In Brief: Hirschsprung Disease

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Characterized by the congenital absence of ganglion cells in the myenteric and submucosal plexuses of the intestine, Hirschsprung disease (HSD) results in abnormalities of intestinal motility that manifest most commonly as colonic obstruction. The aganglionic segment begins at the internal anal sphincter and extends a variable distance proximally. A simple, practical classification of HSD divides it into two types: short segment (S-HSD) and long segment (L-HSD). In the more common S-HSD (75% to 80% of cases), the aganglionic segment is located distal to the splenic flexure and often is limited to the rectosigmoid area. In L-HSD (20% of cases), the aganglionic segment includes and extends proximal to the splenic flexure, sometimes affecting the entire colon (total colonic aganglionosis), and in rare instances, the entire large and small intestine (total intestinal aganglionosis). A controversial variant of HSD is referred to as ultrashort-segment HSD because it is believed to involve less than 5 cm of the distal rectum. Not all authorities believe that this variant is a true entity.

HSD can be sporadic or familial and has a male predominance of about 3.8:1. The incidence varies with ethnicity, with 1.5 per 10,000 live births among Caucasians, 2.1 per 10,000 among African-Americans, 1.0 per 10,000 among Hispanics, and 2.8 per 10,000 among Asians. In siblings, the incidence overall is approximately 3.5%, increasing with the length of the affected segment.

Although HSD usually is an isolated birth defect (70% of cases), it has been reported in association with other disorders. For example, HSD is ten times more frequent in patients who have Down syndrome than would be expected by chance, and approximately 2% of patients who have congenital aganglionosis have Down syndrome. Other disorders associated with congenital megacolon include Waardenburg syndrome, Laurence-Moon-Biedl syndrome, Smith-Lemli-Opitz syndrome, multiple endocrine neoplasia type IIa, and congenital central hypoventilation syndrome (Haddad syndrome). Other nonsyndromic congenital anomalies that have been described as occurring with HSD include, but are not limited to, hydrocephalus, ventricular septal defect, cystic deformities and agenesis of the kidney, imperforate anus, Meckel diverticulum, polyposis of the colon, and cryptorchidism.

HSD results from the failure of craniocaudal migration of the ganglion cell precursors from the neural crest along the gastrointestinal tract during the 5th through the 12th weeks of gestation. The earlier this arrest in migration occurs, the longer is the aganglionic segment. Mutations in at least four different genes have been implicated in the pathogenesis of congenital aganglionosis: the RET tyrosine kinase receptor gene; the gene for one of its ligands, called glial cell line-derived neurotrophic factor; the endothelin receptor B gene; and the gene for its ligand, endothelin-3.

The absence of ganglion cells disrupts the expression of inhibitory parasympathetic nerves in the myenteric plexus of the affected segment. Recently, it has been shown that the inhibitory neurotransmitter nitric oxide also is reduced in the aganglionic segment. The lack of normal inhibitory activity results in tonic contraction of the affected segment, producing obstructive symptoms and dilatation and hypertrophy of the proximal colon.

Most children who have congenital aganglionosis become symptomatic in the first few days to weeks after birth; 99% of term infants and 95% of preterm infants pass meconium by 48 hours of age. A delay in the passage of meconium always should raise the suspicion of HSD. Other symptoms may include infrequent bowel movements, diarrhea, bilious vomiting, abdominal distention, and refusal to feed. Findings on physical examination often include abdominal distention, a contracted anal

sphincter, and an empty rectal vault on digital examination, with the explosive release of foul-smelling stool when the finger is removed.

Enterocolitis, the major cause of morbidity and mortality with HSD, occurs most commonly in children younger than 2 years of age. Clinically, enterocolitis presents with abdominal distention, explosive watery stools, fever, and the hemodynamic instability of hypovolemic shock.

Radiographic, functional, and histologic studies can be used to diagnose HSD. A single-contrast, unprepared barium enema that demonstrates a transition zone between the distal contracted aganglionic segment and the proximal dilated hypertrophied colon is very suggestive, although the absence of a transition does not rule out the condition. Anorectal manometry also may be helpful, detecting physiologic abnormalities associated with aganglionosis. Normally, distention of the rectum induces a reflex relaxation of the internal anal sphincter. With manometry, the expansion of a balloon inserted in the rectum demonstrates the absence of this reflex response in children who have HSD. Anorectal manometry may be particularly useful in children who have ultra short-segment disease (<5 cm), who often have normal barium enema study results.

Rectal suction biopsies or full-thickness rectal biopsies with specimens deep enough to include the submucosa are considered the gold standard for diagnosing HSD. Sometimes the diagnosis is difficult to make because the pathologist is looking for the absence of ganglion cells in the submucosal plexus (looking for a negative rather than a positive). Acetylcholinesterase staining of rectal suction biopsy specimens may be a helpful adjunct because it typically demonstrates an overabundance of hyperplastic axons resulting from the absence of ganglion cells.

Once the diagnosis of HSD is confirmed, surgery is the treatment of choice. Various surgical procedures have been developed and have their own advantages and disadvantages, but each attempts to remove most or all of the aganglionic segment and to reanastomose the normal proximal bowel to the distal rectum or anal canal. The goals of surgery are to establish regular and spontaneous defecation and maintain continence. Although most patients have a good outcome, up to 30% remain constipated or never develop fecal continence.

In the future, it is likely that additional genes and gene products associated with HSD will be defined, perhaps providing new approaches to the diagnosis of the condition as well as novel therapies.

Comment: The genetic aspects of HSD are complex. At least four different gene loci on chromosomes 10, 13, and 20 have been identified, and the association with Down syndrome suggests the possibility of another locus on chromosome 21. HSD can be inherited as either an autosomal dominant or recessive trait, which does not explain why it shows a marked predilection for males. There also are associations with pigmentary abnormalities (Waardenburg syndrome), neural crest disorders (pheochromocytoma), and even congenital central hypoventilation. Given all this heterogeneity, counseling families on the risk of recurrence is, at best, imprecise. In general, the risk is higher when the index child is a girl and also with L-HSD rather than S-HSD. Overall, the risk for recurrence seems to be anywhere from about 1% to nearly 20%. It is hoped that direct mutation analysis eventually will prove to be helpful.

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