Unexpected Death From Enterocolitis After Surgery for Hirschsprung's Disease

Terri L. Marty, Michael E. Matlak, Margo Hendrickson, Richard E. Black and Dale G. Johnson

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Terri L. Marty, MD*; Michael E. Matlak, MD*‡; Margo Hendrickson, MD§; Richard E. Black, MD*‡; and Dale G. Johnson, MD*‡

ABSTRACT. Unanticipated death from enterocolitis occurred in five children 3 weeks to 20 months after uncomplicated reconstruction for Hirschsprung's disease. In each case the presenting symptoms of enterocolitis were mild and were misinterpreted by examining physicians. Within 2 to 12 days of onset of symptoms, unexpected death occurred. Although fatal enterocolitis is a well-known complication of Hirschsprung's disease, emphasis is usually placed on preoperative enterocolitis. Fatal postoperative enterocolitis is not a new entity associated with Hirschsprung's disease, but physician awareness of this possibility is obviously deficient. We strongly recommend extensive parent education and better postoperative communication between the surgeon and the referring physician. ***Pediatrics*** **1995;96:118–121;** ***Hirschsprung's disease, enterocolitis, unexpected death.***

Despite advances in early diagnosis and surgical treatment of Hirschsprung's disease, enterocolitis remains the major cause of death.[1–4] The incidence of preoperative enterocolitis is between 15% and 50%, with a mortality rate of 20% to 50%.[1,5–8] Postoperative enterocolitis occurs between 2% and 33%, with a mortality rate varying between 0% and 30%.[5,9–12] We report five cases of postoperative enterocolitis that resulted in unexpected death. In each case, deceptively benign symptoms lulled the examining physician into initial conservative treatment.

CLINICAL EXPERIENCE

From 1971 to 1993, 182 infants and children were treated at Primary Children's Medical Center for Hirschsprung's disease. Of these children, 177 have had surgical reconstruction for Hirschsprung's disease. Definitive surgical procedures included endorectal pull-through (Soave) in 21%, modified Duhamel in 67%, extended side-to-side ileocolic anastomosis in 8%, and rectal myomectomy in 4%. Five children died from causes unrelated to Hirschsprung's disease. Of the remaining 172 children, follow-up clinical survey information has been obtained from 135 (78%).

The incidence of postoperative enterocolitis in these patients is 37 of 135, or 27.4%. This diagnosis is established on clinical examination. Abdominal distention and explosive stool and flatus with rectal examination are classic findings. During the past 22 years, four children died unexpectedly within 34 days of their definitive operations, and one child died suddenly 20 months later, all of postoperative enterocolitis. The mortality rate for postoperative enterocolitis in this series is 5 of 37, or 13.5%. This is higher than some series reported in the literature, as referenced above. Autopsies were performed on all five children. The presentation of the children who died of postoperative enterocolitis was not appreciably different from the other 32 children who survived. The treatment was nonsurgical in all cases. The fatal case histories are described below.

From the Departments of *Surgery and ‡Pediatrics, University of Utah and Primary Children's Medical Center, Salt Lake City; and the §Department of Pediatric Surgery, Sunrise Hospital, Las Vegas, NV.

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Reprint requests to (D.G.J.) Professor of Surgery and Professor of Pediatrics, University of Utah and Primary Children's Medical Center, 100 N Medical Dr, Suite 2600, Salt Lake City, UT 84113-1100.

CASE REPORTS

Case 1

A male infant with delayed passage of meconium at 48 hours, irregular evacuation, and aganglionosis on initial biopsy had a sigmoid colostomy at 10 days of age. At 7 months he underwent a modified Duhamel-Martin pull-through reconstruction coloanostomy. He had been home 1 week, when he developed rhinitis and fever, followed by vomiting and diarrhea. His family physician prescribed Septra for otitis media. Three days later he was hospitalized at an outside institution for increasing stool frequency, malaise, low-grade fever, and bilious vomiting. Within 24 hours he suffered a generalized seizure, which prompted his transfer to our pediatric intensive care unit. The initial physical examination revealed a lethargic infant with mottled extremities and a distended, tender abdomen. He died 48 hours later despite aggressive fluid resuscitation, broad-spectrum antibiotics (ampicillin, cefotaxime, and clindamycin), and rectal decompression.

Case 2

A male infant with meconium plugs at birth was admitted 2 weeks later with abdominal distention and difficulty stooling. A rectal biopsy confirmed the diagnosis of Hirschsprung's disease, and a sigmoid colostomy was performed. The infant did well and underwent a Duhamel-Martin pull-through reconstruction procedure 9 months later. For the next 19 months, however, he required frequent enemas, stool softeners, and manual disimpaction one to two times per week. He was subsequently readmitted with a distended abdomen and massive fecal impaction. Treatment involved manual disimpaction, enemas, and oral propylene glycol. Within 48 hours, abdominal x-rays and a clinical examination revealed resolution of the impaction. Serum electrolytes were normal. Residual dilatation of the descending colon was thought to be chronic. He was discharged the next day. The parents were instructed to irrigate the rectum with normal saline to prevent recurrent impaction. During the next 2 days the child developed mild diarrhea with vomiting. The family physician was not unduly concerned because of simultaneous gastroenteritis in other family members. He prescribed an oral electrolyte solution. The child was found dead in bed the next morning by his parents.

Case 3

A male infant was referred at 3 months of age for chronic constipation. A rectal biopsy confirmed the diagnosis of Hirschsprung's disease, and a sigmoid colostomy was performed. A Duhamel-Martin pull-through reconstruction was performed at 7 months. Two weeks after discharge, loose stools and minimal vomiting were noted. After 2 days of symptoms, with a diagnosis of gastroenteritis, the parents were advised to start oral electrolytes. That evening, the infant's stools were increasingly frequent and watery, although not explosive or particularly foul smelling. He seemed playful the next morning and was tolerating liquids. Later that day, however, he returned for another evaluation

because of recurrent vomiting and a large amount of liquid stool. While in the pediatrician's waiting room, he had a cardiac arrest and died.

Case 4

A female infant born at 36 weeks presented 11 days later with abdominal distention, vomiting, and bloody diarrhea. She was treated with antibiotics and nasogastric decompression, and she was discharged after stool cultures and a barium enema were negative. Five months later, she was referred because of constipation. The diagnosis of Hirschsprung's disease was established by a rectal biopsy. She was given saline enemas for 10 days before a one-stage Duhamel-Martin pull-through reconstruction. Her postoperative course was unremarkable, and she was discharged within 7 days having satisfactory spontaneous bowel movements. During the fourth week after surgery, she developed fever, liquid stools, abdominal distention, and bilious vomiting. These symptoms were present for 72 hours. She was examined and sent home by pediatric emergency room staff with a diagnosis of gastroenteritis. At a scheduled follow-up the next day she was admitted with lethargy, vomiting, abdominal distention, and fevers. She was given intravenous fluids but nothing by mouth and treated with ampicillin and chloramphenicol. Within 16 hours she became increasingly lethargic and had multiple tonic clonic seizures. She was transferred to the pediatric intensive care unit, and aggressive supportive measures were instituted. Antibiotics were changed to chloramphenicol, vancomycin, and gentamycin, and a rectal tube was placed for decompression. *Clostridium difficile* cultures were positive. Despite aggressive supportive treatment, she died 8 days later.

Case 5

A male infant did not stool until 3 days of age. A barium enema was inconclusive. He continued to have constipation despite rectal dilatations. A sigmoid colostomy was performed 6 weeks later after a rectal biopsy revealed the absence of ganglion cells. One month after surgery, he returned with vomiting and increased colostomy output. An exploratory laparotomy with lysis of adhesions was performed. He did well and returned at 11 months of age for reconstruction by endorectal pull-through. Nine days after discharge, he was seen in the emergency department with abdominal distention, watery stools, and mild lethargy. He was given a saline enema in the emergency department and received a clear liquid diet. The infant returned the next day, because his gastrointestinal symptoms were not improving. Although not toxic in appearance, 30 minutes later he suffered a cardiorespiratory arrest. Prompt resuscitation and aggressive intravenous fluid support were initiated. He was treated with ampicillin, gentamycin, and vancomycin in addition to nasogastric and rectal decompression. Despite aggressive therapy, he died 4 days later.

DISCUSSION

The etiology and pathophysiology of Hirschsprung's enterocolitis are still as poorly understood today as they were three decades ago.[8,13] These case reports illustrate the elusive nature and rapidly fatal course this disease can have. Numerous other reports in the literature confirm initial mild symptoms followed by a rapid, fulminating course.[3,14–19]

Perioperative characteristics of these five cases are summarized in Table 1. All of the infants were diagnosed with Hirschsprung's disease within the first 6 months of life, and none had other comorbid factors. Each patient had routine surgical reconstruction and an uneventful postoperative course. None of the patients had long-segment Hirschsprung's disease. Historically, long-segment involvement has been considered a risk factor for enterocolitis,[5] but more recent studies do not confirm this.[20] Only one of the patients who died had a clinical episode of enterocolitis preoperatively (case 4). It is controversial whether infants with preoperative enterocolitis are at increased risk postoperatively. A number of series state that the incidence is increased postoperatively if enterocolitis was present before surgery.[7,8,13,14] Other studies do not demonstrate this association.[20,21]

Circumstantial data regarding these deaths are reported in Table 2. Laboratory data for the three children who died in the hospital were reviewed. The initial pH values were not significantly acidotic in two of the children (7.43 and 7.36), but the serum carbon dioxide was low,[17,11] and the anion gap was mildly elevated,[11,12] suggesting early metabolic acidosis. Patients 1 and 4 were initially admitted to the ward, and dehydration was estimated to be mild (10%). Retrospectively, their vital signs, physical examinations, and initial urine outputs indicate more severe dehydration. Perhaps if these children had been admitted to the pediatric intensive care unit with more aggressive initial resuscitation and monitoring, their outcomes may have been improved.

Autopsy results are listed in Table 3. No other intra-abdominal catastrophe was found in any of the patients at postmortem examination. Pseudomembranous colitis was found in four patients, two of whom were *C difficile* toxin positive. All of the children with pseudomembranous colitis at autopsy had received antibiotics within 1 month of death. The other patient (case 2) had ischemic necrotizing enterocolitis at postmortem examination. Neither the *C difficile* culture nor a toxin assay were performed in this child, although numerous organisms seen within the mucosa were thought to be consistent with this pathogen. He had not received antibiotics within the month before his death.

The etiology of Hirschsprung's enterocolitis is multifactorial. One important factor is partial functional obstruction at the anal level secondary to increased internal sphincter tone, anorectal stricture, or suture line stenosis. Proximal to this obstruction, the colon becomes distended, with resultant ischemia and bacterial invasion.[8,19,22–24] The hypertonic sphinc-

TABLE 1. Perioperative Characteristics*

Case	Comorbidity or Congenital Anomalies	Perioperative Antibiotics	Intraoperative or Postoperative Complications	Days After Surgery Until Discharge Home
1	None	Amp & Gent ×5 days	None	7
2	None	Amp & Gent ×5 days	None	5
3	None	Amp & Gent ×3 days	None	8
4	None	Amp & Gent ×24 hours	None	7
5	None	Amp & Gent ×7 days	None	9

* Amp, ampicillin; Gent, gentimycin.

TABLE 2. Characteristics Surrounding Death

Case	Age at Death (mo)	Duration of Acute Illness Before Death (d)	Interval From Surgery Until Death (d)
1	8	5	19
2	30	2	20 months
3	8	3	26
4	6	12	34
5	11	4	23

TABLE 3. Autopsy Findings

Case	*C difficile* Toxin	Pseudo-membranes at Autopsy	Ischemic Colitis at Autopsy
1	+	+	–
2	Culture not done; numerous Gram + rods within mucosa	–	+
3	Culture not done; Gram + cocci on pseudomembrane	+	–
4	+	+	–
5	–	+	–

ter results from the underlying disease process and is not corrected by surgical reconstruction. Fecal stasis facilitates bacterial overgrowth and subsequent mucosal invasion by the normal flora, including *C difficile*. Several series have identified *C difficile* as a causative factor in Hirschsprung's enterocolitis, occurring before or after surgery.[25,26]

Systemic antibiotic therapy has been postulated to alter the normal bowel flora and to increase the susceptibility to pseudomembranous colitis associated with *C difficile*.[18,27,28] Ampicillin has been identified as the most common antibiotic associated with this condition,[27] although the role of antibiotics in provoking an attack of pseudomembranous colitis can be debated.[6,25]

Altered gastrointestinal mucosal defense mechanisms are another factor in the etiology of Hirschsprung's enterocolitis, developing before or after surgical reconstruction. Decreased levels of intraluminal immunoglobulin A have been noted, possibly allowing commensal organisms to invade the colon.[13] Qualitative changes of intestinal mucins also have been described. These molecules are important for mechanical and chemical defense mechanisms, and their alterations may allow increased adherence of bacteria to the mucosa.[29–31] A recent study examined the distribution of immunoglobulin-containing cells, T and B lymphocytes within the lamina propria of the rectum in healthy newborns and in those with Hirschsprung's disease. There was no significant difference between these two groups, meaning that this rectal mucosal immune defense has no measurable deficiency in patients with Hirschsprung's disease. Furthermore, in the cohort with Hirschsprung's disease there was no difference in these immune cells between those in whom enterocolitis developed and those in whom it did not.[32] A decreased incidence of preoperative enterocolitis has been seen in breast-fed infants, even when the diagnosis of Hirschsprung's disease is delayed.[12,33] This observation leads one to postulate the protective effect of maternal antibodies. Clearly, more studies regarding the etiology of enterocolitis are needed.

Rotavirus also has been proposed to play a role in the etiology of Hirschsprung's enterocolitis. Rotavirus was documented in 77.7% (seven of nine) of the children in one report during an acute episode of enterocolitis.[34] Other risk factors identified for preoperative enterocolitis include trisomy 21 and a delayed diagnosis of Hirschsprung's disease beyond 1 week of life.[20]

Specific signs and symptoms of Hirschsprung's enterocolitis include lethargy, low-grade fevers, abdominal distention, vomiting, diarrhea, explosive flatus, and stool with a particularly foul odor.[11,15,19] These last two signs are noted with rectal examination; these children often will pass large amounts of gas and liquid stool under pressure after digital dilatation of the anal sphincter. Enterocolitis can develop before the diagnosis of Hirschsprung's disease is established, after a decompressing stoma, and even years after surgical reconstruction.[7,18,24] Most primary care physicians acknowledge enterocolitis as a major complication of Hirschsprung's disease; however, our experience indicates that they are less likely to recognize it after surgical reconstruction.

Timely treatment of Hirschsprung's enterocolitis requires a high index of suspicion. Hospitalization is usually required for intravenous hydration, nasogastric decompression, and, most importantly, transrectal decompression by tube or repeated sphincter dilatations.[14] Stool cultures for both bacterial and viral pathogens should be sent on admission. Antibiotics active against *C difficile* should be started when the diagnosis is suspected, even before stool culture data are available.[6,18] Rectal decompression is the cornerstone of therapy. This needs to be frequent (every 4 to 6 hours), with normal saline rectal irrigations to evacuate the retained stool and gas.[3,12] In our opinion, the volume of the irrigations needs to be at least 10 mL/kg with each irrigation. The child should be allowed to evacuate the fluid spontaneously, when that is possible.

When a child is recovering from enterocolitis, dairy products should be avoided, because lactase is the slowest enzyme to recover activity in the gut.[35] Recurrent enterocolitis may require repeated rectal dilatations or surgical sphincterotomy.[36,37] Intractable cases may even require a diverting stoma.[18]

Because of the tragic histories reported above, we have closely examined and revised our surgical protocol. With the association of Hirschsprung's enterocolitis and *C difficile* psuedomembranous colitis, we discontinue perioperative antibiotics within 48 hours. To maintain rectal decompression postoperatively, prophylactic saline rectal irrigations are performed twice daily by the parents for 3 months and once daily for another 3 months. The incidence of enterocolitis is known to be highest the first 6 months after surgery.[38] Any child who presents with signs or symptoms suggesting enterocolitis is admitted and treated as outlined above. A greater emphasis is placed on parent and referring physician education and communication regarding Hirschsprung's enterocolitis, both preoperatively and postoperatively. It is interest-

ing to note that education of parents with regard to abdominal distention and diarrhea in children with Hirschsprung's disease has been in the literature for more than 30 years.[39] With the changes in our protocol as stated above, we think the morbidity and mortality from Hirschsprung's enterocolitis at our institution has been markedly improved during the last 5 years.

Conclusion

Fatal enterocolitis is a well-known complication of Hirschsprung's disease. In the past, emphasis has usually been placed on preoperative enterocolitis. Fatal postoperative enterocolitis is not a new entity and deserves equal emphasis. As the above histories illustrate, physician awareness of postoperative enterocolitis is deficient. We strongly recommend extensive parent education and better postoperative communication between the surgeon and the referring physician.

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