Hirschsprung's Disease

Identification of Risk Factors for Enterocolitis

DANIEL H. TEITELBAUM, M.D., STEPHEN J. QUALMAN, M.D., and DONNA A. CANIANO, M.D.

From 1975 to 1985, 80 infants and children were treated at a major pediatric hospital for Hirschsprung's disease, 19 (24%) of whom developed enterocolitis. In 9 neonates (18%) and 4 infants (29%) enterocolitis was present at diagnosis of Hirschsprung's disease, while 4 children acquired enterocolitis following a pull-through procedure. Significant risk factors for development of Hirschsprung's-associated enterocolitis (HAEC) were delay in diagnosis beyond 1 week of age and the presence of trisomy 21. HAEC did not occur more frequently in patients with long-segment aganglionosis, nor did an initial episode of HAEC confer a higher risk of recurrent enterocolitis. HAEC following a pull-through procedure was correlated with an anorectal stricture in three of four cases. Although neonates with HAEC had a low mortality rate (5%), their morbidity rate was 30% and their hospitalization was twice as long as neonates without enterocolitis.

DESPITE SIGNIFICANT ADVANCES in the recognition, diagnosis, and operative management of Hirschsprung's disease, enterocolitis remains its major source of morbidity and mortality.[1] Historically, the incidence of Hirschsprung's-associated enterocolitis (HAEC) has approached 50% with a mortality rate of 30%.[2] In recent surveys of 2824 infants and children with Hirschsprung's disease in North America and Japan, HAEC occurred in nearly one fourth of patients, with a mortality rate between 6% and 30%.[3,4]

This study evaluates the occurrence of enterocolitis in 80 infants and children treated for Hirschsprung's disease during the last decade at a major pediatric center. Factors associated with the development of enterocolitis are identified and the medical and economic impact of HAEC is analyzed.

Supported in part by the Children's Hospital Research Foundation, Grant No. 75-050.

Reprint requests and correspondence: Donna A. Caniano, M.D., Department of Pediatric Surgery, Children's Hospital, 700 Children's Drive, Columbus, OH 43205.

Submitted for publication: August 17, 1987.

From the Division of Pediatric Surgery, the Department of Surgery, and the Department of Pathology, Ohio State University College of Medicine, and the Children's Hospital, Columbus, Ohio

Methods

The charts of all patients (80 infants and children) initially treated for Hirschsprung's disease at the Children's Hospital, Columbus, OH between 1975 and 1985 were reviewed. Factors evaluated were sex, age at diagnosis, level of aganglionosis, familial history of Hirschsprung's disease, presence of associated anomalies, signs of HAEC (fever, distention, diarrhea), symptoms of HAEC (prostration, lethargy, crampy abdominal pain), positive cultures (blood, stool, peritoneal), type of colostomy and pull-through procedure, development of HAEC in relation to operative treatment, complications of treatment for HAEC, length and cost of hospitalization, and mortality rate.

Diagnosis of HAEC was made on the clinical findings of abdominal distention, diarrhea, and temperature greater than 38 C.[5,6] Statistical analysis was done using either a paired or unpaired t-test, or chi square analysis. Statistical significance was given for $p < 0.05$.

Results

Total Group

The patients included 60 males (75%); a family history of Hirschsprung's disease was present in 3 (4.7%). Diagnosis of Hirschsprung's disease was made at 30 days of age or less in 51 patients (64%); 31–180 days in 14 (18%); and over 6 months in 15 (18%). The level of aganglionosis was confined to the distal rectum in 2 (2%); rectosigmoid in 66 (83%); transverse colon in 5 (6%); and total colon in 7 (9%).

Trisomy 21 was present in 13 patients (16%). Ten children (77%) with trisomy 21 had other associated congenital anomalies including cardiac (6), central nervous system (1), and gastrointestinal (3). In the 67 patients without trisomy 21, associated congenital anomalies occurred in 16 (24%): cardiac (4), central nervous system (5), genitourinary (2), maxillofacial (3), and skeletal (2).

Initial operative procedures included sigmoid colostomy (60), transverse colostomy (5), ileostomy (8), anal myectomy (2), and cecostomy (1). Three children were treated with daily saline rectal washouts of whom two underwent a subsequent pull-through and one continues nonoperative management. Fifty-nine patients have undergone a definitive pull-through procedure: Duhamel (40); Swenson (10); Soave (7); and anal myectomy (2).

TABLE 1. *Association of Trisomy 21 and Enterocolitis*

	Trisomy 21	Others
Total group (80)	13	67
Enterocolitis (19)	6	13
% with enterocolitis	46*	19

* $p < 0.05$.

TABLE 2. *Clinical Signs and Symptoms in 19 Patients with Enterocolitis*

Sign or Symptom	No. (%)
Abdominal distention	19 (100)
Diarrhea	19 (100)
Temperature > 38C	16 (84)
Bloody stools	4 (25)

HAEC Group

Nineteen of the 80 patients developed at least one episode of HAEC, an incidence of 24%. The level of aganglionosis in patients with HAEC was confined to the rectosigmoid in 16 (85%), transverse colon in 1 (5%), and total colon in 2 (10%). Enterocolitis did not occur at a significantly more frequent rate in patients with longer levels of aganglionosis: 24% for rectosigmoid aganglionosis, 20% for transverse colon aganglionosis, and 29% for total colon aganglionosis.

Of the 19 patients with HAEC, 13 were neonates and infants whose presenting diagnostic sign of Hirschsprung's disease was enterocolitis. Two infants developed HAEC after decompressive enterostomies, while four children acquired enterocolitis after a pull-through procedure. Two of the 13 infants with HAEC at diagnosis developed recurrent enterocolitis (15%), one after colostomy and one after pull-through. Three of the four children with HAEC following a pull-through procedure had recurrences.

Six of the 19 patients with HAEC had trisomy 21 (32%), although trisomy 21 occurred in only 16% of the 80 patients in the total group with Hirschsprung's disease. A significantly ($p < 0.05$) larger proportion of patients with trisomy 21 developed HAEC compared to patients without trisomy 21 (Table 1).

The clinical signs and symptoms of HAEC were abdominal distention (19), diarrhea (19), and temperature greater than 38 C (16) (Table 2). Bloody stools occurred in four patients. Five children had positive blood cultures (27%): *Escherichia coli* (4) and *Enterobacter* and *E. coli* (1). *Bacteroides fragilis* and *E. coli* were cultured from one child's peritoneal fluid. Six patients had infections with enterocyte-adherent organisms based on tissue specimens and tissue assays: toxigenic *E. coli* (4), toxigenic *Clostridium difficile* (1), and *Cryptosporidium* (1).

HAEC in Neonates and Infants

Of the 13 patients with HAEC at diagnosis, 9 were neonates less than 30 days of age and 4 were infants between 1 and 6 months of age. The 9 neonates with HAEC at diagnosis represented 18% of the 51 neonates with Hirschsprung's disease in the total group. The mean age at diagnosis for the neonates with HAEC was 16.6 ± 11.3 d (mean ± SD), significantly later ($p < 0.01$) than the mean age at diagnosis of 4.6 ± 6.5 d for the neonates without enterocolitis. In addition, significantly more neonates presented with HAEC after 10 days of age as compared to neonates without enterocolitis (Fig. 1). The mean age for passage of meconium was 53 ± 12 h in the neonates with HAEC and 40 ± 4 h in neonates without HAEC, a significant difference at $p < 0.05$.

Seven of the 9 neonates with HAEC were considered to have a significant delay in diagnosis. In these patients

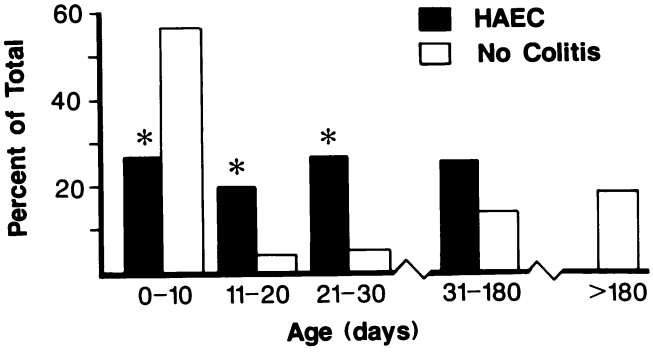

FIG. 1. Mean age at diagnosis of Hirschsprung's disease in days. Enterocolitis was present in significantly more neonates (*$p < 0.05$) diagnosed after 10 days of age.

a history of abnormal or infrequent passage of stools followed by abdominal distention, lethargy, and diarrhea had occurred for 1 or 2 weeks prior to referral. Two neonates became acutely ill and were diagnosed promptly. The first, a 2-day-old, developed emesis and abdominal distention; at laparotomy he had enterocolitis and a cecal perforation. The second neonate, a 6-day-old with trisomy 21 and cardiac anomalies, was referred after 24 hours of foul-smelling diarrhea and lethargy.

Four infants (29%) presented with HAEC between 50 and 70 days of age. In three patients a history of severe constipation with abdominal distention was elicited. The fourth infant had multiple congenital anomalies including trisomy 21, cardiac disease, duodenal stenosis, and infralevator imperforate anus. Constipation persisted following a perineal anoplasty with the acute onset of abdominal distention and diarrhea.

Three neonates with HAEC developed complications before or after colostomy (30%). One infant sustained a cecal perforation secondary to severe colitis, which was not recognized at the initial operation for sigmoid colostomy. On the third postoperative day he developed an evisceration and required reexploration and ileostomy. One neonate sustained a perforation of the sigmoid colon during rectal saline washouts prior to colostomy. A third infant required revision of a sigmoid colostomy for retraction of the stoma.

Neonates with HAEC at diagnosis were hospitalized an average of 25 days compared to an average of 13 days for neonates without HAEC ($p < 0.05$). The average hospital cost for infants with HAEC ($17,810) was significantly greater ($p < 0.01$) than for infants without HAEC ($7,328).

Three infants with HAEC died, all of whom had trisomy 21. However, only one death was directly attributable to HAEC, a mortality rate of 5%. A 2-month-old infant had undergone a right transverse colostomy at 22 days of age for clinical HAEC. He recovered but returned 6 weeks later moribund with HAEC; autopsy confirmed diffuse enterocolitis and a perforation in the ascending colon 5 cm proximal to the colostomy. A second infant with an endocardial cushion defect who had presented with HAEC and recovered following sigmoid colostomy died from progressive cardiac failure. The third infant suffered a fatal aspiration pneumonia having recovered from HAEC.

HAEC Following Operative Procedures

Two infants developed enterocolitis following initial operation: colostomy in one and ileostomy in the other. The first patient was diagnosed at 24 hours of age with Hirschsprung's disease, trisomy 21, and an endocardial cushion defect; a sigmoid colostomy was performed. He returned at 1 month of age with HAEC and recovered without complication. Recurrent enterocolitis has not developed; definitive pull-through has been deferred because of severe cyanotic cardiac disease.

The second infant underwent an ileostomy for total colonic Hirschsprung's disease at 18 days of age. Eight months later he developed enterocolitis and recovered after prolonged total parenteral nutrition. This patient awaits a definitive pull-through procedure.

Five children acquired HAEC following a pull-through procedure, of whom four had no previous episodes. Three patients experienced two or more episodes of HAEC within 2 years of the pull-through. All children with post–pull-through HAEC were evaluated by barium enema, proctoscopy and sigmoidoscopy, colonic biopsy, or anal manometry. In three patients an anorectal stricture was diagnosed: one following a Swenson pull-through complicated by anastomotic leak, and two after uncomplicated Soave and Swenson procedures. All required secondary operations including anal dilatation (1) and internal sphincterotomy (2). A fourth child with severe psychomotor retardation developed multiple episodes of HAEC following an uncomplicated Duhamel pull-through and required an end-ileostomy for ultimate relief. A fifth patient with trisomy 21 developed *Cryptosporidiosis* enterocolitis 2 years after a Duhamel pull-through and recovered without further episodes.

Discussion

Prompt diagnosis of Hirschsprung's disease and expeditious placement of a decompressive enterostomy above the level of aganglionosis have been considered critical factors in the prevention of enterocolitis.[5] Although most pediatric surgical centers strictly adhere to these guidelines, HAEC continues to be a serious, often life-threatening condition. Our study underscores many accepted features of HAEC and, more importantly, identifies potential risk factors for its development.

HAEC has been characterized by an increased incidence and high mortality rate in the neonatal period. In 1962 Bill and Chapman[2] noted that neonates comprised 88% of patients with preoperative HAEC and accounted for all of the deaths. The 1975–1976 survey of 1196 infants and children by the Surgical Section of the American Academy of Pediatrics reported enterocolitis in 15% of patients at diagnosis of Hirschsprung's disease of whom one fourth were less than 3 months of age.[3] The Surgical Section survey concluded that the diagnosis of Hirschsprung's disease should be established by 1 month of age to reduce the incidence of enterocolitis.

In our series 51 of the 80 patients (64%) were diagnosed within the first month of life, yet HAEC occurred

in 9 (18%) of the neonates. Closer evaluation discloses that the average age at diagnosis for neonates with HAEC was 16 days compared to 4 days for neonates without enterocolitis. Furthermore, three fourths of our patients with enterocolitis at diagnosis were less than 1 month of age. Clearly, patients in our series required diagnosis of Hirschsprung's disease early in the neonatal period, as soon as the first week of life, to decrease their risk of enterocolitis.

Three recent series confirm the importance of diagnosis in the early neonatal period. Grosfeld et al.[6] in 1978 reported 89 patients with Hirschsprung's disease of whom 34 (38%) were diagnosed under 1 month of age and 7 (20%) experienced neonatal enterocolitis. In Polley and Coran's 1986 series of 35 neonates with Hirschsprung's disease,[7] the average age at diagnosis was 9.9 days, yet the incidence of enterocolitis was 11%. Twenty-six neonatal cases of Hirschsprung's disease were reviewed by Klein et al.[8] in which diagnosis and decompressive enterostomy were accomplished by 2 weeks of age and no cases of HAEC were documented. Our data in conjunction with these reports substantiates the necessity of diagnosis of Hirschsprung's disease early in neonatal life.

If Hirschsprung's disease requires diagnosis within the first several days of life to decrease the risk of enterocolitis, then a high index of suspicion and aggressive evaluation are necessary. The medical histories of the 51 neonates with Hirschsprung's disease in our series identify an abnormal stooling pattern characterized by delayed meconium passage, infrequent stools, or no spontaneous stools. As Swenson et al.[9] stated in 1973, ". . . it is clear that failure to pass meconium within the first 24 hours of life, . . . is the objective information which should alert the physician to the possibility of congenital megacolon." Implementation of Dr. Swenson's now classic observation would have most likely eliminated all but two of our neonatal and infant cases of HAEC.

The well-recognized association of trisomy 21 and Hirschsprung's disease has been reported in 3% of cases,[4,9] while more recent series note a 15% occurrence.[6,7] The higher incidence of trisomy 21 in our series (16%) allows for several observations. First, patients with trisomy 21 comprised one third of all cases of enterocolitis. Second, 46% of the infants and children with trisomy 21 developed HAEC in comparison to only 19% of patients without trisomy 21. Third, associated anomalies were present in three fourths of the patients with trisomy 21 but in only one fourth without trisomy 21. Fourth, the three deaths in our series occurred in patients with trisomy 21; one death was directly attributable to HAEC. The other two infants died of associated problems following recovery from an episode of enterocolitis. Based on these findings, we believe that Hirschsprung's disease in an infant or child with trisomy 21 should be viewed as a strong risk factor for development of enterocolitis. Patients with trisomy 21 have marked deficiencies in T cell-mediated cytotoxicity and in interferon production[10] and possible derangements in humoral immunity.[11] It may be that infants and children with trisomy 21 are more susceptible to HAEC and less immunologically capable of recovery. No study has addressed the functional integrity of gastrointestinal immunity in patients with trisomy 21 and Hirschsprung's disease.

Enterocyte-adherent organisms were present in the colonic specimens in one third of our patients with HAEC. These organisms were not identified in the tissue specimens of patients without enterocolitis. Enterocyte-adherent organisms may have a role in the pathogenesis of HAEC, or the presence of enterocolitis may predispose the intestinal mucosa to attachment of enterocyte-adherent organisms. *Clostridium difficile* toxin has been isolated more frequently from young children with HAEC than from healthy patients with Hirschsprung's disease,[12] suggestive of a possible causal relationship.

Previous authors have reported that infants and children with long-segment aganglionosis are at an increased risk to develop enterocolitis.[3,4] Patients in our study with longer levels of aganglionosis (transverse and total colon) did not acquire HAEC more frequently than patients with rectosigmoid disease. Most likely, this discrepancy relates to the majority of our cases of long-segment aganglionosis achieving diagnosis and treatment in the neonatal period.

An initial episode of enterocolitis at diagnosis of Hirschsprung's disease has been considered a predisposing factor for further episodes.[5,9] However, recurrent HAEC occurred in only two cases (15%) in our series, one of which developed after a pull-through procedure complicated by an anorectal stricture. In the second case an infant with trisomy 21 acquired a diffuse, fatal enterocolitis 6 weeks following recovery from his first episode of HAEC.

Enterocolitis acquired after a pull-through procedure was most frequently the result of an anorectal stricture in our series. Standard diagnostic investigation including barium enema, rectal biopsy, and anal manometry was helpful in elucidating the etiology of the dysfunctional pull-through procedure. Following appropriate secondary operations to relieve the anorectal stricture, no child suffered additional episodes of HAEC.

Neonatal enterocolitis at diagnosis of Hirschsprung's disease imposes the risk of increased morbidity and extended hospitalization. One third of the neonates with HAEC in our series experienced a major complication

requiring a second operative procedure. The dilated, thin-walled, and friable colon with enterocolitis must be handled with meticulous, gentle technique, and the colostomy must be carefully constructed to avoid postoperative evisceration and stomal prolapse. Neonates with HAEC were hospitalized twice as long as neonates without enterocolitis, and they incurred significantly higher medical expenses.

The low mortality rate of 5% for patients with HAEC in our series compares favorably with other reports.[3,5] This low mortality rate is misleading, however, because two infants died from other causes (cardiac disease and aspiration) immediately after recovery from an enterocolitis episode.

We conclude that enterocolitis continues to be a major cause of morbidity and mortality in infants and children with Hirschsprung's disease. Elimination of neonatal enterocolitis requires diagnosis of Hirschsprung's disease within the first several days of life. Significant risk factors for HAEC include a delay in diagnosis beyond 1 week of age and the presence of trisomy 21. Although neonates with enterocolitis have a longer and costlier hospitalization, recovery without recurrent episodes of HAEC can be anticipated for most patients.

Acknowledgments

The authors gratefully acknowledge William D. Gariott for technical assistance and Mrs. Karen Hansley for preparation of the manuscript.

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