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Advances in Hirschsprung Disease Genetics and Treatment Strategies: An Update for the Primary Care Pediatrician

Deepika D'Cunha Burkardt, DO[1], John M. Graham Jr, MD, ScD[2], Scott S. Short, MD[2], and Philip K. Frykman, MD, PhD, MBA, FACS, FAAP[2]

Abstract

Hirschsprung disease (HSCR) is a multigenic condition with variable presentation. Most commonly, it presents in the neonatal period as a functional intestinal obstruction secondary to failure of caudal migration of the enteric nervous system. Classically, this manifests as dilated proximal bowel and constricted distal bowel with absent ganglia and hypertrophic nerve trunks. When recognized early, medical and surgical therapies can be instituted to minimize associated morbidity and mortality. This article reviews current understanding of the etiology of HSCR, its multigenic associations, the historical evolution of HSCR diagnosis and treatment, and current HSCR therapies.

Keywords

Hirschsprung disease, congenital megacolon, aganglionosis, enteric nervous system, Hirschsprung-associated enterocolitis, genetics, intestinal neuronal dysplasia

Introduction

Hirschsprung disease (HSCR) is defined as congenital absence of parasympathetic ganglia in the submucosal and myenteric plexi of the distal bowel likely secondary to failure of migration of neural crest cells during development and affects 1 in 5000 children.[1] The disease results in a functional obstruction of the colon leading to constipation and, in many cases, enterocolitis. Prior to development of successful surgical therapies, mortality rates were reported as high as 88% with outcomes likely dependent on severity of disease phenotype.[2] HSCR may be short-segment (up to 85% of cases), defined as an absence of ganglion cells extending from the anorectal junction to the splenic flexure, or long-segment disease (approximately 10% of cases), defined as aganglionosis extending proximal to the splenic flexure.[3] Although somewhat rare (5% to 7% of all HSCR cases), total colonic aganglionosis may be present in up to 60% of children with long-segment disease.[3]

Overall, the disease is more common among boys with many studies reporting a 4:1 prevalence.[4] While most US studies report high prevalence among Caucasian populations compared with minority groups, overall incidence appears highest among Asians (2.8/10 000), followed by African Americans (2.1/10 000), Caucasians (1.5/10 000), and Hispanic populations (1.0/10 000).[5] The advent of recent advances in molecular genetics has resulted in better understanding of HSCR, its variable presentations, and underlying genetics. This article reviews current understanding of the etiology of HSCR, the historical evolution of HSCR diagnosis and treatment, and current HSCR therapies.

Current Understanding of Etiology

Hirschsprung disease is a widely recognized congenital condition with multiple approaches to therapy, and once treated, most children have a good to excellent quality of life. It has also been associated with a number of heritable conditions, including trisomy 21, single gene mutations, syndromes and recently, inflammatory bowel disease.[6,7]

[1]Wright State University School of Medicine, Dayton, OH, USA
[2]Cedars-Sinai Medical Center, Los Angeles, CA, USA

Corresponding Author:
Philip K. Frykman, Division of Pediatric Surgery, Cedars-Sinai Medical Center, 8635 West Third Street, Suite 675W, Los Angeles, CA 90048, USA.
Email: philip.frykman@cshs.org

The underlying problem in HSCR is failure of normal development of the enteric nervous system (ENS) following abnormal neural crest cell migration, proliferation, differentiation, and/or survival. The ENS originates from neural crest cells, which migrate in a rostral to caudal direction to provide enteric innervation to the alimentary tract between the third and seventh week of gestation.[8] Traditionally, it has been thought that arrest in caudal migration of neural crest-derived cells along the hindgut resulted in HSCR. However, recent data from murine models have challenged this dogma through demonstration that trans-mesenteric migration of neural crest cells results in a substantial contribution to the hindgut ENS.[9] Regardless of the specific migratory pattern leading to normal ENS formation, the failure to populate the hindgut with ENS results in the HSCR phenotype. There are a number of genes and syndromes that have been identified to be important in the pathogenesis of HSCR (Table 1).

Known Genes Associated With HSCR

RET and RET Ligands. The *RET* protooncogene, on the long arm of chromosome 10 is one of the receptor tyrosine kinases, cell-surface molecules that transduce signals for cell growth and differentiation and plays a critical role in normal ENS proliferation. The RET gene, which maps on chromosome 10 (10q11.2) and encodes for a tyrosine kinase receptor, is implicated in the vast majority of HSCR cases, both isolated and syndromic cases. Patients can either have mutations in the coding sequence,[15] or a noncoding polymorphism in an enhancer element located in intron 1, that leads to decreased *RET* expression and results in a hypomorphic allele.[16] Mutations in *RET* account for up to 35% of sporadic HSCR and 50% of familial cases.[8] The proteins glial-derived neurotrophic factor (*GDNF*)[17] and *NRTN* (or NTN; neurturin)[18] are 2 RET ligands, and GDNF family receptor α1 (GFRα1) is a RET co-receptor, which together play key roles in the control of ENS differentiation. During development, GDNF is expressed sequentially in the esophagus, stomach, small intestine, and cecum thereby serving as a concentration gradient to attract ENS cells expressing *RET* and the co-receptor GFRα1. Studies have demonstrated that formation of the GDNF–RET–GFRα1 complex is necessary to prevent aganglionosis, and the presence of GFRα1 is necessary for transmesenteric migration of neural crest cells.[8,9,19] Interestingly, mutations in these ligands and/or co-receptor can be found in only a very small minority of HSCR cases and can occur in association with a *RET* mutation.[1,17,18]

Although *RET* mutations are common, the penetrance is low and is evident in approximately 50% of familial HSCR cases. Nonetheless, mutations in *RET* are found in 70% to 80% of patients with long-segment HSCR and there have been reports of homozygous *RET* mutations in patients presenting with a total colonic aganglionosis.[1,20,21] Males carrying *RET* coding region mutations are more likely to be affected than females carrying the same mutation, and affected males are less likely to reproduce, producing a transmission distortion and an asymmetrical parental transmission origin.[16,22] Haploinsufficiency, the presence of a single functioning copy of a gene, is responsible for most cases of *RET*-associated HSCR. However, at least one mouse study[23] reports that loss of both alleles is needed to induce aganglionosis, and Emison et al[16] suggested a "two hit" hypothesis from their analysis of 882 probands. They likened HSCR to retinoblastoma.

Mutations resulting in partial or complete loss of function of the *RET* protein can result in HSCR, whereas mutations that cause constitutive activation of the *RET* protein result in medullary thyroid cancer, or multiple endocrine neoplasia (MEN 2A and MEN 2B) syndromes.[24] *RET* signaling pathways (in association with vitamin A) are known to influence the embryogenesis of the urinary bladder, particularly the insertion of the distal ureters into the bladder, and the formation of the trigonal wedge. Hence, it is not surprising that a defect of *RET* signaling may also result in urogenital anomalies as part of the clinical phenotype.[25]

If monogenic nonsyndromic HSCR is evident, molecular genetic testing of *RET* should be considered. HSCR-associated mutations have been described in each of the 20 *RET* exons and no single specific defect is particularly common. In addition, because of incomplete penetrance of mutant alleles, it is difficult to predict the phenotypic effect of a given sequence change. In some circumstances (eg, a family with highly penetrant, long-segment HSCR), *RET* molecular genetic testing may be helpful in providing genetic counseling. Some groups recommend testing for MEN2-associated mutations in *RET* in all individuals with HSCR. If a *RET* mutation is not identified, molecular genetic testing of *EDN3* and/or *EDNRB* may be pursued.

EDNRB *and* EDN3. The endothelin receptor B gene (*EDNRB)* on the long arm of chromosome 13 codes for a G-protein coupled receptor that binds endothelins, small proteins with potent vasoactive effects. *EDNRB* interacts with the ligand, endothelin-3 *(EDN3*), which is activated through posttranslational modification by endothelin-converting enzyme 1 (encoded by *ECE1*). Mutations in *EDNRB* and the ligand *EDN3* account for approximately 10% of individuals with HSCR.[1] Additional case reports of HSCR patients with an *ECE1* mutation have also been described.[26]

Mouse developmental models have demonstrated that *EDNRB* and *EDN3* gene expression are necessary at a critical stage of neural crest development, particularly the migration of both melanoblasts and enteric neuroblasts (ENS precursors).[27] In 2004, Zhu et al[28] found that as ENS precursors migrate toward the colon, a spatiotemporal enhancer of the *EDNRB* gene is activated by *Sox10*, a SRY-related transcription factor that has a known association with HSCR. Homozygous mutations of the *EDNRB* gene result in deafness and pigmentary anomalies (piebaldism) in humans, while mouse models of HSCR result in piebaldism but not deafness.[29]

Other Genes. *ZEB2* or zinc-finger E box-binding homebox 2 is a gene that codes for a DNA-binding transcription repressor. Mutations or deletions in the *ZEB2* gene lead to Mowat–Wilson syndrome, which can result in HSCR with microcephaly, agenesis of the corpus callosum, seizures, intellectual disability, short stature, submucosal cleft palate, heart defects, and hypospadias.[30,31] *PHOX2B* mutations have been associated with congenital central hypoventilation syndrome (CCHS) and an increased risk for HSCR. The mutations are mostly heterozygous polyalanine expansions, with higher numbers of alanine expansions observed in more severe phenotypes.[32]

Syndromic HSCR

Congenital anomalies are associated with HSCR in 5% to 32% of patients.[33] These anomalies may be linked to a single gene or part of a recognizable genetic or chromosomal syndrome. Single gene (or monogenic) causes for syndromic HSCR can be inherited in an autosomal dominant, autosomal recessive, or X-linked fashion.[1] Since HSCR is a disorder of neural crest cell migration, it is not difficult to imagine other associated neurological abnormalities. Syndromes associated with HSCR and central nervous system abnormalities include CCHS (also called Haddad syndrome when associated with HSCR), or Ondine's curse. Mowat–Wilson syndrome and Goldberg–Shprintzen syndrome not only share the features of HSCR, intellectual disability, developmental delay, seizures, and microcephaly but also have other distinguishing clinical features and distinctive facial features.[34] Other syndromes that have HSCR as a common or occasional feature are listed in Table 1. Interestingly, the *RET* risk allele in patients with some syndromes, such as Bardet–Biedle syndrome, Down syndrome, and CCHS, is more commonly found in patients with HSCR than patients with the same syndrome without HSCR. However, this is not true for Mowat–Wilson syndrome and Shah–Waardenberg IV syndrome, in which the *RET* risk allele is not more common in patients with HSCR.

Chromosomal Abnormalities

Down syndrome (trisomy 21) is the most common chromosomal abnormality associated with HSCR, with an estimated 0.6% to 3.0% of individuals with Down syndrome suffering coexisting HSCR.[1,31] Jannot et al[10] recently performed a dose-dependent association study on chromosome 21 in 26 patients with Down syndrome and their parents. They identified associated SNPs in intron 3 of the *DSCAM* gene at 21q22.2-22.3, a neural cell adhesion molecule, which is largely expressed in the developing nervous system and enteric nervous system development and thought to be partially responsible for the intellectual disability and visceral anomalies (eg, intestinal atresia, HSCR) in Down syndrome. Furthermore, they replicated association of HSCR with this region of chromosome 21 in an independent sample of 220 nonsyndromic HSCR Caucasian patients and their parents and demonstrated involvement of *DSCAM* by network analysis and assessment of *SOX10* regulation. Thus, DSCAM is involved as a HSCR susceptibility locus, both in Down syndrome and HSCR isolated cases.

Other syndromes include Deletion 10q, which is associated with long-segment HSCR and includes the deletion of *RET*. Deletion 13q is associated with short segment HSCR and deletion of the *EDNRB* gene while deletion of 2q22 is associated with both long- and short-segment HSCR and Mowat–Wilson syndrome caused by deletion of the *ZEB2* gene.[31] Similar pathophysiology occurs with deletions and duplications of 17q21.[15] With the advent and use of chromosomal microarrays, the frequency of chromosomal causes has increased as more submicroscopic copy number variations are being detected.

Use of chromosomal microarrays for patients with HSCR and associated malformations can be quite useful in identifying an underlying condition when no specific syndrome is evident. If the patient has a specific syndrome, such as Mowat–Wilson syndrome, then syndrome-specific gene testing can be performed. If there is no obvious syndrome apparent in a patient with associated malformations, then exome or whole genome sequencing can be useful in identifying an underlying condition and providing appropriate counseling. The genetics of HSCR is complex and can involve mutations in more than 30 different genes.

Clinical Suspicion

Most cases (90%) of HSCR are recognized in the neonatal period, and should be considered in term infants who fail to pass meconium in the first 24 hours of life.[6] Preterm infants often have dysmotile bowel and may have delayed passage of meconium in the absence of

Table 1. Genetic Associations With HSCR.

Name	Genetic Loci (Gene)	
Monogenic HSCR		
RET	10q11.2	
GDNF	5p13.2	
NRTN	19p13.3	
EDNRB	13q22.3	
EDN3/ET3	20q13.32	
ECE1	1p36.12	
SOX10	22q13.1	
ZFHX1B	2q22	
PHOX2B	4p12	
DSCAM	21q22.2	
TCF4	18q21	
Syndromic HSCR		Most Common Features
Down Syndrome/ Trisomy 21	Chr 21 (*DSCAM*)[10]	Intellectual disability, short stature, ligament laxity, hypotonia, brachy/microcephaly, hypogonadism, craniofacial dysmorphism, congenital heart disease, umbilical hernia, epicanthal folds, HSCR (severe constipation/other GI anomalies), hypothyroidism, hematologic malignancies
Deletion 10q	10q11.2 (*RET*)	HSCR, MEN 2A, medullary thyroid carcinoma
Deletion 13q	13q22 (*EDNRB*)	Long-segment HSCR
Deletion 2q22	2q22.3 (*ZEB2/ZFHX1B*)	Short- or long-segment HSCR and Mowat–Wilson syndrome (see below)
Bardet–Biedl syndrome	14 genes: *BBS1* *BBS2* *BBS3/ARL6* *BBS4* *BBS5* *BBS6/MKKS* *BBS7* ***BBS8/TTC8*** *BBS9/B1* *BBS10* *BBS11/TRIM32* *BBS12* *BBS13/MKS1* *BBS14/CEP290* (20% unknown)	1°: Rod-cone dystrophy (retinitis pigmentosa), postaxial polydactyly, truncal obesity, learning difficulties, hypogonadism/genital anomalism, renal malformations leading to end-stage renal disease 2°: Craniofacial dysmorphism, Developmental delay +/− behavioral abnormalities, eye anomalies, mild hypertonia, diabetes, orodental anomalies, cardiovascular defects, HSCR[11,12]
Cartilage-hair hypoplasia syndrome	9p21-p12 (*RMRPR*)	Short stature with short limbs (cartilage hypoplasia on skeletal biopsy), fine and light colored hair, lymphopenia with susceptibility to viral illness, HSCR/malabsorption
Congenital central hypoventilation syndrome (Haddad syndrome)	4p12 (*PMX2B/ PHOXB2*), 12q23.2 (*ASCL1*) rarely by: 10q11.2 (*RET*), 5p13.2 (*GDNF*), 20q13.32(*EDN3*), 11p14.1(*BDNF*)	Abnormal control of respiration in the absence of neuromuscular, lung, cardiac or CNS–brainstem disease, associated with HSCR (Haddad syndrome–16% CCHS patients), neuroblastoma, ganglioneuroma, craniofacial anomalies
Familial dysautonomia (Riley–Day)	9q31 (*IKBKAP*)	Episodic hypertension and tachycardia (vasomotor instability), defective lacrimation, cyclic vomiting, impaired taste, HSCR Cases of glomerulosclerosis (absent sympathetic nerve terminals in renal arteries)

(continued)

Table 1. (continued)

Name	Genetic Loci (Gene)	
Fryns syndrome		Typically lethal in neonatal period Craniofacial dysmorphism with clouded cornea, diaphragm defects, distal limb defects, lung hypoplasia, urogenital anomalies
Goldberg–Shprintzen	10q22.1 (*KBP/KIAA1279*)	HSCR, microcephaly, short stature, learning disabilities, craniofacial dysmorphism, hypotonia
Neuronal intestinal dysplasia B	10q11.2 (*RET*)	Type B [NIDB]—hyperplasia of submucosal plexuses proximal to HSCR (Type A [very rare]—infants with diarrhea, bloody stools/ intestinal spasticity—hypoplasia/aplasia of intestinal sympathetics)
L1 syndrome (X-lined hydrocephalus)	Xq28 (*L1CAM*)	Stenosis of the aqueduct of sylvius (leading to hydrocephalus), HSCR
MEN 2A/Sipple syndrome	10q11.2 (*RET*)	Pheochromocytoma, medullary thyroid carcinoma/ parafollicular thyroid carcinoma
MEN 2B	10q11.2 (*RET*)	Mucosal neuroma, pheochromocytoma, thyroid carcinoma
Mowat–Wilson syndrome	2q22.3 (*ZEB2/ZFHX1B*)	Facial dysmorphism, eye defects microcephaly with agenesis of the corpus callosum, intellectual delay/disability with speech impairment, seizures, foot/ankle anomalies Congenital heart defects (pulmonary artery/valve defects), pectus anomalies Genitourinary defects, HSCR (and chronic constipation in those without HSCR)[13]
NF1	17q11.2 (*NF1*)	Lisch nodules, café-au-lait spots, fibromatous tumors of the skin
Pitt–Hopkins syndrome[14]	18q21.2(*TCF4*)	Intellectual disability, wide mouth, intermittent hyperventilation followed by apnea, low IgM (without immunodeficiency)
Smith–Lemli–Opitz	11q12-q13 (*DHCR7*)	Intellectual disability, microcephaly, hypotonia, craniofacial dysmorphism, congenital heart defects, postaxial polydactyly, urogenital hypoplasia
Waardenburg–Shah syndrome	13q22 (*EDNRB*), 20q13.32 (*ET3*), 22q13.1 (*SOX10*)	Abnormalities of pigmentation of hair/skin/eyes, sensorineural hearing loss, HSCR
Waardenburg type 4A	13q22 (*EDNRB*)	Abnormal pigmentation of hair, skin, eyes, sensorineural hearing loss, HSCR
Idiopathic-Associated Congenital Anomaly		
CNS—Dandy–Walker malformation, microcephaly		
CVS—ASD, VSD, PDA, tetralogy of Fallot		
GI—Malrotation, imperforate anus, Meckel diverticulum		
GU—Cryptorchidism, hypospadias, kidney malformation, ureteral fistula		

Abbreviations: HSCR, Hirschsprung disease; GI, gastrointestinal; MEN 2A, multiple endocrine neoplasia type 2A; CNS, central nervous system; CCHS, congenital central hypoventilation syndrome; NIDB, neuronal intestinal dysplasia type B; IgM, immunoglobulin M; NF, neurofibromatosis; CVS, cardiovascular system; ASD, atrial septal defect; VSD, ventricular septal defect; PDA, patent ductus arteriosus; GU, genitourinary.

HSCR. Other patients may present with signs of intestinal obstruction, vomiting, abdominal distention relieved by enemas or rectal stimulation, enterocolitis, or severe constipation.[1,15] Enterocolitis is the most common cause of HSCR-associated mortality and is most commonly associated with diarrhea, explosive stools, abdominal distension, and radiologic evidence of bowel obstruction or mucosal edema.[35,36] However, presentation is variable, and recognition of Hirschsprung-associated enterocolitis (HAEC) can be difficult prior to diagnosis of HSCR. Unfortunately, delays in diagnosis can increase risk of mortality in patients with HAEC presenting with

rectal bleeding, toxic megacolon, and impending shock.[37] Hence, early consultation of a pediatric surgeon when the diagnosis of HSCR is suspected cannot be overemphasized.

As previously elaborated, children with Down syndrome, family history of HSCR, or family history of MEN 2A/2B, Mowat–Wilson syndrome, neurofibromatosis, or Waardenburg syndromes have increased risk of HSCR and clinicians should have a lower threshold to evaluate these children for HSCR in the appropriate clinical setting.[38]

Differential Diagnosis

While HSCR should be a primary consideration for any neonate presenting with constipation, failure to pass meconium, ileus, abdominal distention, and/or signs of intestinal obstruction, other etiologies warrant consideration in the differential diagnosis. These include:[15,39]

1. Meconium ileus is due to increased viscosity of intestinal mucous and often associated with cystic fibrosis.[40] Nonoperative management generally consists of gastrograffin enema with or without the use of *N*-acetylcysteine to clear inspissated meconium in the terminal ileum. Surgical intervention is required when nonoperative management fails to evacuate the large meconium ileus while maintaining intestinal continuity and length.[41]
2. Other causes of intestinal obstruction should also be considered. This is a relatively long differential, which includes but is not limited to intestinal atresia, intestinal web, malrotation, functional immaturity, and external compression secondary to Ladd's bands or intra-abdominal mass.
3. Functional intestinal obstruction secondary to prematurity, congenital hypothyroidism, maternal infection, maternal intoxication, or maternal therapies (eg, magnesium).

Diagnostic Modalities

In infants and children suspected of having HSCR, imaging studies are the least invasive test to obtain first (Figures 1 and 2). Plain radiographs often show considerable bowel distention, which is nonspecific for HSCR. Water-soluble contrast enema is the best study to evaluate for a funnel-shaped transition zone between normal and aganglionic bowel, and to exclude other pathology.[42] The enema allows one to calculate the "rectosigmoid index," or the ratio of the rectal diameter to the diameter of the sigmoid colon. If the ratio is less than 1, or the sigmoid is larger than the rectum, then HSCR should be considered.[15,43] Although enemata may delineate anatomy and provide evidence for HSCR, the histopathologic transition zone is often discordant with radiologic imaging and must be delineated by biopsy (Figure 3). Use of other diagnostic methods, including anorectal manometry, has been well described but are infrequently used for diagnosis of HSCR, with many authors believing that manometry is unnecessary in most cases.[44]

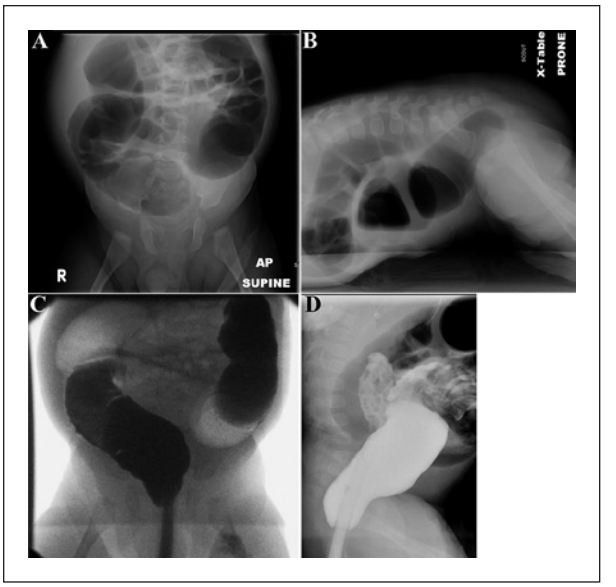

Figure 1. Barium enema performed in a 3 month-old boy with a history of constipation. (A) Anterior–posterior (AP) supine and (B) cross-table lateral (prone position) scout images demonstrating a markedly dilated sigmoid colon that is larger than the rectum. (C) AP and (D) lateral fluoroscopic images, respectively, of a barium enema demonstrating a low transition zone approximately 4 cm from the anal verge. Images courtesy of Department of Radiology, Children's Medical Center, Dayton, Ohio.

Initially, diagnosis of HSCR relied on the relatively insensitive combination of clinical exam with radiologic imaging. Swenson et al[45] were the first to differentiate HSCR from other pathology using open rectal biopsy. Dobbins and Hill[46] later substantiated the role of suction rectal biopsy by submucosal identification of ganglion cells in 280 biopsies from 149 normal controls. To increase sensitivity and specificity on pathologic evaluation, acetylcholinesterase staining was used and found to be a reliable method of discerning HSCR from other pathology.[47] More recently, calretinin, a calcium signaling protein, has been used and may be more effective than acetycholinesterase by offering improved detection of HSCR in suboptimal samples.[47,48] Today, when

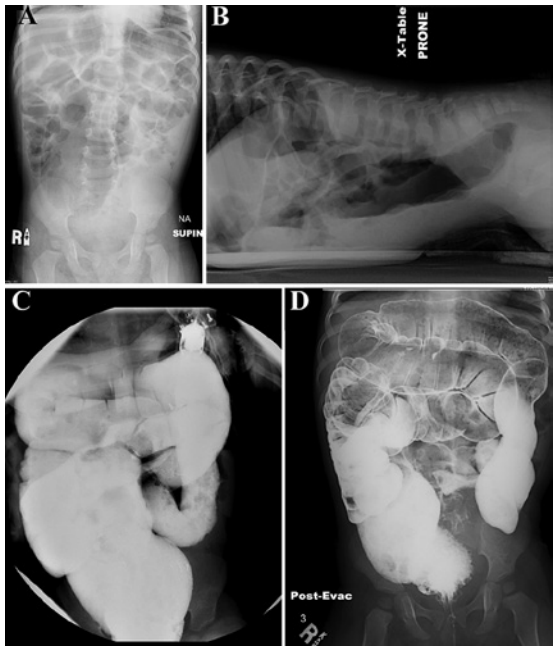

Figure 2. Barium enema performed on a 20 month-old child with long-standing history of constipation. (A) The anterior–posterior (AP) supine and (B) cross-table lateral (prone position) scout images demonstrating dilated small bowel and colon. (C) Fluoroscopic image from the barium enema demonstrating dilated colon with rectosigmoid inversion consistent with HSCR. (D) Postevacuation image demonstrates poor evacuation of contrast with persistently dilated loops of colon.
Images courtesy of Department of Radiology, Children's Medical Center, Dayton, Ohio.

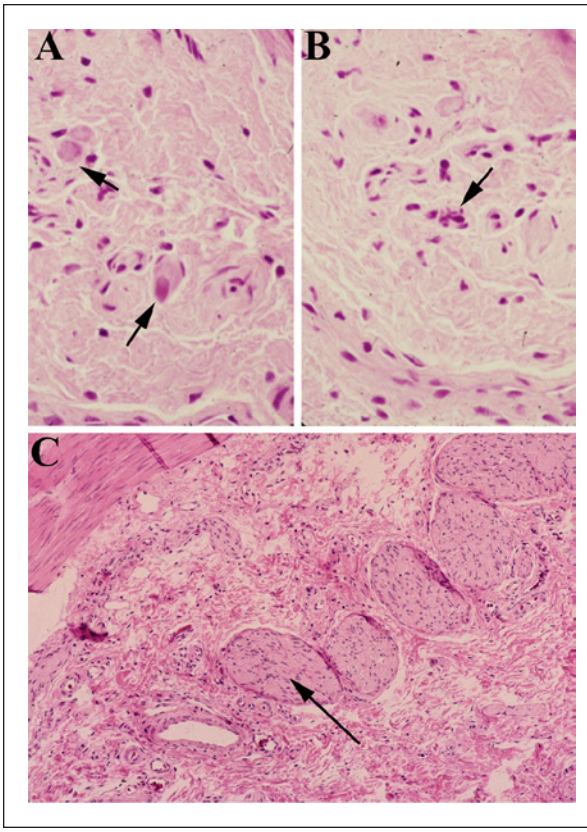

Figure 3. Photomicrographs showing histologic findings of normal and aganglionic colon. (A) Normal ganglionic colon with arrows demonstrating ganglion cells in Meissner's plexus. (B) Rectal biopsy from an aganglionic segment, with arrow demonstrating eosinophilic neural infiltrates. (C) Full-thickness section of aganglionic colon with arrow demonstrating hypertrophic nerve trunks in Meissner's plexus.
Images courtesy of L. David Mirkin, MD, Children's Medical Center, Dayton, Ohio.

clinical suspicion arises, a suction rectal biopsy may be performed at bedside with a sensitivity of 93% and specificity of 98%.[49]

Historic and Current Therapy

Widespread recognition of congenital megacolon as a distinct disease entity occurred following the 1886 report by Danish pediatrician Harald Hirschsprung, and the 1908 review by Finney describing "congenital idiopathic dilation of the colon."[50] These initial reports prompted further study to understand the pathophysiology of HSCR and recognize the underlying dysfunction of the ENS in 1928.[51]

Despite recognition of abnormal innervation of the bowel in the setting of HSCR, the etiology remained incompletely understood and remained a topic of debate with authors positing inflammatory, congenital anomalies, neuromuscular defects, and mechanical etiologies (eg, muscular hyperplasia).[2] During this period, a number of surgical methods were instituted, including lumbar sympathectomy to relax distal bowel, resection of the normal but dilated proximal colon, and attempts at spinal anesthesia.[51-53] Surgical therapy was viewed as a salvage therapy for failure of medical therapies, which included use of enemata, liquid paraffin, mineral oil, colonic massage, Mecholyl (a sympathetic stimulant), and Syntropan (a parasympathetic inhibitor).[54,55] Failure of therapy was frequent and mortality was reported to be as high as 74% in some series.[54]

A definitive method of repair was developed by Orvar Swenson, who observed recurrence of disease in patients following closure of colostomy in children who had previously undergone diversion to relieve obstructive symptoms. Furthermore, he evaluated children

following diversion and detailed resolution of bowel dilation in the proximal segment and demonstrated maintenance of proximal, but not distal bowel propulsive actions.[53] In 1949, Dr Swenson described his technique for removing the constricted distal portion of the colon and rectum, with preservation of the anal sphincter, and demonstrated the first "cure" of HSCR in 33 of 34 patients.[53,56]

While Swenson's procedure remains a common procedure for treatment of these patients, it involves dissection of the rectum near the pelvic nervous plexi and is occasionally associated with urinary and sexual dysfunction. An alternative procedure was described by Asa Yancey in 1952 to reduce the risk of injury to pelvic nerves, and later redescribed by Franco Soave.[57,58] This "Soave" procedure consisted of a combined abdominal and perineal approach that preserved a muscular sleeve of rectum by division of the seromuscular layer of colon at the level of the pelvic fascia and dissection of the submucosal plane of the rectum. Following complete dissection of the plane and removal of the mucosal and submucosal sleeve, the normal colon was pulled through the rectal muscular cuff and anastomosed just proximal to the anal sphincter complex.[58] In 1960, Bernard Duhamel[59] described his procedure where the rectum was divided at the level of the peritoneal reflection, and the aganglionic rectosigmoid portion of bowel resected. Next, the proximal normal bowel was brought down through the retrorectal space and anastomosed in a side-to-side fashion to the posterior portion of the remaining aganglionic rectal segment.[59] Martin and Altemeier[60] modified this approach leaving the rectum intact to act as a reservoir and avoid injury to the internal sphincter that was associated with Duhamel's initial description. Other less commonly performed methods to correct HSCR include posterior sagittal abdominoperineal pull-through and Rehbein's procedure.[61] The Rehbein procedure, which was commonly performed in Europe, consisted of resection of the aganglionic segment with retention of the rectal stump. The proximal colon was then anastomosed to the aganglionic segment in an end-to-end fashion.[62] Because of long-term development of severe constipation in many patients secondary to retained aganglionic segment it has fallen out of favor.[63]

To date, no randomized prospective trials have compared Swenson's operation, Soave's technique, and the modified Duhamel procedure; all 3 procedures have been performed widely with similar outcome.[64] With earlier recognition of HSCR, surgeons began to modify the above techniques and many began to perform corrective surgery in a single stage (in the appropriate patient) rather than placing a diverting colostomy prior to definitive repair. Since the 1990s, several minimally invasive techniques have been developed for the treatment of HSCR. These include Georgeson's laparoscopic approach with laparoscopic biopsy to clearly delineate the transition zone, mobilization of the sigmoid colon, and performance of a transanal endorectal mucosal dissection and anastomosis.[65] Later Langer and de la Torre-Mondragon described a complete transanal approach without the use of a trans-abdominal procedure in children with rectosigmoid disease.[64] A recent meta-analysis found that the transanal approach offered decreased operative times, decreased length of hospitalization, and better outcomes with regard to continence and constipation compared with the more traditional trans-abdominal approaches.[66] Although this analysis suggests that the transanal approach is superior, randomized studies are lacking and the transanal group consisted of younger children with shorter follow-up times.

Outcomes

Despite major improvements in quality of life and marked reductions in mortality over the past century, many complications remain following correction of HSCR. These include abnormal bowel function, poor anal sphincter performance, incontinence, constipation, sexual dysfunction, urinary dysfunction, and enterocolitis.[67]

Current review of bowel function following correction of HSCR demonstrates that only about 50% of children will develop optimal bowel function.[67] Inability to hold back defecation (40%), fecal soiling (48%), constipation (30%), and social problems (29%) are frequent in HSCR patients with short-segment disease.[68] Outcomes are generally worsened with longer segment disease, and several studies report frank fecal incontinence in more than one third of these children.[67,69] Similarly, children with HSCR and Down syndrome, or other significant co-morbidities such as recurrent enterocolitis, have poorer bowel function, and at least one study reported an incontinence rate of 87% among patients with Down syndrome.[70,71]

Poor or abnormal function of the anal sphincter is partially responsible for difficulties in bowel function, although there is some evidence that sphincter damage may occur during operative correction of HSCR.[72] However, most cases of poor sphincter function are secondary to the disease process with many children having abnormal resting and maximal anal canal pressures compared to normal controls.[72,73] The overall delayed stool transit times and relative dysmotility in these children likely exacerbate associated sphincter disorders, and may be partially responsible for the observed high rate of constipation, which complicates 30% to 100% of repaired HSCR.[68,73,74]

Long-term urinary and sexual function following repair of HSCR is not well reported, but dysfunction is

known to occur secondary to dissection near the pelvic plexi. Children with HSCR are known to have bladder capacities that are an average of 87% greater than normal and studies reported enuresis in 5.4% to 14.3% of these children.[75] Sparse data are available regarding sexual function in these patients. One retrospective study reported 0.9% incidence of dyspareunia and 0.6% incidence of erectile dysfunction in a series of 330 patients.[76]

Enterocolitis is the most serious HSCR complication and remains the most common cause of mortality in this population. While not completely understood, enterocolitis occurs more frequently in children with long segment disease, those with Down syndrome, and those with a positive family history of HAEC.[6] The overall incidence varies, with enterocolitis complicating 18% to 50% of children in the preoperative period and up to 22% in the postoperative period.[6,77] Early recognition and institution of therapy is critically important to prevent associated morbidity and mortality. Therapy includes institution of antibiotic therapy (metronidazole if stable, ampicillin, gentamicin, and metronidazole if ill), intravenous fluid resuscitation (bolus 20-40 mL/kg of isotonic crystalloid), and institution of rectal washouts with warm saline.[6] Rectal washouts should be performed with a large bore catheter and instillation of 10 to 20 mL/kg of saline 2 to 4 times daily. It is critically important to ensure complete evacuation of fluid with each irrigation. Those presenting in septic shock with severe HAEC may require diversion if there is inadequate response to resuscitative efforts.

Conclusion

Despite the relative frequency of long-term morbidity associated with HSCR, there has been marked progress in treatment and management of the disease over the past half century. Current mortality rates are less than 1%,[78] and there has been marked improvement in understanding of HSCR etiologies. Improved diagnostic tools and optimization of surgical care remain as the cornerstone of therapy. Recognition of underlying genetic conditions allow for familial counseling and may provide the tools to developing future therapies.

Declaration of Conflicting Interests

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