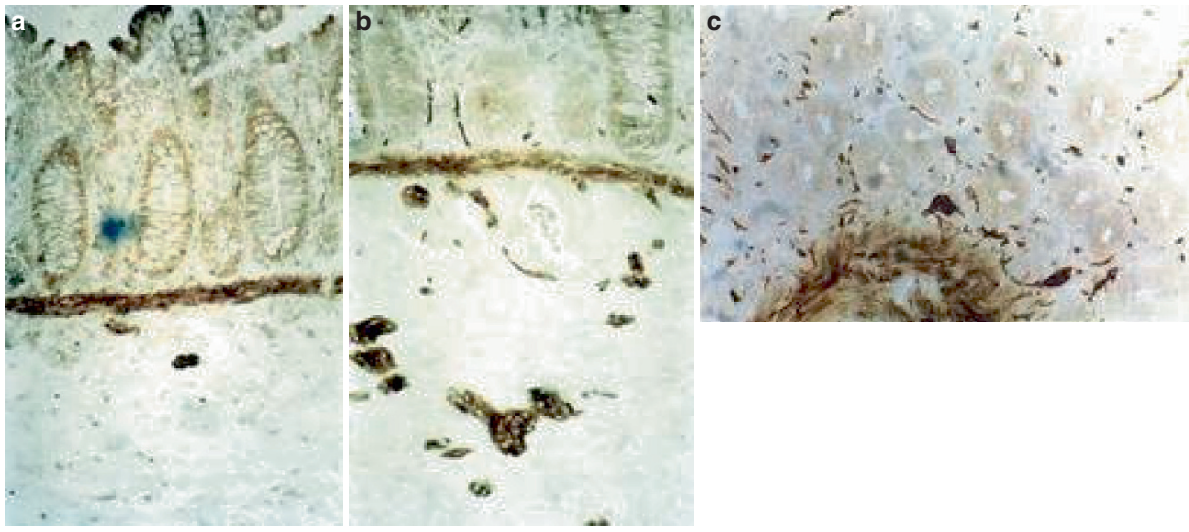

Fig. 46.9 Ache staining of suction rectal biopsy. (**a**) Normal biopsy showing a submucosal ganglion. (**b**) Biopsy from a patient with intestinal neuronal dysplasia shows hyperganglionosis and giant ganglia in the submucosa. (**c**) Ectopic ganglia in the lamina propria in a patient with IND

manometry, which shows the absence of rectosphincteric reflex on rectal balloon inflation. Previously, IASA has been referred to as ultrashort segment Hirschsprung's disease (HD). The ultrashort segment Hirschsprung's disease, which is a rare condition, is characterized by an aganglionic (AChE) activity in the lamina propria and increased AChE activity in the muscularis mucosae. Many patients who are considered to have ultrashort HD on abnormal anorectal mamometric findings show presence of ganglion cells and normal acetylcholinesterase (AChE) activity in suction rectal biopsies. Many investigators have therefore suggested that the term IASA is more suitable because it reflects more accurately failure of relaxation of the internal sphincter, which is the causative factor in this condition. The exact pathogenesis and pathophysiology of IASA is not understood fully. Altered intramuscular innervation has been reported in IASA and this is believed to be responsible for the motility dysfunction seen in these patients.

Posterior internal sphincter myectomy has been recommended as the treatment of choice for patients with internal sphincter achalasia. Recently, intraanal injection of botulinum toxin has been used to treat patients with IASA. This treatment modality has been found to be safe and effective but only as short-term treatment in these children.

46.8.4 Smooth Muscle Cell Disorders

These patients who show no apparent innervation abnormalities in the pathologic specimens demonstrate abnormalities of smooth muscle cells on electron-microscopy. The outcome of smooth muscle disorders is usually poor. There are two main types of smooth muscle cell abnormalities, perinuclear vacuolation and "central core" degeneration. Patients with Megacystis microcolon intestinal hypoperistalsis syndrome (MMIHS) usually have central core degeneration of smooth muscle cells. MMIHS is a rare and the most severe form of functional intestinal obstruction in the newborn. The major features of this congenital and usually lethal anomaly are abdominal distension, bile-stained vomiting and absent or decreased bowel peristalsis. Abdominal distension is a consequence of the distended, unobstructed urinary bladder with or without upper urinary tract dilation. Most patients with MMIHS are not able to void spontaneously. The outcome of smooth muscle disorders is generally fatal. The need for surgical intervention should be weighed carefully and individualized because most explorations have not been helpful and are probably not necessary.

Further Reading

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