Hirschsprung Disease

Alternative Names
HSCR
Hirschsprung Disease 1
HSCR1
Megacolon, Aganglionic
MGC
Aganglionosis, Total Intestinal

WHO International Classification of Diseases
Congenital malformations, deformations and chromosomal abnormalities

OMIM Number
142623

Mode of Inheritance
Autosomal dominant

Gene Map Locus

Description
Hirschsprung disease is a congenital disorder with the incidence of 1 per 5000 live births. It is characterized by the absence of intestinal ganglion cells in the nervous plexuses in the distal part of the digestive tract. The disease affects the rectum and sigmoid colon in 80% of cases, or is more extensive. Hirschsprung's disease is suspected in cases of low gastrointestinal obstruction in the neonatal period, or in cases of chronic severe constipation in childhood. It is diagnosed by pathological examination of rectal biopsies that include the submucosa. After standard staining, multiple sections are scrutinized for neuronal cells. Acetylcholinesterase staining is performed on a frozen fragment to demonstrate the hyperplasia of cholinergic fibers that is very suggestive of Hirschsprung's disease. This hyperplasia decreases from the rectum to the splenic flexure of the colon. Hyperplasia of extrinsic nerve fibers and rarefaction of neuromuscular junctions in Hirschsprung's disease may be demonstrated immunohistochemically. Differential diagnosis includes chronic intestinal pseudo-obstructions.

The treatment for Hirschsprung's disease is, most often, anastomosis of the normally innervated gut to the anal canal. Peri- or pre-operative biopsies assist surgery, but their interpretation is difficult in the transitional zone. The examination of the surgical specimen allows measurement of the aganglionic segment and transitional zone.

Hirschsprung's disease is associated with other digestive or extra-digestive abnormalities in 5 to 30% of patients. Associated abnormalities may delay the diagnosis and treatment of Hirschsprung's disease.

Molecular Genetics
In the etiology of Hirschsprung disease, various genes play a role. These are: RET, EDNRB, GDNF, EDN3, SOX10, NTN3, and ECE1. Mutations in these genes may result in dominant, recessive or multifactorial patterns of inheritance. Diverse models of inheritance, coexistence of numerous genetic disorders and detection of numerous chromosomal aberrations together with involvement of various genes confirm the genetic heterogeneity of Hirschsprung disease. Hirschsprung disease might well serve as a model for many complex disorders in which the search for responsible genes has only just been initiated. It seems that the most important role in its genetic etiology plays the RET gene, which is involved in the etiology of at least four diseases: multiple endocrine neoplasia, type IIA (MEN2A), multiple endocrine neoplasia, type IIB (MEN2B), Hirschsprung disease (HSCR; aganglionic megacolon), and medullary thyroid carcinoma (MTC).
Epidemiology in the Arab World

Iraq
Nowaczyk et al. (1997) reported an infant girl with Hirschsprung disease, postaxial polydactyly, and atrial septal defect who was born to a consanguineous Iraqi couple.

Morocco
In 1998, Brooks et al. reported three children from a large, consanguineous, Moroccan family with Hirschsprung disease, mental retardation, microcephaly, and specific craniofacial dysmorphism. A fourth child showed similar clinical features, with the exception of Hirschsprung disease. The association of these abnormalities in these children represents the Goldberg-Shprintzen syndrome (Mowat-Wilson syndrome).

Palestine
In two Palestinian Muslim consanguineous families that lived in the same village, Dudin and Rambaud-Cousson (1993) found seven cases of lethal infantile osteopetrosis. In two of the seven persons, short-segment Hirschsprung disease (142623), a probably independent disorder, was also present. Both patients died early.

Saudi Arabia
Sayed and Al-Alaiyan (1996) reported a full-term infant with Hirschsprung disease who was diagnosed to have hypertrophic pyloric stenosis (HPS) and agenesis of corpus callosum (ACC). Sayed and Al-Alaiyan (1996) suggested that these three conditions are due to an underlying pathophysiologic mechanism.

Mansour and Zahrani (2002) analyzed 27 consecutive cases of endoscopic colonic biopsies and surgical colectomy specimens of both male and female cases presented with Hirschsprung disease in King Abdul Aziz University Hospital, Jeddah. Data on all colonic biopsies and colectomies. The mean age of presentation was 3.33 with a prominent predilection for males. Out of 27 cases 18 (66.7%) were males and 9 (11.4%) were females. All the 27 (100%) patients presented with constipation, 15 (55.5%) patients had abdominal distension and no patient presented with diarrhea.

In 2003, Khan et al. studied the incidence of Hirschsprung's disease in children who presented with constipation to a specialist paediatric surgical unit in Saudi Arabia. During a 5-year period, 355 rectal biopsies were performed on 182 neonates, infants and children presenting with chronic constipation or intestinal obstruction: 25 (14%) were diagnosed with Hirschsprung disease. In 13 cases (8%) of suction and 2 cases (2.5%) of full thickness rectal biopsies, specimens were inadequate to diagnose Hirschsprung disease. The mean age of all patients was 2.9 years and that of patients diagnosed with Hirschsprung disease was 3.64 months. Nineteen patients with Hirschsprung disease were diagnosed in the first month, 5 in 1-12 months and 1 at 4 years of age. Khan et al. (2003) found that along with onset of constipation convincing indications for rectal biopsy to exclude Hirschsprung disease were as follows: those infants and children who do not pass meconium within 48 hours, have low intestinal obstruction of unknown cause, severe constipation, chronic abdominal distension and failure to thrive.

Tunisia
In two girls born to consanguineous Tunisian parents, Attie et al. (1995) described features of both Waardenburg syndrome and Hirschsprung disease. Neither affected sister had dystopia canthorum. However, both had deafness, white forelock, and heterochromia iridis, as well as Hirschsprung disease. One year later, Bonnet et al. (1996) reported a Tunisian infant of consanguineous parents with pigmented disorders, congenital deafness and long-segment Hirschsprung disease. Her elder sister had the same disorders but with short-segment aganglionosis. Their father, mother and two brothers are healthy without history of deafness, constipation or pigmented disorder. Bonnet et al. (1996) confirmed that this Waardenburg-Hirschsprung association seems to be a distinct clinical entity with a possible autosomal recessive mode of inheritance. They also suggested that Waardenburg-Hirschsprung complex is a distinct genetic entity and at least one additional locus altering cranial neural crest cell development is responsible for pleiotropic features observed in this association.

United Arab Emirates
Sztriha et al. (2003) reported a girl who had Hirschsprung disease in association with distinct facial appearance, microcephaly, agenesis of the corpus callosum and mental retardation (Mowat-Wilson syndrome). Mutation analysis of the zinc finger homeobox 1 B (ZFHX1B) gene revealed a de novo 7 bp deletion (TGGCCCC) at nucleotide 1773 (1773delTGGCCCC) resulting in a frameshift and leading to a termination codon at amino acid residue 604 (604 X) in exon 8 C.
Al Talabani et al. (1998) studied the pattern of major congenital malformations in 24,233 consecutive live and stillbirth at Corniche hospital, which is the only maternity hospital in Abu Dhabi, between January 1992 and January 1995. A total of 401 babies (16.6/1,000), including 289 Arabs, were seen with major malformation. The consanguinity rate among the parents of malformed babies was 47% of which 72% were first cousin marriages compared to 32% in the general population. Sporadic conditions accounted for 26% of the cases. In their study, Al Talabani et al. (1998) observed two cases of Hirschsprung disease in families from the United Arab Emirates. Recurrence was not reported in other members of the families. Al Talabani et al. (1998) concluded that their study was very close to representing the true incidence of congenital abnormalities in the United Arab Emirates, as they investigated over 98% of deliveries in Abu Dhabi, the capital of United Arab Emirates.

References

Contributors
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