



Hirschsprung Disease, Susceptibility to, 1

Alternative Names

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

Record Category

Disease phenotype

WHO-ICD

Congenital malformations, deformations and chromosomal abnormalities > Other congenital malformations of the digestive system

Incidence per 100,000 Live Births

11-50

OMIM Number

142623

Mode of Inheritance

Autosomal dominant

Gene Map Locus

Xq28, 20q13.2-q13.3, 10q11.2, 5p13.1-p12, 4p12

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, co-existence 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

Bahrain

Al-Ras Romani et al. (1982) studied eight Bahraini children diagnosed with Hirschsprung's disease. Majority of the patients were neonates, presenting with delay in passing meconium, lazy bowel motion, and occasional abdominal distension in the first week of life. Barium enema in these patients showed variable colonic distension above a normal or narrowed rectum. In the older patients, a hugely dilated colon above a mildly narrowed rectum could be visualized by the barium enema. Endo-rectal pull through was performed on at least three of the patients, and all these patients had full post-operative recovery, without any incidence of anastomotic leak or fecal fistula. Neither was anal stenosis, or fecal incontinence seen in these patients, even after 9-months of follow-up. Al-Ras Romani et al. (1982) concluded that Hirschsprung's disease was very common among the Bahraini population, and estimated its incidence at 1/4000. In 2000, Rasromani and colleagues described a 2-day-old boy who presented with bile stained vomiting, and delay in passing meconium. The infant weighed 3.7 kilograms and showed marked abdominal distension, increased bowel sounds, and an empty rectum. Gross dilatation of the large intestine extending to the proximal sigmoid colon was visible upon barium enema. Rectal biopsy was performed, which confirmed Hirschsprung's disease, involving the rectum and sigmoid colon. The patient was managed conservatively till nine-months of age, at which time he underwent a laproscopic pull-through with primary colo-rectal anastomosis. Follow-up for the subsequent three years revealed no complications.

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.

Kuwait

Ziad et al. (2006) conducted a retrospective study by at Al Sabah and Ibn Sina Hospitals covering the years 1994-2004 to determine the clinical and pathological characteristics of Hirschsprung disease (HD) in Kuwait. Throughout the study period, 268 pediatric subjects underwent forceps/suction rectal (91 cases) or open biopsies (11 cases) for the examination of HD. The diagnosis of HD was confirmed in 102 patients aged between one day and 13 years. Approximately 21% of HD subjects were older than 4 months, 14 cases were older than one year, and, out of those, 8 patients were aged 2 to 3 years. The study included 87 males and 15 females, with a strong male predominance detected within the group aged less than one year. Subjects

experienced several clinical features including constipation (82%), abdominal distension (9%), intestinal obstruction (6%), and intestinal perforation (3%). Two neonates suffered from cecal perforation and one patient aged 50 days experienced rectal perforation. In addition, two subjects experienced intestinal obstruction correlated with necrotizing enterocolitis and one of them passed away following a rectal biopsy. Out of the 102 HD patients, only 89 were available for a follow-up, and out of those, 70 subjects older than one year experienced short segment disease with a male predisposition of 22.3:1, 8 cases (8 males:2 females) suffered from total colonic aganglionosis (TCA), 5 subjects (4 males:1 female) experienced aganglionosis that developed to ileum/jejunum, 9 patients endured long segment HD, and 2 cases had ultra short-segment HD. Moreover, 6 patients suffered from further congenital abnormalities including Down's syndrome (2 patients), Rubenstein Taybi syndrome (1 patient), Meckel's diverticulum (1 case), and Waardenburg syndrome (2 male siblings born to consanguineous parents with 3 normal female daughters). Ziad et al. (2006) demonstrated a strong male predominance (5.8:1) of HD in Kuwait and proposed the importance of parental education and the necessity for further epidemiological studies of HD with concentration on genetics and consanguinity.

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).

Oman

Rajab et al. (1997) retrospectively studied the features and the factors involved in the pathogenesis of Hirschsprung's disease (HD) in Omani patients, by collecting data on Omani patients with possible HD from the pediatric surgery registry in Oman during the six years period from 1989 to 1994. Doubtful or negative rectal biopsy results were excluded. Out of 261,000 live births, 85 Omani babies were diagnosed with HD, making the frequency of HD in Oman 1 in 3,070, which was more than that in the expatriate population whose frequency was 1 in 4000. The incidence showed geographical variation with the highest incidence of 1 in 1800 found in the North Eastern Region (North Sharqia), followed by North Batena (1 in 2000), and the Capital Area (1 in



4200). The males outnumbered the females with a ratio of 2.9:1, but the ratio was reduced in the long segment HD. Most of the patients (81%) presented by the age of six months, with 61% presenting in the first month of life, and only 7% had presented between two and five years of age. Six families had positive family history. Three families had an additional affected sibling and one family had an affected first cousin. In addition, two families, who had four out of eight affected siblings, all of whom died, showed features of Waardenburg's syndrome (long segment of HD, piebaldism and deafness). The rate of consanguinity in HD was found to be higher than that of the general population, being 75% when compared to 23.8% in the general population. On analyzing the tribal distribution of HD, it was found that 54 tribes were involved, with one fifth of the cases (18.8%) belonging to two tribes, and three or less affected children were found within a tribe in most cases. In terms of the length of the aganglionic segment, most of the cases had recto-sigmoid aganglionosis (53 patients; 45 males and 8 females), followed by short segment involvement (21 patients; 12 males and 9 females), long segment involvement (7 patients; 3 males and four females), and total aganglionosis (4; 3 males and 1 female). Problems in the neonatal period were present in six children, but they improved by the age of one to three years without surgical intervention. In addition to HD, other congenital anomalies were present in 23 patients. These included Down's syndrome (9), renal tract anomalies in (4), and gastrointestinal anomalies (2). The effects of birth order rank and paternal age on the development of HD were found not to be significant, but the maternal age (26.4 years) was found to be significantly greater than the mean maternal age of the general population (23.3 years). It was also found that there was no seasonal variation, as the proportion of cases born in the hot months of March till August were not significantly different from those born in the cold months of September till February. Rajab et al. (1997) explained the reason of increased frequency of HD in Oman to the increased prevalence of recessive mutations due to the increased consanguinity and suggested that detailed study of isolated inbred populations might identify such mutations.

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 (33.3%) were females. All the 27 (100%) patients presented with constipation, 15 (55.5%) patients had abdominal distension and no patient presented with diarrhea. In the same year, Asindi et al. (2002) conducted a prospective study to evaluate the prevalence and pattern of congenital malformations of the gastrointestinal tract among the Saudi newborn population in Aseer region from January 1995 to December 2000. A total of 1386 Saudi infants were admitted into the neonatal intensive care unit of Aseer Central Hospital. Of these, 12.4% were confirmed to have congenital malformation of the gastrointestinal tract; male/female ratio of 1.7:1. The total number of live births by Saudi mothers in Aseer region during the period was 128,093, giving an incidence rate of 1.3 per 1000 live births. The 172 newborns presented with 174 anomalies of the gastrointestinal tract including 14 cases (or 8%) with Hirschsprung's disease.

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 pigmentary 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 pigmentary 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 homeo box 1 B (ZFX1 B) gene revealed a de novo 7 bp deletion (TGGCCCC) at nucleotide 1773 (1773 delTGGCCCC) 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.

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Related CTGA Records

Anus, Imperforate

Endothelin Receptor, Type B

Mowat-Wilson Syndrome

Osteopetrosis, Autosomal Recessive

Pyloric Stenosis, Infantile Hypertrophic 1

Rearranged during Transfection Protooncogene

Waardenburg-Shah Syndrome

External Links

http://www.gfmer.ch/genetic_diseases_v2/gendis_detail_list.php?cat3=146

<http://www.hon.ch/HONselect/RareDiseases/EN/C06.175.439.html>

<http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hirschsprung-ov>

http://www.orpha.net/static/GB/hirschsprung_disease.html

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