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Long-term outcomes for children with very early-onset colitis: Implications for surgical management

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ABSTRACT

Purpose: The timing of J-pouch surgery following colectomy for children with very early-onset colitis is controversial, with some advocating early reconstruction and others delaying reconstruction because of fear that the colitis may be owing to Crohn's disease (CD). We sought to determine the long-term incidence of CD in this population and whether there may be clinical features that predict the risk of CD.
Methods: Children with noninfectious colitis diagnosed prior to age 10, who underwent subtotal colectomy and ileostomy from 2000 to 2015, were reviewed.
Results: Twenty-five children were identified. Median age at presentation was 5.4 years. Four were initially diagnosed with CD (16%), 14 with ulcerative colitis (UC) (56%), and 7 with inflammatory bowel disease unclassified (IBD-U) (28%). Eight eventually had pouch surgery. Five of the children with an initial diagnosis of UC or IBD-U developed findings that changed the diagnosis to CD at a median age of 13.4 (range 10.3 to 16.7) years. None had any indicators of CD at the initial presentation.
Conclusions: Approximately one quarter of patients with very early-onset colitis originally diagnosed as UC or IBD-U had a reclassification in diagnosis to CD over time. J-pouch reconstruction should be delayed until adolescence in children with very early-onset colitis.
Level of Evidence: 2C

The incidence of inflammatory bowel disease (IBD) in children is increasing, and more frequently diagnosed at younger ages [1,2]. IBD diagnosed in early childhood has been described as phenotypically different than that of older children or adults [3–5]. Colonic involvement is more common in very early-onset IBD (VEO-IBD), making it sometimes difficult to distinguish between the colitis of Crohn's disease (CD) and ulcerative colitis (UC) or inflammatory bowel disease unclassified (IBD-U), which was previously referred to as indeterminate colitis [2,6–11]. Additionally, children with early-onset disease are more likely to have a change in their diagnosis from their initial IBD subtype [2,4,12].

The chance that the diagnosis may change from either UC or IBD-U to CD has led some to question the timing of reconstruction of intestinal continuity following subtotal colectomy and ileostomy. The creation of an ileal pouch-anal anastomosis (IPAA), or J-pouch, is an accepted surgical therapy for treatment of patients with UC. Patients typically have improved quality of life and good functional outcomes following the procedure [12]. IPAA for patients with CD is more controversial; although some adult studies have shown favorable outcomes, the presence of CD is an important determinant of pouch-related morbidity, including chronic pouchitis, pouch fistulae, and pouch failure [13–18]. In a study of patients who had a delayed diagnosis of CD, only half retained their pouch at 10-year follow-up [16].

Few studies have focused on the outcomes of children with IPAA, specifically those with very early-onset colitis, whose disease is more likely to be reclassified following pouch creation. There are currently no recommendations about timing of IPAA in children with VEO-IBD. The purpose of this study was to examine the long-term incidence of Crohn's disease in this population and determine if there are any clinical features that predict the risk of CD. We also reviewed the timing of change in diagnosis in relationship to pouch formation.

1. Methods

This was a retrospective study approved by the Research Ethics Board of The Hospital for Sick Children. The research database of children with pediatric-onset IBD, which is managed by one of the authors (AM), was queried for all patients with colitis who underwent subtotal colectomy from ages 0 to 10 years from January 1, 2000, to November 9, 2015. Data were collected prospectively at the time of recruitment, which occurred at diagnosis or any point later in time, and updated at

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six-month intervals. Hospital health records were retrospectively reviewed to collect information regarding admissions and outpatient visits. Children were defined as having very early-onset disease if they were diagnosed prior to age 10 [19]. Patients were excluded if they had infectious colitis, were diagnosed at an older age, or had undergone only a segmental colon resection.

Hospital charts were reviewed for the age at diagnosis, the extent of disease, initial diagnosis, family history, age at colectomy, age at reconstructive surgery, features of Crohn's disease, diagnosis at long-term follow-up, IBD serologies (anti-Saccharomyces cerevisiae antibody (ASCA), perinuclear antineutrophil cytoplasmic antibody (pANCA)), and genetic mutation analysis. Endoscopic, imaging, and pathologic reports were reviewed to confirm diagnosis of IBD subtype. All patients had endoscopy with biopsy to establish their diagnosis. Patients were then divided into three categories (CD, UC, IBD-U), based on clinical and pathological assessments. Patients who underwent reconstruction did so in 3 stages: subtotal colectomy with end ileostomy, followed by completion proctectomy with IPAA and loop ileostomy, and then loop ileostomy closure. Outcomes of surgery were obtained from operative notes, clinic notes, and discharge summaries. Patients were followed clinically and endoscopy performed if patients were symptomatic. Long-term follow-up was reviewed through hospital records; patients were transitioned to adult care at age 18.

Data were analyzed using descriptive and summary statistics. Results were presented as medians or as frequencies, as appropriate. Time to change in diagnosis was graphed as a Kaplan–Meier curve using SPSS software version 24 (IBM Corporation, New York, USA).

Table 1
Demographics, disease characteristics, and medical treatment by diagnosis at presentation.

Diagnosis at Presentation	CD (n = 4)	UC (n = 14)	IBD-U (n = 7)
Age at Diagnosis (y)	7.2	5.2	6.0
Female	2 (50%)	7 (50%)	4 (57%)
Ethnicity			
Caucasian	4 (100%)	2 (14%)	5 (71%)
Black	0 (0%)	1 (7%)	0 (0%)
Ashkenazi Jewish	0 (0%)	0 (0%)	1 (14%)
South Asian	0 (0%)	6 (43%)	1 (14%)
Other	0 (0%)	5 (36%)	0 (0%)
Extent of Colitis at Diagnosis			
Pan-colitis	0 (0%)	13 (93%)	7 (100%)
Skip areas	2 (50%)	0 (0%)	0 (0%)
Left-sided	1 (25%)	1 (7%)	0 (0%)
Unknown	1 (25%)	0 (0%)	0 (0%)
Extraintestinal manifestations			
Arthritis	1 (25%)	3 (21%)	1 (14%)
Dermatologic	0 (0%)	0 (0%)	0 (0%)
Ocular	0 (0%)	1 (7%)	0 (0%)
Hepatic	0 (0%)	0 (0%)	0 (0%)
Medical treatment prior to colectomy			
Antibiotics	2 (50%)	2 (14%)	5 (71%)
Anti-TNF	3 (75%)	7 (50%)	7 (100%)
Imuran	0 (0%)	5 (36%)	4 (57%)
Methotrexate	1 (25%)	1 (7%)	2 (29%)
Steroids	3 (75%)	12 (86%)	7 (100%)
5-ASA	2 (50%)	10 (71%)	6 (86%)
Serologies			
ASCA			
Positive	0 (0%)	0 (0%)	1 (14%)
Negative	1 (25%)	5 (26%)	3 (43%)
Not drawn	3 (75%)	9 (64%)	3 (43%)
pANCA			
Positive	1 (25%)	3 (21%)	1 (14%)
Negative	2 (50%)	2 (14%)	4 (57%)
Not drawn	1 (25%)	9 (64%)	2 (29%)

Abbreviations: CD = Crohn's disease; UC = ulcerative colitis; IBD-U = inflammatory bowel disease unclassified; y = years. TNF = tumor necrosis factor; ASA = acetylsalicylic acid; ASCA = anti-Saccharomyces cerevisiae antibody; pANCA = perinuclear antineutrophil cytoplasmic antibody.

Table 2
Outcomes following subtotal colectomy and end ileostomy.

Diagnosis at presentation	CD (n = 4)	UC (n = 14)	IBD-U (n = 7)
Age at Colectomy (y)	10.1	7.1	9.2
Complications			
Intraabdominal abscess	0 (0%)	0 (0%)	0 (0%)
Wound infection	0 (0%)	0 (0%)	0 (0%)
Stoma complications	2 (50%)	2 (14%)	3 (43%)
Small bowel obstruction	0 (0%)	2 (14%)	1 (14%)
Number going on to pouch surgery	1 (25%)	6 (43%)	1 (14%)
Median time from colectomy to pouch surgery (mo)	11.7	32.7	10.7

Abbreviations: CD = Crohn's disease; UC = ulcerative colitis; IBD-U = inflammatory bowel disease unclassified; y = years; mo = months.

2. Results

A total of 25 children with very early-onset colitis underwent subtotal colectomy with end ileostomy. Demographic information and disease characteristics are listed in Table 1. Thirteen were female (52%) and 12 were male (48%). Nine patients (36%) had a family history of IBD. The median age at diagnosis was 5.4 years (range 1.3 to 10 years). Patients were followed for a median time of 7.1 years after their initial diagnosis. The most common diagnosis at initial presentation was ulcerative colitis (n = 14, 56%), followed by IBD-U (n = 7, 28%) and Crohn's disease (n = 4, 16%). The majority of patients had no prior medical history; two patients had a history of seizures, one had chronic granulomatous disease, one had autism, and one had trisomy 9. All but one patient had medical therapy prior to colectomy.

IBD serologies were performed for some patients. Ten patients had ASCA sent; one patient had a positive result. Thirteen had pANCA drawn, five of which had a positive result. Whole exome sequencing (WES) was performed in 24 children. Of the 24 children, three had genetic variants identified on WES: NOD2, TRIM22, and FOXP3. The child with the NOD2 mutation was initially diagnosed with IBD-U, and later with Crohn's. Both children with the TRIM22 and FOXP3 mutations had Crohn's, and had no change in diagnosis. There were not enough data to form a correlation between these results and the last diagnosis on follow-up.

The median age at subtotal colectomy was 7.4 years. Outcomes following the first surgery are listed in Table 2. Overall, eight patients (32%) had one or more complications. Six UC patients, one IBD-U patient, and one CD patient underwent pouch surgery, at a median time of 2 years following their colectomy. The one child with IBD-U who underwent a J-pouch did so following a change in diagnosis to ulcerative colitis. The child with CD was given this diagnosis initially, and then underwent subtotal colectomy. The pathology from this first surgery came back as more consistent with UC. Because of this, the child eventually underwent pouch surgery. Interestingly, the final diagnosis at last follow-up was “IBD-U favoring Crohn's disease”, given the severity of ulcerations in the pouch.

Eleven patients had a change in their initial diagnosis, which occurred at a median age of 11 years (Table 3). Fig. 1 shows the timeline of disease change. Five of these patients went on to have a pouch surgery; the median age at which their diagnosis changed was also

Table 3
Patients with a change in disease subtype.

Diagnosis	Number of patients	Median age when diagnosis changed (y)	Number of patients undergoing IPAA
CD to IBD-U	1	9.8	1
UC to CD	2	14.9	1
UC to IBD-U	3	10.4	2
IBD-U to CD	3	13.4	0
IBD-U to UC	2	7.7	1

Abbreviations: CD = Crohn's disease; UC = ulcerative colitis; IBD-U = inflammatory bowel disease unclassified; y = years; IPAA = ileal pouch-anal anastomosis.