Hirschsprung's Disease: Clinical Features

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8

8.1 Introduction

Hirschsprung's disease (HD) is a relatively common cause of intestinal obstruction in the newborn [1]. It is characterized by absence of ganglion cells in the distal bowel beginning at the internal sphincter and extending proximally for varying distances. In the human fetus, neural crest-derived neuroblasts first appear in the developing esophagus at 5 weeks of gestation, and then migrate down to the anal canal in a craniocaudal direction during the 5th to the 12th week of gestation. The absence of ganglion cells in HD has been attributed to a failure of migration of neural crest cells [2, 3]. The earlier the arrest of migration the longer the aganglionic segment is. The absence of ganglion cells results in absent peristalsis in the affected bowel and the development of functional intestinal obstruction.

Although Harald Hirschsprung [4] first described this disease in 1888, the pathological features were not understood until the 1940s when Whitehouse and Kernohan demonstrated that the aganglionosis within the distal colon or rectum was the cause of the functional obstruction [5]. In 1948, Swenson and Bill reported rectosigmoidectomy with preservation of the sphincter as the optimal treatment for HD [6]. In recent years, the vast majority of cases of HD are diagnosed in the neonatal period and many centers are now performing one-stage pull-through operations in the newborn period with minimal morbidity and encouraging results [7].

8.2 Incidence

Several studies on the frequency of HD have been reported. The incidence of HD is estimated to be 1 in 5,000 live births and ranges from 1 in 2,000 to 1 in 12,000 live births (Table 8.1) [8–17]. A large survey of HD cases from the California Birth Defects Monitoring Program (1983–1997) found an incidence of 1.5 in 10,000 live births in whites, 2.1 in 10,000 live births in African-Americans, 1 in 10,000 live births in Hispanic and 2.8 in 10,000 live births in Asians [18]. Recently, a nationwide survey from Japan found an incidence of HD of 1 in 5,343 live births between 1998 and 2002 [19].

8.3 Classification

While the internal anal sphincter is the constant inferior limit, patients can be classified as classical segment HD when the aganglionic segment does not extend beyond the upper sigmoid, long-segment HD when aganglionosis extends to the splenic flexure or transverse colon, and total colonic aganglionosis when the aganglionic segment extends to the colon and a short segment of terminal ileum [20]. Table 8.2 shows the level of aganglionosis in different series with more than 100 patients studied [10, 11, 13, 19, 21–25]. Total intestinal aganglionosis with absence of ganglion cells from duodenum to the rectum is the most rare form of HD [26, 27].

8.4 Sex

It has long been recognized that males are more commonly affected than females with a male:female ratio of 4:1 [10, 11, 13, 17, 19, 21, 22, 24]. The male preponderance is less evident in long-segment HD, where the male:female ratio is 1:1–2:1 [10, 22, 24] and is even reversed in total colonic aganglionosis, where the male:female ratio is 0.8:1 [11]. The reason for these skewed ratios is unclear; no X-linked loci have been described in HD.

Table 8.1 Incidence of Hirschsprung's disease

Year	Reference	Incidence	Area
1962	16	1 in 12,000	Bremen
1963	8	1 in 2,000–10,000	Britain
1964	15	1 in 4,700	Denmark
1967	9	1 in 5,000	Cincinnati
1983	10	1 in 4,500	Southeast Scotland
1984	17	1 in 5,682	Baltimore
1984	11	1 in 4,697	Japan
1985	12	1 in 4,417	British Columbia
1994	13	1 in 7,165	Denmark
1997	14	1 in 3,070	Oman
1998	18	1 in 5,405	California
2005	19	1 in 5,343	Japan

Table 8.2 Classification of Hirschsprung's disease

Reference	Patients (*n*)	Rectosigmoid aganglionosis (%)	Long-segment aganglionosis (%)	Total colonic aganglionosis (%)
21	498	72.5	23.7	3.8
22	998	74	17	9
11	1562	79.4	11.6	12.6
10	103	81.6	18.4	–
23	874	74.6	22	3.5
24	179	88.8	3.9	7.3
13	161	88.2	8.7	3.1
25	105	72.4	19	8.6
19	1103	77.6	13	9.4

Badner et al. [28] demonstrated that recurrence risk to siblings is dependent upon the sex of the person affected and the extent of the aganglionosis. If the index patient is female, the proportion of affected siblings is higher. The recurrence risk to siblings also increases as the aganglionosis becomes more extensive (Table 8.3) [28, 29].

8.5 Race

Recently, the California Birth Defects Monitoring Program have found the highest incidence of HD among Asians with a frequency of 2.8 in 10,000 live births followed by African-Americans with a frequency of 2.1 in 10,000 live births [18]. Goldberg, in a previous epidemiological study, found the incidence of HD among non-white males to be 3.76 in 10,000 live births [17]. In 1979, a survey of the Members of the Surgical Section of the AAP found no differences in the incidence of HD among whites and African-Americans; however, they found that long-segment disease occurs significantly less frequently in nonwhites than in whites [22]. Sherman et al. later confirmed these findings [23]. Although the highest incidence of HD reported in the literature is 1 in 3,070 from a survey in Oman, this is unlikely to be due to racial differences but to a high consanguinity rate [14].

8.6 Heredity

Genetic factors have been implicated in the etiology of HD. HD is known to occur in families. The reported in-

Table 8.3 Recurrence risk to siblings in Hirschsprung's disease

Segment affected	Sex of index patient	Sex of sibling	Recurrence risk (%)
Rectosigmoid HD	Male	Male	5
	Male	Female	1
	Female	Male	5
	Female	Female	3
Long segment HD	Male	Male	17
	Male	Female	13
	Female	Male	33
	Female	Female	9

cidence of familial cases in rectosigmoid HD varies from 3.6% to 7.8% in different series [7]. A familial incidence of 15% to 21% has been reported in total colonic aganglionosis and 50% in the rare total intestinal aganglionosis [28]. Schiller et al. [30] reported 22 infants belonging to four families from Gaza, who had either documented or clinically suspected HD. Of these infants, 13 underwent laparotomy and multiple intestinal biopsies, 10 had total intestinal aganglionosis, 1 had total colonic aganglionosis, 1 had near total colonic aganglionosis, and only 1 had rectosigmoid HD. Engum et al. [31] reported 20 patients with HD in 12 kindreds. The level of aganglionosis was rectal or rectosigmoid in eight, left colon in two, transverse or right colon in two, and total colonic ganglionosis with variable small bowel involvement in eight.

HD occurs as an isolated trait in 70% of patients [32]. A chromosomal abnormality is associated with HD in 12% of patients, trisomy 21 being by far the most frequent (>90%). The relationship with Down's syndrome also tends to suggest a probable genetic component in the etiology of HD. Down's syndrome is the most common chromosomal abnormality associated with aganglionosis and has been reported to occur in 4.5–16% of all patients with HD [24, 33, 34]. Associated congenital anomalies are found in 18% of HD patients and include gastrointestinal malformations, cleft palate, cardiac malformations, craniofacial anomalies, and polydactyly [32]. Other chromosomal abnormalities that have been described in association with HD include interstitial deletion of distal 13q, partial deletion of 2p, reciprocal translation, and trisomy 18 mosaic. A number of unusual hereditary syndromes have been reported in patients with HD. These include Shah-Waardenburg syndrome, multiple endocrine neoplasia (MEN) type 2 syndrome, congenital central hypoventilation syndrome (Ondine's curse), Goldberg-Shprintzen syndrome, Kaufman-McKusick syndrome, Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome, Cartilage-hair hypoplasia syndrome, and syndromes with HD and distal limbs anomalies (Table 8.4) [24, 29, 32, 34, 35].

The genetics of HD display three characteristics: (1) the penetrance of mutations is generally low, (2) there is a sex difference in the penetrance and expression of mutations, and (3) the penetrance of a gene mutation depends upon the extent of aganglionosis in affected family members [35]. Most identified gene mutations associated with HD are best thought of as susceptibility genes, i.e. the mutation increases an individual's odds of having HD, but is not predictive of the abnormality [35]. So far, eleven HD susceptibility genes have been identified in humans, namely the protooncogene RET (RET), glial cell line-derived neurotrophic factor (GDNF), neurturin (NTN), endothelin B receptor (EDNRB), endothelin 3 (EDN3), endothelin-converting enzyme 1 (ECE1), SOX10, Phox 21, GFRq1 and SIP1 genes [32, 36]. RET mutations account for 50% of familial and 15–35% cases of sporadic HD, whereas EDNRB mutations are found in 5% of HD patients. Disease-associated mutations in the other nine genes are rarer, and in some cases have been documented in only one family [20, 37].

In isolated HD, adequate recurrence risk figures will be provided by taking into account the sex and length of the aganglionic segment in the patient and the gender of the sibling [28, 29]. Risk of recurrence of the disease is greater in relatives of an affected female than an affected male. Risk of recurrence is also greater in relatives of a patient with long-segment compared to short-segment disease. For example, the recurrence risk in a sibling of a female with aganglionosis beginning proximal to the splenic flexure is approximately 23% for a male and 18% for a female, whereas the recurrence risk in a sibling of a male with aganglionosis beginning proximal to the splenic flexure is approximately 11% for a male and 8% for a female. These risks fall to 6% and below for siblings of a patient with short-segment disease (Table 8.3) [29]. The recurrence risk and prognosis of syndromic HD and HD associated with chromosomal abnormalities depends on the recurrence risk of the associated syndrome rather than on the HD [32, 35, 37].

Table 8.4 Partial list of syndromes associated with Hirschsprung's Disease

Syndrome	Features
Neurocristopathies	
Shah-Waardenburg	Pigmentary anomalies, deafness
Congenital central hypoventilation	Abnormal autonomic control of respiration
Multiple endocrine neoplasia 2A	Medullary thyroid carcinoma, pheochromocytoma, hyperplasia of the parathyroid
Non-neurocristopathies	
Goldberg-Shprintzen	Cleft palate, hypotonia, microcephaly, mental retardation
HD with limb anomalies	Polydactyly, brachydactyly or nail hypoplasia with other assorted anomalies
BRESEK	Brain abnormalities, retardation, ectodermal dysplasia, skeletal malformations, Hirschsprung's disease, ear/eye anomalies, kidney dysplasia
Bardet-Biedl	Pigmentary retinopathy, obesity, hypogenitalism, mild mental retardation, postaxial polydactyly
Kaufman-McKusick	Hydrometrocolpos, postaxial polydactyly, congenital heart defect

8.7 Clinical Presentation

Hirschsprung's disease should be considered in any child who has a history of constipation dating back to the newborn period. The median age at which children are diagnosed with HD has progressively decreased over the past decades with greater awareness of the disease. In a survey conducted in 1979 by the Members of the Surgical Section of the AAP, the diagnosis of HD was made in the first month of life in 8% of patients; by 3 months of age the diagnostic rate had risen to 40% [22]. In a nationwide survey from Japan from 1978 to 1982, the diagnosis of HD was made in the first month of life in 48.7% of patients [11]. Recently, the Australian Paediatric Surveillance Unit in a prospective survey from 1997 to 2000 has reported that the diagnosis of HD in the newborn period is made in 90.5% of patients [25]. The neonate with HD is usually a full-term baby [11, 24, 38, 39] and presents with a distended abdomen, feeding intolerance with bilious aspirates or bilious vomiting and classically, with delay in the passage of meconium (Fig. 8.1). In many cases a rectal examination or rectal irrigation causes passage of meconium and relief of acute intestinal obstruction.

Among normal full-term infants, 98% pass meconium in the first 24 hours of life and the remainder will pass their first stool by 48 hours [40]. It has always been said that over 90% of HD infants fail to pass meconium in the first 24 hours of life [1]. However, several authors have found that more than 40% of HD newborns pass meconium in the first 24 hours of life [25, 39]. Thus one should not be dissuaded from carrying out a rectal suction biopsy by the absence of a history of delayed passage of meconium. Diarrhea, fever and abdominal distension in HD are always symptoms of enterocolitis, and this remains the most serious complication of this disease [20]. The reported incidence of enterocolitis ranges from 12% to 58%, and it can be seen before or after a pull-through operation [25, 41–43]. A recent survey has found the incidence of preoperative enterocolitis to be much higher in patients who had the diagnosis of HD established in the postneonatal period, stressing the importance of a prompt diagnosis [25]. A prenatal history suggestive of intestinal obstruction is rare, except in children with total colonic aganglionosis [44]. Occasionally, a diagnosis of HD should be considered in the presence of unexplained perforation of the cecum or appendix, although this is a rare presentation [21, 38, 45]. Some children do not become obstructed in the neonatal period and present later in infancy or in adulthood with severe constipation, chronic abdominal distension and failure to thrive [46, 47]. This is most common among breast-fed infants who may develop constipation around the time of weaning [1]. Rectal examination of patients with HD may show a tight anus [46]; however, some authors think this finding is unreliable [1]. The differential diagnosis for each presentation is shown in Table 8.5. After a careful history and physical examination, the diagnostic steps may include radiographic studies, anorectal manometry and a rectal biopsy.

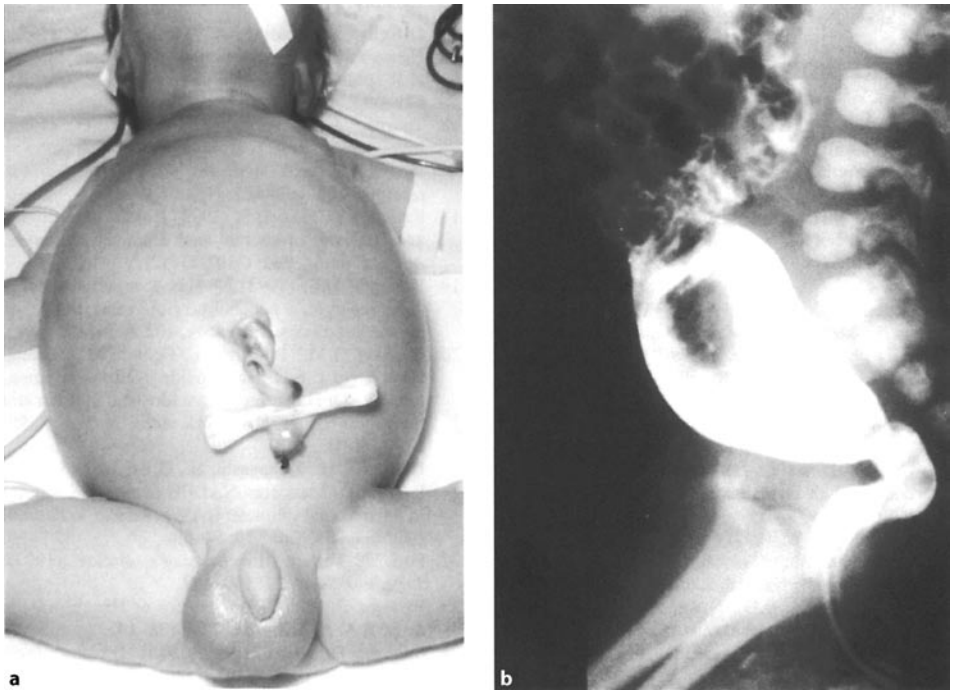

Fig. 8.1 **a** Newborn with Hirschsprung's disease **b** Barium enema in the same infant

Table 8.5 Differential diagnosis of Hirschsprung's disease

Neonatal bowel obstruction	**Meconium ileus resulting from cystic fibrosis**
	Ileal or colonic atresia
	Meconium plug syndrome
	Malrotation
	Congenital band
	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

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