Phenotypic Features and Longterm Outcomes of Pediatric Inflammatory Bowel Disease Patients with Arthritis and Arthralgia

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ABSTRACT. ***Objective.*** The natural history of pediatric inflammatory bowel disease (IBD) patients with joint involvement has not been clearly described. Thus, we aimed to investigate phenotypic features and clinical outcomes of this distinct association.

Methods. The medical records of patients with pediatric IBD diagnosed from 2000 to 2016 were reviewed retrospectively. Main outcome measures included time to first flare, hospitalization, surgery, and biologic therapy.

Results. Of 301 patients with Crohn disease (median age 14.2 yrs), 37 (12.3%) had arthritis while 44 (14.6%) had arthralgia at diagnosis. Arthritis and arthralgia were more common in women (p = 0.028). Patients with arthritis and arthralgia demonstrated lower rates of perianal disease (2.7% and 4.5% vs 16.9%, p = 0.013), whereas patients with arthritis were more likely to be treated with biologic therapy (HR 2.05, 95% CI 1.27–3.33, p = 0.009). Of 129 patients with ulcerative colitis (UC; median age 13.7 yrs), 3 (2.3%) had arthritis and 16 (12.4%) had arthralgia at diagnosis. Patients with arthralgia were treated more often with corticosteroids (p = 0.03) or immunomodulator therapies (p = 0.003) compared with those without joint involvement. The likelihood to undergo colectomy was significantly higher in patients with arthralgia (HR 2.9, 95% CI 1.1–7.4, p = 0.04). During followup (median 9.0 yrs), 13 patients developed arthritis (3.3%). Arthralgia at diagnosis was a significant predictor for the development of arthritis during followup (HR 9.0, 95% CI 2.86–28.5, p < 0.001).

Conclusion. Pediatric IBD patients with arthritis have distinct phenotypic features. Arthralgia at diagnosis is a predictor for colectomy in UC and a risk factor for the development of arthritis during followup. (First Release September 1 2017; J Rheumatol 2017;44:1636–43; doi:10.3899/jrheum.170168)

Key Indexing Terms:
CROHN DISEASE CHILDREN SACROILIITIS ULCERATIVE COLITIS

Inflammatory bowel disease (IBD) is a group of chronic immune-mediated diseases involving the gastrointestinal tract that can be classified into 2 main subtypes: Crohn disease (CD) and ulcerative colitis (UC). Around 25% of all patients with IBD are diagnosed during childhood[1]. The incidence of IBD and specifically pediatric IBD is rising steadily, particularly in Western countries[2,3].

Musculoskeletal manifestations are the most common extraintestinal manifestations (EIM) in IBD, accounting for nearly 20–30% of patients[4]. These can be divided into peripheral arthritis and axial arthropathies. In both adults and children with IBD, peripheral arthritis occurs in about 10–20% of patients with CD and 5–10% with UC, respectively[5]. It is well established that the risk of developing peripheral arthritis increases with the extent of colonic disease and that arthritis most commonly follows luminal disease activity[6]. In contrast, axial arthropathies are less frequent and occur in 3–5% of patients while not paralleling IBD activity[7]. In a recent metaanalysis, the calculated prevalence of sacroiliitis in patients with IBD was 10%, of ankylosing spondylitis was 3%, and that of peripheral arthritis was 13%[8]. Arthralgia, though not defined as a "pure" EIM, is a common complaint in patients with IBD. In the pediatric IBD population, the prevalence of arthralgia was found to be 17% and 14.9% in CD and UC, respectively, whereas the prevalence of arthritis was only 4.4% and 1.8%, respectively[9], roughly similar to adult patients with IBD[10].

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As for gastrointestinal and joint inflammation in IBD, both manifestations were suggested to share a common inflammatory etiology. Common mechanistic features include Th17 activation, Th1 predominance in the intestinal mucosa, and increased expression of Toll-like receptor (TLR)-4 and TLR-2 in antigen-presenting cells from patients with both diseases[11]. Demetter, *et al*[12] showed that expression of E-cadherin is high in the gut of patients from both groups. The physiological implications of arthralgia and their possible prognostic consequences are not well established. In adults with fibromyalgia and its musculoskeletal symptoms, serum concentrations of interleukin (IL)-2, IL-6, IL-8, and anti-tumor necrosis factor (TNF) were significantly elevated[13,14], suggesting that joint pain might represent a systemic inflammatory process that by itself might be associated with more severe bowel inflammatory activity. Nevertheless, arthralgia may simply represent an underlying, subclinical enthesitis, as was shown in previous studies[15,16].

Although arthritis is the most common EIM in both adult and pediatric populations, very few studies have analyzed this phenotype's longterm outcome. Adult studies reached controversial conclusions[17,18] while 1 pediatric study[19] found a marginal tendency to a more severe phenotype. Hence, in our study, we aimed to analyze the phenotypic features and specific longterm clinical outcomes of both arthritis and arthralgia in children with IBD.

MATERIALS AND METHODS

Patients. Data were obtained retrospectively from medical records of pediatric patients who were diagnosed with IBD at the ages of 0 to 18 years between January 2000 and June 2016 at the Schneider Children's Medical Center, the largest children's hospital in Israel, serving as both a primary and tertiary center for more than 1 million inhabitants. Diagnosis of IBD was based on the accepted clinical, endoscopic, and histologic criteria[20]. All patients with a minimum of 6-month followup were included. A total of 301 patients with CD and 129 patients with UC were included.

Description of variables. At diagnosis, demographic, anthropometric, clinical, laboratory, radiological, and endoscopic data were recorded for each patient. Height, weight, and body mass index were converted to age- and sex-adjusted SD scores (Z scores) using US Centers for Disease Control growth charts. Disease activity for patients with CD was assessed using the abbreviated Pediatric Crohn's Disease Activity Index (PCDAI), short PCDAI, and the Harvey-Bradshaw Index (HBI)[21,22,23]. Disease activity for patients with UC was assessed using the Pediatric Ulcerative Colitis Activity Index (PUCAI)[24]. Disease phenotype at diagnosis was categorized according to the Paris classification[20]. Elevated liver enzymes were defined as alanine aminotransferase and aspartate aminotransferase > 45 U/l or γ-glutamyl transpeptidase > 27 U/l at diagnosis. For the statistical analysis, IBD unclassified patients (17, 4%) were analyzed within the patients with UC group. Data collected throughout the followup period included therapeutic regimens (medical and surgical) and subsequent outcomes (hospitalizations and exacerbations). Flare (disease exacerbation) was defined as HBI ≥ 5 and suggestive symptoms for CD and PUCAI ≥ 10 for UC. Following data collection, patients in each disease category (CD and UC) were designated into 1 of 3 groups: (1) patients with no joint signs/symptoms at diagnosis, (2) patients with arthritis (found in physical examination and documented by the treating physician during a medical encounter) at diagnosis, and (3) patients with complaints of arthralgia at diagnosis, defined as localized, persistent pain in joint(s) at rest, with no evidence of arthritis during physical examination. Physical exercise-related joint pain was not regarded as arthralgia. Patients with arthritis in joint(s) and arthralgia in other joint(s) were classified as having arthritis.

Arthritis was further defined according to the 3 types of IBD-related arthritis: type 1, oligoarthritis of large joints; type 2, polyarthritis of small joints, both defined as peripheral arthritis; and type 3, axial arthritis, which includes sacroiliitis and AS. Disease outcomes were defined as time to first flare, hospitalization, surgical intervention, and biologic therapy.

Data analysis. Categorical variables were presented as frequency and percentage. Continuous variables were evaluated for normal distribution using histogram and Q-Q plots. Normally distributed continuous variables were described as mean and SD, and non-normally distributed continuous variables were reported as median and interquartile range (IQR). Continuous variables were compared using ANOVA, independent sample Student t test, Kruskal-Wallis, or Mann-Whitney test, as appropriate. Categorical variables were compared using the chi-square test or Fisher's exact test. Length of followup was evaluated using a reverse censoring method. Time to first flare, hospitalization, surgical intervention, and biologic therapy during followup was described using Kaplan-Meier plots (showing multivariate analysis of outcomes). Univariate and multivariate Cox regression were used to evaluate the crude and adjusted association between exposure and outcomes. The multivariate model included age at diagnosis, sex, and variables with a significant level of $p < 0.2$ at the univariate analysis. When 2 variables that were highly correlated reached the significance level of $p < 0.2$, the most significant variable was included. All statistical tests were 2-tailed and $p < 0.05$ was considered as statistical significance. All statistical tests were performed using SPSS (IBM Corp., released 2015. IBM SPSS statistics for Windows, version 23). The study protocol was approved by the local Internal Review Board at the Rabin/Schneider Medical Center (RMC 0320-10).

RESULTS

The entire cohort was composed of 430 patients, 301 patients (70%) with CD and 129 patients with UC or IBD unclassified. Median age at diagnosis was 14.0 years (IQR 11.2–16.2 yrs) with 184 women (43%).

Patients with CD. Of the 301 patients with CD followed in this study, 37 (12.3%) had arthritis while 44 (14.6%) had arthralgia at diagnosis. The clinical characteristics of the 3 groups — patients with arthritis, patients with arthralgia alone (no signs of arthritis), and patients without joint involvement — are summarized in Table 1. The median age was 14.2 years (IQR 12.0–16.0), with 126 women (42%). Patients were followed for a median duration of 9.1 years (IQR 4.7–12.3). Out of the arthritis group, 26 (70%) had peripheral arthritis, 4 (11%) had axial arthritis, and 7 (19%) had both. Of the 33 patients with peripheral arthritis (with or without axial involvement), 27 patients (82%) presented with type 1 IBD-related arthritis whereas 6 patients (18%) presented with type 2. The most common involved joints were ankles (19 patients, 58%), followed by knees (17 patients, 52%) and joints of the upper extremities (11 patients, 33%). Hip involvement was the least common site of involvement (5 patients, 15%). All patients with axial involvement had sacroiliitis and none presented with AS. Fifteen patients (41%) presented with arthritis prior to the CD diagnosis, with a median time of –1.1 years (IQR –0.4 to –3.8). There was no difference in time of presentation between types of arthritis. Of the 44 patients with arthralgia, 29 patients (66%) presented with pain in < 5 joints whereas

Table 1. Characteristics of patients with Crohn disease according to joint involvement.

Characteristics	No Joint Involvement, n = 220	Arthralgia, n = 44	Arthritis, n = 37	p
Sex (female), n (%)	82 (37.4)	25 (56.8)	19 (51.4)	0.028
Family history of IBD, n (%)	42 (19.3)	19 (43.2)	10 (27.0)	0.003
Perianal disease, n (%)	37 (16.9)	2 (4.5)	1 (2.7)	0.013
Elevated liver enzymes, n (%)	1 (0.5)	2 (4.5)	4 (10.8)	0.001
Positive ASCA, n (%)	63 (56.8)	14 (58.3)	10 (35.7)	0.119
Granuloma, n (%)	77 (36.0)	18 (40.9)	7 (20.0)	0.121
Paris behavior, n (%)				
B1	153 (70.2)	35 (79.5)	25 (67.6)	0.588
B2	50 (22.9)	7 (15.9)	11 (29.7)	
B3	15 (6.9)	2 (4.5)	1 (2.7)	
Paris location, n (%)				
L1	67 (31.3)	16 (37.2)	11 (30.6)	0.266
L2	26 (12.1)	5 (11.6)	9 (25.0)	
L3	121 (56.5)	22 (51.2)	16 (44.4)	
HBI, mean (SD)	6.4 (± 2.8)	7.4 (± 3.4)	6.5 (± 2.7)	0.110
Short PCDAI, mean (SD)	35.7 (± 17.1)	40.2 (± 18.6)	36.8 (± 16.6)	0.305
Abbreviated PCDAI, mean (SD)	21.9 (± 4.4)	23.7 (± 10.8)	19.5 (± 10.3)	0.159
Age at diagnosis, yrs, median (IQR)	14.0 (12–15.8)	14.2 (12.1–15.9)	14.2 (11.8–16.1)	0.943
Weight Z score, median (IQR)	–0.6 (–1.57 to 0.15)	–0.6 (–1.57 to 0.38)	–0.28 (–1.22 to 0.49)	0.292
Height Z score, median (IQR)	–0.5 (–1.25 to 0.20)	–0.38 (–1.00 to 0.20)	–0.11 (–0.9 to 0.58)	0.153
BMI Z score, median (IQR)	–0.5 (–1.33 to 0.21)	–0.50 (–1.35 to 0.50)	–0.30 (–1.24 to 0.30)	0.816
Hemoglobin, g/dl, median (IQR)	11.2 (10.5–12.0)	10.9 (10.1–12.1)	10.5 (9.7–11.7)	0.043
Albumin, g/dl, mean (SD)	3.6 (± 0.45)	3.66 (± 0.51)	3.72 (± 0.45)	0.379
CRP, mg/dl, median (IQR)	3.5 (1.7–6.5)	4.5 (1.5–7.3)	5.0 (2.2–10.1)	0.074
ESR, mm/h, median (IQR)	50.0 (35.0–70.0)	50.0 (38.0–65.0)	56.00 (43.0–82.5)	0.202

IBD: inflammatory bowel disease; ASCA: anti-*saccharomyces cerevisiae* antibody; HBI: Harvey-Bradshaw Index; PCDAI: Pediatric Crohn's Disease Activity Index; IQR: interquartile range; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

the rest (34%) had multiple joints symptoms. The most common site for joint pain was the knees (33 patients, 75%), followed by ankles (24 patients, 55%), joints of the upper extremities (18 patients, 41%), back (15 patients, 34%), and hip (11 patients, 25%).

Female sex was more common in patients with arthralgia or arthritis than those without joint involvement (56.8%, 51.4%, and 37.4%, respectively, p = 0.028). Positive family history of IBD (first-degree relatives) was twice as common in patients with arthralgia as in those with arthritis or without joint involvement (43.2% vs 27.0% and 19.3%, respectively, p = 0.003). Perianal disease was significantly less common in patients with arthritis and arthralgia than in those without joint involvement (2.7% and 4.5% vs 16.9%, respectively, p = 0.013). Regarding laboratory findings, hemoglobin levels at diagnosis were lower in patients with arthritis and arthralgia compared with no joint involvement (10.5 g/dl and 10.9 g/dl vs 11.2 g/dl, respectively, p = 0.043), whereas C-reactive protein (CRP) was marginally increased in these groups (5.0 mg/dl and 4.5 mg/dl vs 3.5 mg/dl, respectively, p = 0.074). Elevated liver enzymes were more common in patients with arthritis (10.8% vs 4.8% in arthralgia and 0.5% in no joint involvement, p = 0.001), but the sample group was very small (7 patients). In the multivariate analysis, significance was maintained for all described associations except hemoglobin levels. Other laboratory findings, including anti-*saccharomyces cerevisiae* antibody, anthropometric measures, and activity indices upon diagnosis did not differ among groups. Patients with arthritis had a higher proportion of isolated colonic disease (25.0% vs 11.6% in patients with arthralgia and 12.1% in patients with no joint involvement); however, it did not reach statistical significance (p = 0.266). Patients with arthritis were more likely to receive a biological induction treatment at diagnosis than those with arthralgia or with no joint involvement (16.2% vs 0.0% and 2.3%, respectively, p = 0.001). Other induction regimens including corticosteroids and exclusive enteral nutrition demonstrated no significant difference among study groups.

Multivariate analysis of specific disease outcome is presented as Kaplan-Meier curves (Figures 1A–D). Overall, 154 (51%) of patients received biological therapy, either adalimumab (ADA) or infliximab (IFX). Patients with arthritis were twice as likely to receive biological therapy as patients with no joint involvement (HR 2.05, 95% CI 1.27–3.33, p = 0.009). Time to initiation of biological treatment occurred significantly earlier in patients with arthritis, with a median time to treatment of 3.73 years (95% CI 0.0–7.9) as opposed to 6.54 years (95% CI 4.9–8.1) in patients with arthralgia and 7.57 years (95% CI 4.8–10.4) in patients with no joint involvement (Figure 1A). Of the 22 CD

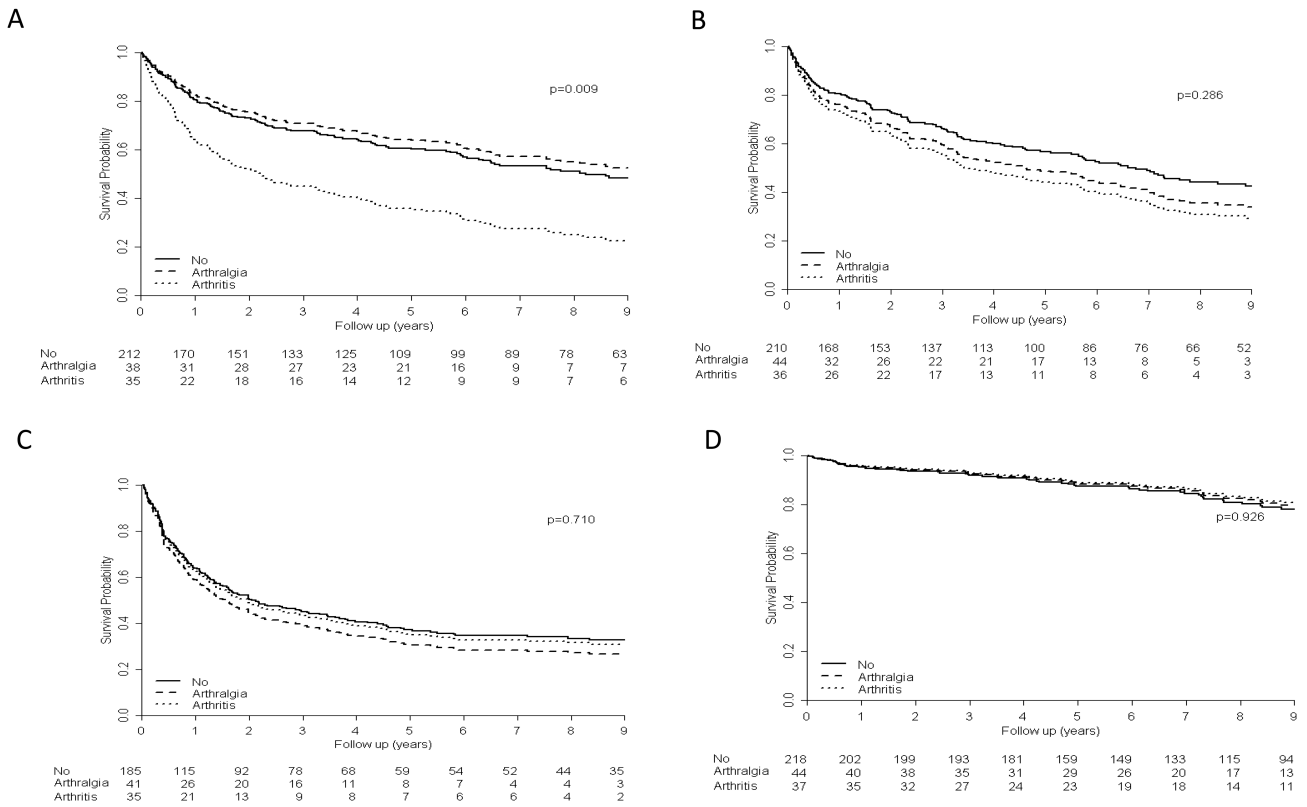

Figure 1. Kaplan-Meier estimates of patients with Crohn disease remaining free of disease outcome according to type of joint involvement. (A) Time to biologic therapy. (B) Time to first hospitalization. (C) Time to first flare. (D) Time to first surgical intervention. Bottom: number of patients at risk.

patients with arthritis (12 with peripheral arthritis, 4 with sacroiliitis, and 6 with both) treated with anti-TNF, 12 patients (55%) received IFX and the rest received ADA. Initial response was observed in 16 patients overall (73%), with response rates of 78% (14/18) with peripheral arthritis and 60% (6/10) for sacroiliitis.

Following initial diagnosis, the majority of patients (163, 54%) were hospitalized at least once. Patients with arthritis or arthralgia were marginally more likely to be hospitalized than those without joint involvement (HR 1.22, 95% CI 0.75–1.99, and HR 1.40, 95% CI 0.92–2.10, respectively), with no statistical significance (p = 0.286). Median time to first hospitalization was 5.79 years (95% CI 1.5–10.1), 4.14 years (95% CI 1.4–6.9), and 6.60 years (95% CI 4.7–8.5) in patients with arthritis, arthralgia, and no joint involvement, respectively (Figure 1B).

The majority of patients (171, 57%) had at least 1 flare following diagnosis. Median time to first disease flare was 1.98 years (95% CI 1.3–2.7) across the entire cohort. Time to first flare did not show any significant difference between study groups (Figure 1C). Over the course of the study, 76 patients (25%) underwent bowel resection. Time to first surgery did not differ between groups (Figure 1D). When stratifying the longterm outcomes according to the type of arthritis, no significant differences were observed between groups.

At the end of followup, the rate of complicated disease (stricturing or fistulizing) did not differ significantly between groups, though there was a tendency toward more complicated disease in the arthritis group compared with the arthralgia and no joint involvement groups (46% vs 40% vs 32%, p = 0.1).

Patients with UC. Of the 129 patients with UC followed in our study, only 3 (2.3%) had arthritis and 16 (12.4%) had arthralgia at diagnosis. The clinical characteristics of patients with arthralgia and without it (n = 126) are summarized in Table 2. The median age was 13.7 years (IQR 11.1–15.8), with 56 women (44.4%). Patients were followed for a median duration of 8.5 years (IQR 5.1–12.0). Of the patients with arthritis, 1 presented with type 1 arthritis, 1 with sacroiliitis, and 1 with both. Of the 16 patients with arthralgia, 8 patients (50%) had pain in fewer than 5 joints and the rest in several (≥ 5) sites. Similar to patients with CD, the most common sites for arthralgia were the knees (11 patients, 69%), followed by ankles (9 patients, 56%), joints of the upper extremities (7 patients, 44%), back (5 patients, 31%), and hip (2 patients, 13%).

Age, sex, and family history of IBD did not differ between groups. Regarding laboratory findings, albumin levels were significantly lower in patients with arthralgia compared with those without (3.7 g/dl vs 4.2 g/dl, p = 0.029), whereas CRP

Table 2. Characteristics of patients with ulcerative colitis according to joint involvement.

Characteristics	No Joint Involvement, n = 110	Arthralgia, n = 16	p
Sex (female), n (%)	48 (43.6)	8 (50)	0.632
Family history of IBD, n (%)	24 (22.0)	4 (25.0)	0.755
Elevated liver enzymes, n (%)	10 (9.1)	1 (6.7)	1.000
Positive pANCA, n (%)	63 (67.0)	11 (84.6)	0.336
Paris severity (S1), n (%)	29 (26.9)	8 (53.3)	0.067
Paris extent, n (%)			
E1	16 (14.8)	0 (0.0)	0.214
E2	18 (16.7)	1 (6.7)	
E3	22 (20.4)	3 (20.0)	
E4	52 (48.1)	11 (73.3)	
PUCAI, median (IQR)	35.0 (25.0–45.0)	40.0 (25.0–53.7)	0.355
Age at diagnosis (yrs), median (IQR)	13.7 (10.9–15.5)	13.9 (11.7–16.5)	0.339
Weight Z score, mean (SD)	–0.30 (± 1.19)	–0.44 (± 1.00)	0.653
Height Z score, mean (SD)	–0.13 (± 0.99)	–0.17 (± 0.94)	0.877
BMI Z score, mean (SD)	–0.22 (± 1.20)	–0.40 (± 1.08)	0.579
Hemoglobin, g/dl, median (IQR)	12.0 (10.5–13.1)	12.3 (11.1–13.2)	0.575
Albumin, g/dl, median (IQR)	4.2 (4.0–4.5)	3.7 (3.4–4.2)	0.029
CRP, mg/dl, median (IQR)	0.28 (0.08–0.70)	0.86 (0.32–1.27)	0.006
ESR, mm/h, median (IQR)	15.0 (10.0–30.0)	36.0 (11.0–48.0)	0.109

IBD: inflammatory bowel disease; pANCA: perinuclear antineutrophil cytoplasmic antibodies; PUCAI: Pediatric Ulcerative Colitis Activity Index; IQR: interquartile range; BMI: body mass index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

was increased (0.86 mg/dl v 0.28 mg/dl, p = 0.006). Other laboratory findings, including perinuclear antineutrophil cytoplasmic antibodies, as well as activity indices and anthropometric measures upon diagnosis, showed no differences between groups. Patients with arthralgia had a higher proportion of pancolitic disease (73.3% vs 48.1%), and lower proportion of proctitis (0.0% vs 14.8%), but this was not statistically significant (p = 0.214). Patients with arthralgia were significantly more likely to have a steroid induction treatment (81.3% vs 52.7%, p = 0.032) and immunomodulatory maintenance during the first year after diagnosis (87.5% vs 47.3%, p = 0.003). The significance of hypoalbuminemia, elevated CRP, and induction treatments was maintained in the multivariate analysis.

Multivariate analysis of disease outcomes is presented as Kaplan-Meier curves (Figures 2A–D). Following initial diagnosis, the majority of patients (102, 81.0%) had at least 1 flare. Patients with arthralgia were twice as likely to have a flare during followup (HR 2.17, 95% CI 1.25–3.78), which was statistically significant in the univariate analysis (p = 0.005), but fell short of statistical significance in the multivariate analysis (p = 0.628; Figure 2C). Median time to first flare in patients with arthralgia was shorter in patients with arthralgia (0.38 yrs, 95% CI 0.2–0.6 vs 1.71 yrs, 95% CI 1.1–2.4).

Patients with arthralgia were 3 times more likely to undergo colectomy than patients with no joint involvement (HR 2.90, 95% CI 1.13–7.43, p = 0.04). Colectomy occurred significantly earlier in patients with arthralgia, with a mean time to surgery of 10.49 years (95% CI 7.1–13.9) as opposed to 14.12 years (95% CI 13.1–15.1) in patients with no joint involvement (Figure 2D).

Following initial diagnosis, the majority of patients (79, 63%) in the cohort were hospitalized at least once. Patients with arthralgia were 1.7 times more likely to be hospitalized than those without joint involvement (HR 1.70, 95% CI 0.92–3.16), but with no statistical significance in the uni- and multivariate analysis (Figure 2B).

Overall, 43 patients (34%) received biological therapy, either ADA or IFX. Time to first biological treatment did not differ between groups (Figure 2A). All 3 patients with arthritis received IFX. Initial response was observed in 2 patients overall (67%) with equal response rates of 50% (1/2) for each type of arthritis.

Arthralgia as a risk factor for arthritis. During a followup period of 9.0 years (IQR 4.9–12.2), 13 patients (9 CD, 4 UC) out of 390 patients with IBD without arthritis at diagnosis developed arthritis (3.3%) at a median time of 3.7 years (IQR 2.1–7.1). Within patients with arthralgia at diagnosis, 8/60 (13.3%) developed arthritis in contrast to 5/330 (1.5%) of patients with no joint involvement at diagnosis (HR 9.0, 95% CI 2.86–28.5, p < 0.001). Nine patients (69%) developed type 1 arthritis whereas 4 patients (31%) developed sacroiliitis. Figure 3 describes the Kaplan-Meier survival curve for being free of arthritis according to the presence of arthralgia at diagnosis. Other variables at diagnosis such as sex, age, and disease severity were not associated with the risk of developing arthritis during disease course.

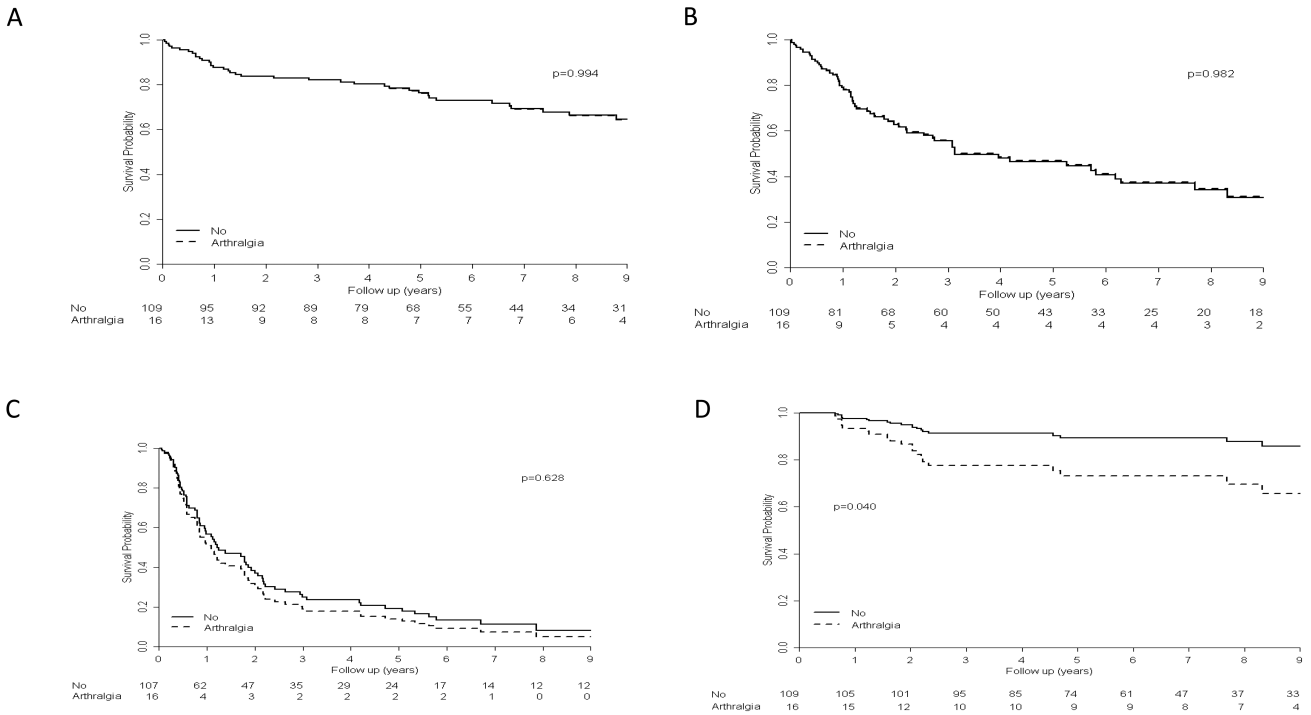

Figure 2. Kaplan-Meier estimates of patients with ulcerative colitis remaining free of disease outcome according to type of joint involvement. (A) Time to biologic therapy. (B) Time to first hospitalization. (C) Time to first flare. (D) Time to first surgical intervention. Bottom: number of patients at risk.

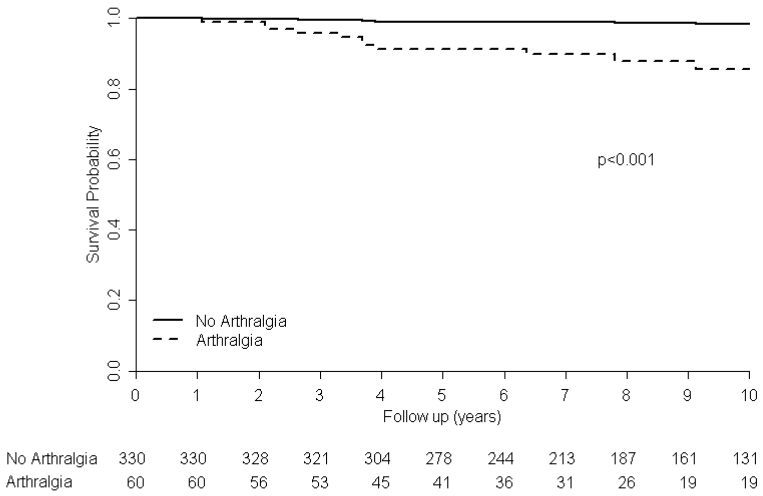

Figure 3. Kaplan-Meier survival curve of patients with inflammatory bowel disease who developed arthritis during a median followup of 9 years according to the presence of arthralgia at diagnosis. Bottom: number of patients at risk.

DISCUSSION

In our present study, which describes one of the largest cohorts of pediatric IBD patients with and without joint involvement, we found that IBD patients with arthritis and IBD patients with arthralgia have distinct phenotypes at diagnosis. In patients with CD, arthritis was not associated with worse disease outcome whereas it was, expectedly, associated with higher risk for stepping up to biologic therapy. Intriguingly, in patients with UC, arthralgia (which is not considered EIM) was associated with worse disease outcomes, including higher risk for colectomy. For the entire cohort, arthralgia was demonstrated to pose significant risk for the development of arthritis during disease course.

The prevalence of arthritis or arthralgia at diagnosis in our

cohort was not significantly different from those found in previous pediatric studies[9,25,26]. Female preponderance (in both patients with arthritis and arthralgia) and a positive correlation with disease activity were demonstrated in previous studies[9,26]. However, the associations between both arthritis and arthralgia to higher rates of IBD family history and lower prevalence of perianal disease are surprising, and in view of other similarities in disease behavior, over time it may be suggested that IBD patients with arthralgia have an "intermediate" phenotype that somewhat resembles IBD patients with arthritis. There is no clear explanation for the described finding of the association of arthritis and arthralgia with a lower rate of perianal disease and it might simply represent a different phenotype. Nevertheless, it was shown that presence of granulomas (representing a more invasive luminal disease) is associated with a higher prevalence of perianal disease[27]. In our cohort, the prevalence of granulomas was almost 2-fold greater in patients without arthritis, and even though it did not reach statistical significance, it might imply a plausible explanation. The association of arthritis with elevated liver enzymes might stem from a greater inflammatory burden as reflected by higher CRP (on the verge of statistical significance) in this group. Still, the number of patients with elevated liver enzymes is small, so this association should be interpreted with caution.

The observed association between arthritis at diagnosis of CD and early biological treatment is somewhat expected because in contrast to luminal lesions, the IBD-related joint lesions are more structural and less reversible, so early biological treatment aiming toward remission of joint disease is essential to prevent irreversible damage. This association is also plausibly attributed to the efficacy of anti-TNF treatment in arthritis and to the fact that this treatment is one of few effective therapies in patients with sacroiliitis. The response rate of both peripheral arthritis and sacroiliitis to anti-TNF treatment demonstrated in our study (75% and 58%, respectively) is in the range of recently reported response rates both in adults[28] and in children[29].

A substantial proportion of patients with arthritis at diagnosis of IBD (41%) presented with arthritic symptoms in distinction and prior to IBD diagnosis. This observation suggests that patients with arthritis should be closely monitored for bowel symptoms with low threshold for appropriate diagnostic tests. Indeed, ileocolonoscopies performed in adults with spondyloarthropathies, without clinical intestinal symptoms, have shown mucosal and lamina propria inflammatory infiltrates of the ileal and colonic mucosa in a substantial proportion of patients[30,31]. In pediatric patients with arthritis, the longterm risk for developing IBD was shown to be about 15%[32,33].

One of the most intriguing findings of our study is the association of arthralgia with a more severe disease at diagnosis and a higher colectomy rate during a median followup of 8.5 years in patients with pediatric UC. The small number of UC patients with arthritis (3 patients) at diagnosis prevented a separate analysis of this phenotype. However, patients with arthralgia demonstrated consistent features of a more severe disease including higher rates of hypoalbuminemia, elevated CRP, more extensive disease, and a higher risk for both corticosteroid and immunomodulatory treatment following diagnosis. The most striking finding is an HR of 2.9 for colectomy in UC patients with arthralgia. It may be suggested, for the first time to our knowledge, that arthralgia is a major risk factor for both a more severe disease at diagnosis and for colectomy at the long term. Naturally, this finding requires further supportive evidence from future studies.

In our cohort, 3.3% of patients with IBD developed overt arthritis within a median followup of 9 years from diagnosis. This rate corresponds with the rate reported by Jose, *et al*[25] in a followup of 15 years. Despite the small number of patients who developed arthritis (13 patients), we could demonstrate that arthralgia at diagnosis was a significant predictor for arthritis during disease course. Although this association is somewhat straightforward, it was never demonstrated in previous studies. Arthralgia is commonly regarded as a benign symptom, thus it is sometimes ignored. The potential detrimental consequences of arthralgia suggest that patients with arthralgia should be more closely monitored for the possible occurrence of arthritis.

Despite the relatively large cohort size, comprehensive analysis of outcomes, and novel findings shedding more light on this common phenotype, our study has several limitations. First, the retrospective design of the study limited complete data collection, including specific arthritis characteristics such as type and number of involved joints, as well as other important features including the PCDAI, calprotectin, and endoscopic severity indices. Also, the number of children with joint involvement in this cohort is relatively small, and therefore the findings may be at risk of type II error.

Pediatric IBD patients with arthritis and arthralgia have a distinct phenotype whereas arthralgia in patients with pediatric UC is associated with worse disease outcome. Arthralgia in patients with pediatric IBD appears to be a risk factor for the development of arthritis during disease course. These findings warrant further supportive evidence from future retrospective and prospective studies.

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