Clinical Patterns and Outcome of Early-Onset Inflammatory Bowel Disease

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ABSTRACT

We sought to determine whether extremely-early-onset childhood inflammatory bowel disease (age <6 years; 20 ulcerative colitis [UC], 8 Crohn disease [CD]), 2 indeterminate, sequentially diagnosed) was clinically more severe than in older children (6–17 years; 19 UC, 39 CD, 2 indeterminate). Early-onset UC was marked by less abdominal pain at presentation, but an aggressive course with a significant reduction in weight-for-age, increased use of immunosuppressants, and more surgery. Children with early-onset CD were more likely to have bloody stools at presentation and an isolated colitis. This study supports the suggestion that inflammatory bowel disease phenotype differs in early-onset disease.

Key Words: child, Crohn disease, early onset, inflammatory bowel disease, ulcerative colitis

METHODS

A retrospective, comparative, descriptive analysis was performed in patients <6 years of age presenting with IBD—both ulcerative colitis (UC) and Crohn disease (CD)—at the Royal Children’s Hospital Melbourne or Monash Medical Centre between January 2000 and December 2007. These are the only 2 centers in our state that manage extremely young children with IBD. Patients were identified from the local IBD database (8,9). Diagnoses were based on endoscopic and histological findings. The next 2 consecutively diagnosed patients ages between 6 and 18 years were selected as comparators for each early-onset child. Ethical approval was obtained. Statistical analysis used GraphPad Instat (San Diego, CA) with mean and standard deviation (SD), or median with interquartile range (IQR) if not normally distributed.

RESULTS

Thirty children ages <6 years were diagnosed as having IBD during the 8-year study period. These constituted the “younger” group and represented 8% (30/360) of all of the children newly diagnosed as having IBD presenting at our hospitals during that period. Their median age was 3.0 years (IQR 2.0, 4.4), with 19 boys (8 CD, 20 UC, 2 indeterminate colitis [ID]). These represented 3% (8/235) of the total of those newly diagnosed as having CD for the same period, 20% (20/98) of UC, and 7% (2/27) of ID. The mean follow-up period was 4.9 years (SD 2.5). Sixty comparator “older” children had a median age 12.4 years (IQR 10.2, 14.4; 40 boys [39 CD, 19 UC, 2 ID]). Their mean follow-up period was 4.5 years (SD 2.4). UC was significantly more frequent in the younger group. No further analyses were undertaken of the children with ID.

Children whose UC was diagnosed before the age of 6 years were less likely to have a history of significant abdominal pain at presentation than the older children (Table S1, http://links.lww.com/MPG/A344). The proportions with bloody stools, diarrhea, weight loss, and fever were similar, as were duration of symptoms and presence of a family history. Hematological parameters were similar. The average albumin level was less at presentation, but the proportion whose albumin was below the normal range was the same in each group (n = 1). Phenotypic features at presentation are presented in Table S2 (http://links.lww.com/MPG/A345). The proportions with concomitant joint symptoms (younger 1/20 vs older 2/19), skin lesions (younger 0/20 vs older 0/19), or hepatobiliary disease (younger 3/20 vs older 2/19) were similar.

At presentation the age-adjusted weight and height z scores were similar (younger mean weight-for-age z score −0.20 [SD 1.17] vs older 0.24 [SD 0.83], P = 0.29; younger mean height-for-age z score −0.10 [SD 1.27] vs older 0.18 [SD 1.04], P = 0.54). Clinical severity as measured by the Pediatric Ulcerative Colitis Activity Index (PUCAI) was similar (younger mean PUCAI 45 [SD 20] vs older 37 [SD 14], P = 0.20).

Similar proportions of both UC groups were initially treated with systemic steroids (younger 14/20, older 10/19). After 2 years, a higher proportion of the younger group had started immunosuppressants (azathioprine), although this failed to reach statistical significance (younger 12/20 vs older 5/19, P = 0.054). There was a
significant and similar reduction in PUCAI 1 year after diagnosis in both the younger and older children to a mean of 11 (SD 17) and 6 (SD 10), respectively (P < 0.001 for both groups). Three of the younger group and none of the older group had a colectomy by the end of the 4-year follow-up period (P = 0.6). Although the mean weight-for-age z score for the younger group was less than for the older group at diagnosis and all time points up to 4 years afterward, this did not achieve statistical significance (Fig. S1, http://links.lww.com/MPGA/A347); however, when the weight-for-age z scores were pooled for all of these periods, the younger group were lighter for their age than the older group (young mean weight-for-age z score 0.01 [SD 1.11] vs older 0.42 [SD 0.88], P < 0.05). There was no significant difference between the 2 groups in terms of outcome for height at 1, 2, 3, or 4 years after diagnosis.

Early-onset CD was more likely to be associated with a history of bloody stools, but less likely to have abdominal pain than older children (Table S3, http://links.lww.com/MPGA/A346). Laboratory values were not significantly different. Children with early-onset CD were significantly less likely to have small bowel or ileal involvement. Phenotypic features are presented in Table S2 (http://links.lww.com/MPGA/A345). The proportions with concomitant joint symptoms (young 2/8 vs old 5/39), mouth ulcers (young 2/8 vs old 7/39), skin lesions (young 2/8 vs old 2/39), or hepatobiliary disease (young 0/8 vs old 2/39) were similar.

At presentation the age-adjusted weight and height z scores were not significantly different between younger and older groups (Fig. S1, http://links.lww.com/MPGA/A347). The Pediatric Crohn’s Disease Activity Index (PCDAI) was also similar in both groups (young mean PCDAI 23 [SD 16] vs older 28 [SD 12], P = 0.33).

Systemic steroid treatment was initially provided for a similar proportion of both the younger (6/8) and older (29/39) CD groups. After 2 years, a similar proportion of both groups had been commenced on immunosuppressants (young 3/8 vs older 12/39, P = 0.6). There was a significant and similar fall in PCDAI after 1 year in both the younger and older children to a mean of 12 (SD 16) and 11 (SD 11), respectively (P < 0.001 for both groups). There was no significant difference between the 2 groups in terms of outcome for growth in height or weight at 1, 2, 3, or 4 years after diagnosis. Pooled weights-for-age across all outcome points were not significantly different between the 2 groups.

**DISCUSSION**

Our study describes the presentation and clinical course of UC and CD in 90 Australian children, comparing 2 different age ranges. We had postulated that early-onset disease, first presenting in children <6 years of age, would be more extensive and severe than in those first presenting at an older age (6–18 years).

In this study, UC was the most frequently diagnosed form of IBD in younger children, with twice as many younger children affected in our study compared with those with CD. In older children this ratio was reversed. A similar finding has been noted in other studies (2,5,10). In this article we have deliberately separately addressed the findings for UC and CD.

In relation to UC, most clinical features were similar at first presentation in the younger and older children, with the exception of abdominal pain, which was significantly less common in the younger group. This has not previously been reported in studies that have compared presenting features of UC in children at different ages (2,10), but may represent a maturational difference, with younger children less likely to report abdominal pain, particularly given that there was a similar finding in CD.

We found differences between the 2 age groups in hemoglobin and albumin at presentation; however, when age-related differences in reference ranges were taken into account, there was no statistically significant differences in the proportion of children who were anemic at presentation.

Local laboratory reference ranges for albumin are identical for both age groups (26–38 g/L). Although the number of children with hypoalbuminemia in each group was the same, the difference in mean albumin level between the 2 groups is significant. Lower albumin level may be a proxy for more severe disease in younger children in terms of nutrition, and this is in agreement with the lower pooled weight for age z score in the younger group; however, the mean albumin in the younger group was just within the lower end of the normal range, and hence the clinical significance of this finding is uncertain. In addition, another single-center study found no significant differences in these parameters between similarly aged groups at first presentation with UC (2).

The extent of colonic involvement in early-onset UC has been variably reported. Our findings of no significant difference between the 2 age groups is in agreement with the study of Paul et al (2) in 33 children age <5 years at presentation with UC. Heyman et al (4), in a larger group (n = 85) of children first diagnosed as having UC age <6 years, found a nonsignificant trend toward more extensive colitis in the younger age group. In contrast, Van Limbergen et al (7) in a similar study to ours, found evidence of more extensive colitis in younger compared with older children presenting with UC.

The earlier use of immunosuppressants and time to surgery has been used as a proxy for aggressive disease (7). In this study, the trend toward earlier use of immunosuppressants suggested that younger children with UC experienced a more severe clinical course following diagnosis than older children. Although more of the younger children had a colectomy by the end of the study period, this difference did not achieve statistical significance. We found no other studies that compared this parameter between younger and older children with UC. There is certainly evidence that time to first use of immunosuppressants and colonic resection are generally shorter in children compared with adults (7). This, however, may reflect variations in individual treatment approaches between pediatric and adult gastroenterologists. The strength of our study is that both younger and older children were being cared for concurrently by the same pediatric gastroenterologists. Within our own state, virtually all of the children are managed within the pediatric health care system rather than by adult gastroenterologists.

Although there are some subtle differences, overall, we have found little evidence that younger children with UC have a more severe phenotype at first presentation. There was, however, evidence to support the suggestion that the subsequent natural history runs a more aggressive clinical course than in older children. This is consistent with a study of patterns of mucosal inflammation by Robert et al (11), which showed that the histopathological features of UC in children with UC <10 years of age are less severe and that histological features in the older age group (10–17 years) become more severe and approach that of adults.

In relation to CD, those presenting as younger children were more likely to have bloody stools and less likely to have abdominal pain. The relative reduction in abdominal pain has been noted in previous studies (3) and, as discussed above, may relate to age-related difficulties in obtaining a history. In contrast to children with UC, there were no significant differences between the 2 groups in laboratory parameters. Small bowel involvement was much less frequent in the younger group of children first presenting with CD, which is in agreement with other studies (2–4,12). Van Limbergen et al (7) found that a group of 53 children age <8 years at first diagnosis with CD were more likely to have isolated oral, anal, or colonic disease than older children, and less likely to have small bowel involvement. Heyman et al (4) reported on the clinical characteristics of 75 children with CD first diagnosed at
age <6 years and also observed that small bowel involvement was less likely. It has been suggested that this relates to age-related differences in the presence of Peyer patches, which have been postulated to have a pathophysiological role in ileal CD (12). In addition, this finding suggests caution in labeling isolated colitis as UC in younger children.

The chief limitation of this and the few other studies (2,4,7,10) that have examined this area is the relatively small number of children who present at age <6 years with IBD. We had no infantile-onset severe patients, which, many postulate, relates to single gene defects and likely differ from our patient group. Despite this, our findings for CD are similar to other studies in which the natural history of CD in children at age <6 years was, if anything, less complicated compared with older children (3). Overall, this first study in an Australian population adds to the growing body of data that IBD in young children has different phenotypic patterns from that presenting in older children. These features appear to differ between UC and CD. Early-onset disease in UC appears to be associated with evidence of a more aggressive natural history, whereas the main distinguishing feature of early-onset CD is the relative reduction in ileal involvement. One issue of substantial concern is the as yet unanswered question whether there is an added risk for malignancy in early-onset disease given the large recent increase in UC and in CD in children (8,9). Long-term outcomes for this early-onset group will need to continue to be monitored carefully.

REFERENCES


