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Enthesitis is an Extraintestinal Manifestation of Pediatric Inflammatory Bowel Disease

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Abstract

Background—Enthesitis is an extra-intestinal manifestation of inflammatory bowel disease (IBD) in adults. However, little has been published about the prevalence or characteristics of enthesitis in pediatric IBD.

Methods—We conducted a cross-sectional study of children and young adults ages 4–21 years with IBD. Subjects were recruited among those receiving routine care in a gastroenterology clinic. All subjects underwent a clinical examination of the entheses and joints, and completed a study questionnaire.

Results—We enrolled 43 subjects, who had a median age of 16 years and a median time from IBD diagnosis of 2.7 years. 32 subjects (74%) had Crohn disease, 10 subjects (23%) had indeterminate colitis, and 1 subject (2%) had ulcerative colitis. At least one tender enthesis was present in 21% of subjects and 12% had more than 2 tender entheses. The most commonly affected entheses were located at the inferior patella, the femoral greater trochanter, and the proximal humerus. The presence of enthesitis was associated with a higher intensity of recent musculoskeletal pain (p=0.03).

Conclusions—Enthesitis is a prevalent extra-intestinal manifestation of pediatric IBD and is associated with increased musculoskeletal pain. Future studies should evaluate the functional and long-term impact of enthesitis on children with IBD.

Keywords

Enthesitis; inflammatory bowel disease; extra-intestinal manifestations; enthesitis-related arthritis

Introduction

Patients with inflammatory bowel disease (IBD) suffer from a variety of different inflammatory complications beyond intestinal disease. Among the most prevalent extra-intestinal complications of IBD is arthritis, even among children [1]. Arthritis has been reported in as many as 14–25% of pediatric IBD patients [2,3]. More recent studies of

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extraintestinal manifestations in pediatric IBD patients reported peripheral arthritis in around 4%[4,5]. Other extra-intestinal manifestations may include aphthous stomatitis (range 3.4–8% affected), erythema nodosum (1.6–2.8%), uveitis (0.7–1.8%), ankylosing spondylitis (0.4%), and pyoderma gangrenosum (0.3%)[4,5].

In addition to arthritis, children with IBD can develop enthesitis, which is inflammation at the bony insertion sites of ligaments, tendons, and fascia. Several studies report enthesitis in adult IBD patients, with prevalence ranging from 7 to 50%[6–10]. Chronic enthesitis can lead not only to functional disability but also structural changes, including osteopenia, bony cortex irregularities and erosions, soft tissue calcifications, and abnormal new bone formation[11,12].

Enthesitis is frequently found in normal children[13] as well as children with juvenile idiopathic arthritis (JIA) [14,15], particularly those with the enthesitis-related arthritis (ERA), undifferentiated, and oligoarticular-extended categories[16]. One study identified evidence of spondyloarthropathy in 19 (24%) of 78 patients with newly diagnosed IBD[17]; 4 of these 19 subjects had enthesitis detectable on clinical examination. The enthesitis examination in that study was limited to 4 bilateral sites, including 3 on the lower extremities.

Although enthesitis is an extra-intestinal manifestation of pediatric IBD[18], little is known about the frequency, location, and impact of enthesitis among children and young adults with IBD. Our study helps to more fully characterize the overall prevalence and pattern of enthesitis in a cross-sectional cohort of subjects with pediatric IBD.

Materials and Methods

Patients

The source population for this study was a convenience sample of children with IBD who were evaluated in a pediatric gastroenterology clinic for routine IBD care in April 2011. Eligible subjects were ages 4 to 21 years old with a diagnosis of Crohn disease (CD), ulcerative colitis (UC), or indeterminate colitis (IC), previously confirmed by endoscopic biopsy. Subjects were excluded from the study if they were previously diagnosed with irritable bowel syndrome or an amplified pain syndrome, such as reflex neurovascular dystrophy; or if they were unable to reliably report pain accurately, for example, due intellectual disability or autism. During the study enrollment period, 58 subjects with IBD were screened and 43 (74%) were enrolled. Among those not enrolled, 7 declined participation and 8 were ineligible. Reasons for exclusion were a known history of an amplified pain syndrome (n=5), inability to report pain accurately (n=2), and lack of an IBD diagnosis (n=1).

Musculoskeletal examination

All subjects received a full musculoskeletal examination. All subjects were examined by one investigator (DBH) and 9% were examined by a second investigator (PFW) to determine inter-rater reliability. Investigators were blinded to the specific diagnosis and clinical history of all subjects examined, including their IBD subtype, any ongoing musculoskeletal symptoms, and any history of arthritis. Arthritis was defined as joint swelling accompanied by pain or limited range of motion. The standardized enthesitis exam for this study consisted of the examiner applying enough pressure with the thumb to blanch the nailbed at each of the following sites: supraspinatus insertion at humeral greater tuberosity, common flexor tendon insertion at medial epicondyle, and the common extensor tendon insertion at lateral epicondyle, hip extensor insertion at greater trochanter, quadriceps femoris insertion at superior portion of patella, patellar ligament insertion at inferior pole of patella, patellar

ligament insertion at tibial tuberosity, achilles tendon insertion at calcaneus, and plantar fascial insertion at the calcaneus. Enthesitis was defined as tenderness to palpation. In addition to the joint and enthesis examination, all patients were palpated at 3 bilateral muscular control sites that included the trapezius, proximal lateral forearm, and lateral buttock.

Data collection

A study questionnaire consisting of demographic and historical questions was completed by the parents or guardians, and, when appropriate, the subjects themselves. Following this encounter, a chart review of all enrolled subjects was completed to characterize their IBD diagnosis, other associated complications and extraintestinal manifestations, current medication use, and prior and current laboratory data. Wherever possible, clinical information about prior diagnoses obtained from the study questionnaire was confirmed by medical record review.

Statistical analysis

Subject demographic and clinical characteristics were summarized using percentiles or medians with interquartile (IQR) and/or total ranges. The association of clinical characteristics and enthesitis was determined using Wilcoxon rank-sum or Fisher's exact tests, as appropriate. P-values less than 0.05 were considered statistically significant. Stata 12 (Stata-Corp, College Station, TX, USA) was used for all statistical analyses.

Approval

The study was approved by the Institutional Review Board.

Results

Subject demographics are summarized in Table 1. Subjects had a median age of 16 years (IQR 12–18). There were equal numbers of males and females, and three-quarters of subjects were white. Thirty-two subjects (74%) had CD, 10 subjects (23%) had IC, and 1 subject (2%) had UC. Additional clinical information about the subjects' IBD, medication use, laboratory data, and self-reported pain and activity levels are listed in Table 2.

At least one tender enthesis (range 1–13) was observed in 21% of the subjects, while 12% had 3 or more tender entheses (Table 3). The most commonly affected entheses were the patellar ligament insertion on the inferior patella, the hip extensor insertion at the greater trochanter, and the supraspinatus insertion at the humeral greater tuberosity. For any given enthesis site, subjects had symmetric tenderness half of the time. Among those subjects examined by two investigators, there was clinical agreement about the presence or absence of enthesis tenderness at 71/72 sites (98.6%). No subjects had active arthritis.

The median parental or self-assessment of musculoskeletal pain intensity within the last week was 0 (no pain) (IQR 0–6). Subjects with at least 1 tender enthesis reported a higher intensity of pain than those without enthesitis ($p=0.03$) (Table 4). There was no association between enthesitis and several other clinical variables, including IBD subtype, increased IBD activity index, elevated inflammatory markers, and levels of physical activity.

Subjects with enthesitis were more likely to have tenderness at more muscular control sites than those without enthesitis ($p<0.01$). Tenderness at 1 or more muscular control sites was observed in 89% of subjects with enthesitis and only in 24% of subjects without enthesitis. Tenderness at the control sites of the trapezius, proximal lateral forearm, and lateral buttock

in subjects with enthesitis was found in 67%, 56% and 44%, respectively. In comparison only 18%, 12% and 0% of subjects without enthesitis were tender at the same control sites.

Regarding other extraintestinal manifestations, one subject (2%) had a history of arthritis, and another subject had previously documented enthesitis (Table 1). Psoriasis and erythema nodosum were each previously diagnosed in two subjects (5%). No subjects had a history of uveitis or pyoderma gangrenosum.

Discussion

This cross-sectional study demonstrates that about 1 in 5 children and young adults with IBD have enthesitis as defined by tenderness on examination. The prevalence of enthesitis was greater than other inflammatory extraintestinal manifestations, including arthritis (2%) and erythema nodosum (5%). Interestingly, subjects with enthesitis tended to report greater intensity of recent musculoskeletal pain, suggesting that enthesitis has a notable impact. This observation is in accordance with the finding that enthesitis is an independent predictor of increased pain intensity in children with ERA [16].

The rate of enthesitis in our study is in accordance with that found in a smaller previous study of children with newly diagnosed IBD, in which 21% (4/19) had enthesitis [17]. A study of 234 healthy children aged 8–16 showed that 16% had at least 1 tender enthesis (after excluding the metatarsal heads, which are commonly tender in normal children). In comparison, two-thirds of children with the ERA category of JIA had at least 1 tender enthesis [19].

One study in JIA patients showed that enthesis tenderness on examination does not always correspond to ultrasound abnormalities [14]. However, radiographic evidence of inflammation was statistically more likely in those areas with tenderness. Interestingly, half of those sites with radiographic enthesitis lacked any associated clinical exam findings, suggesting that subclinical enthesitis may be prevalent. In accordance, a recent study of adults with IBD without any musculoskeletal symptoms or abnormal exam findings, reported that a majority had radiographic findings suggesting subclinical enthesitis, including erosions and abnormal bloodflow in 16% [20]. These findings were not found in control subjects. This study supports the hypothesis that enthesitis is a prevalent IBD extra-intestinal manifestation and that many patients have subclinical musculoskeletal manifestations that can lead to articular damage.

The presence of more pain intensity over the past week, as well as more frequent tenderness at the muscular control sites in subjects with enthesitis, raises the question of whether tenderness at the entheses reflects an inflammatory process, lower pain thresholds, or a combination of the two. A future study comparing physical examination to ultrasound findings may answer this question. One hypothesis is that undertreated enthesitis could predispose affected individuals to experience more pain elsewhere. The study of healthy school children also showed that those with enthesis tenderness also reported tenderness at control sites at lower applied pressures [13]. Nevertheless, in our subjects the presence of enthesitis did not seem to affect their level of activity.

This study had several limitations. First, this was a pilot study with a limited set of subjects, each examined at a single point in time. As such we were underpowered to assess the relationship between enthesitis with other clinical characteristics, including arthritis, HLA-B27 positivity, and IBD phenotype and disease activity. Previous studies of children and adults with IBD, for example, have showed that arthritis tends to occur more commonly among those with colonic disease [3,21,22]. Future studies should be powered to make these statistical comparisons.

Additionally, our cohort consisted predominantly of individuals with well-controlled bowel disease and few other extraintestinal manifestations (including arthritis), who were receiving treatment with disease modifying anti-rheumatic agents or biologics. One could speculate that patients with less active intestinal disease may be at lower risk for other extraintestinal inflammatory conditions. Many of the therapies used to control the intestinal disease of IBD also are effective for arthritis and enthesitis, including TNF antagonists (used by almost half of subjects), salicylate derivatives (used by over 75%), cytotoxic medications such as methotrexate (along with azathioprine and 6-methylpurine, used by 33%), and oral steroids (used by 16%). Perhaps this explains why the proportion of our subjects with enthesitis was similar to the background prevalence among otherwise healthy children [13]. The widespread use of these therapies, often in combination, for many children with IBD may also explain the lower rates of arthritis emerging from more recent studies [5,23] in comparison with older studies [2,3]. Of note, several potentially eligible subjects with more active bowel disease declined participation in this study. The inclusion of subjects with more severe bowel disease in future studies may identify a higher proportion of patients with enthesitis.

In conclusion, enthesitis is a prevalent extra-intestinal manifestation of children and young adults with IBD that is significantly associated with reported musculoskeletal pain. The most commonly affected entheses were the patellar ligament insertion at inferior pole of patella, hip extensor insertion at greater trochanter, and supraspinatus insertion at humeral greater tuberosity. Further studies should address the impact of enthesitis on function, quality of life, and pain intensity over time in children and young adults with IBD. Future studies should also investigate the presence of subclinical enthesitis by imaging, the association of enthesitis with IBD bowel activity and arthritis, and response of enthesitis to therapy.

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Table 1

Subjects

Clinical characteristic	N (%)
Age, median (IQR)	16 (12–18)
Gender	
Male	22 (51)
Race	
White	33 (76)
Black	8 (20)
Other	2 (5)
IBD type	
Crohn disease	32 (74)
Ulcerative colitis	1 (2)
Indeterminate colitis	10 (23)
Other medical conditions	
Arthritis	1 (2)
Enthesitis	1 (2)
Erythema nodosum	2 (5)
Pyoderma gangrenosum	0
Acute anterior uveitis	0
Psoriasis	2 (5)
Total	43

Legend: IBD: inflammatory bowel disease; IQR: interquartile range

Table 2

Clinical characteristics of study subjects by IBD type

	All (N=43)	CD (N=32)	UC (N=1)	IC (N=10)
Time from diagnosis (years), median (IQR)	2.7 (1.3–4.8)	2.8 (1.3–4.5)	2.6	3.2 (1.4–5.8)
Bowel surgery,† n (%)	10 (23)	10 (32)	0	0
Location (CD), n (%)	-	-	-	-
Small intestine only	-	2 (6)	-	-
Large intestine only	-	3 (9)	-	-
Small and large intestine	-	27 (84)	-	-
Location (UC/IC), n (%)	-	-	-	-
Rectosigmoid	-	-	0	1 (10)
Left sided	-	-	0	7 (70)
Pancolitis	-	-	1 (100)	2 (20)
Medications, n (%)	-	-	-	-
TNF inhibitor	20 (46)	15 (47)	1 (100)	4 (40)
Steroids*	7 (16)	6 (19)	0	1 (10)
5-ASA	34 (79)	24 (75)	1 (100)	9 (90)
Immune modulators**	14 (33)	10 (31)	0	4 (40)
Antibiotics***	10 (23)	7 (22)	1 (100)	2 (20)
Nutritional****	9 (21)	8 (25)	0	1 (10)
Pediatric Activity Index, ° median (IQR)	-	2.5 (0–6.3)	40	0 (0–0)
Labs	-	-	-	-
HLA-B27+, n (%)	0/1 (0)	-	-	0/1 (0)
ANCA+, n (%)	8/15 (53)	5/10 (50)	1/1 (100)	2/10 (20)
Hemoglobin, median (IQR)	13.4(12.5–14.3)	13.1(12.5–14.3)	13.3	13.7(11.8–14.4)
Albumin, median (IQR)	4.4 (4.2–4.7)	4.4 (4.2–4.6)	4.2	4.6 (4.3–4.8)
ESR, median (IQR)	6 (3–12.5)	6 (3–16)	4	4 (3–8)
Joint pain in last week (VAS 0–10), median (IQR)	0 (0–2)	0 (0–1)	0	1 (0–3)
Activity level, n (%)	-	-	-	-
Not active	1 (2)	1 (3)	-	0
A little active	7 (16)	7 (23)	-	0
Regular activity	19 (44)	12 (40)	-	7 (70)
Pretty active	11 (26)	9 (30)	-	2 (20)
Very active	3 (7)	1 (3)	1 (100)	1 (10)

Legend: IBD: inflammatory bowel disease; CD: Crohn disease; UC: ulcerative colitis; IC: indeterminate colitis; IQR: interquartile range; TNF: tumor necrosis factor; 5-ASA: 5-aminosalicylic acid; ANCA: anti-neutrophil cytoplasmic antibody; ESR: erythrocyte sedimentation rate; VAS: visual analog scale.

† Bowel surgery refers to intestinal procedures (e.g., resection, ostomies) not including feeding tube insertion/ removal or biopsies.

* Steroids signifies systemic corticosteroid use, either oral or rectal.

** Immune modulators include azathioprine, 6-methylpurine, and methotrexate.

*** Antibiotics used for intestinal disease, such as ciprofloxacin or metronidazole.

**** Nutritional formulas, taken either orally or via feeding tube, for intestinal disease and nutrition.

° PCDAI (Pediatric Crohn Disease Activity Index) or PUCAI (Pediatric Ulcerative Colitis Activity Index, which was calculated for UC and IC subjects).

Table 3

Distribution of enthesitis among study subjects

Enthesis	Any N (%)	Unilateral N (%)	Bilateral N (%)
Patellar ligament insertion at inferior pole of patella	5 (12)	4 (9)	1 (2)
Hip extensor insertion at greater trochanter	4 (9)	2 (5)	2 (5)
Supraspinatus insertion at humeral greater tuberosity	4 (9)	1 (2)	3 (7)
Common flexor tendon insertion at medial epicondyle	2 (5)	1 (2)	1 (2)
Patellar ligament insertion at tibial tuberosity	2 (5)	1 (2)	1 (2)
Plantar fascial insertion at the calcaneus	2 (5)	1 (2)	1 (2)
Common extensor tendon insertion at lateral epicondyle	1 (2)	0 (0)	1 (2)
Quadriceps femoris insertion at superior portion of patella	1 (2)	0 (0)	1 (2)
Achilles tendon insertion at calcaneus	1 (2)	1 (2)	0 (0)

Table 4

Comparison of features among subjects with and without enthesitis

	No enthesitis (N=34)	Enthesitis (N=9)	p-value
Age, median (IQR)	16.5 (12.4–17.4)	14.9 (12.1–16.9)	0.53
Gender, N (%)	-	-	-
Male	18 (53)	4 (44)	0.21
IBD type, N (%)	-	-	-
CD	26 (76)	6 (67)	0.55
UC	1 (3)	0	0.60
IC	7 (21)	3 (33)	0.42
History of bowel surgery†, N (%)	8 (24)	2 (22)	0.93
Joint pain in the prior week (VAS 0-10), median (IQR)	0 (0,1)	1 (1, 2)	0.03
Activity level, N (%)	-	-	0.29
Not active	1 (3)	0	-
A little active	5 (15)	2 (22)	-
Regular activity	14 (41)	5 (56)	-
Pretty active	10 (29)	1 (11)	-
Very active	3 (9)	0	-
Labs, median (IQR)	-	-	-
Hemoglobin	13.3 (12.2, 14.2)	14.6 (13.8, 15)	0.13
Albumin	4.4 (4.2, 4.6)	4.5 (4.3, 4.7)	0.59
ESR	5.5 (3, 12)	9 (6, 15.5)	0.44
Tender control sites on exam, median (IQR)	0 (0, 0)	3 (2, 3)	<0.01

Legend: IQR: interquartile range; CD: Crohn disease; UC: ulcerative colitis; IC: indeterminate colitis; VAS: visual analog scale; ESR: erythrocyte sedimentation rate

† Bowel surgery refers to intestinal procedures (e.g., resection, ostomies) not including feeding tube insertion/ removal or biopsies