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Original Research

Extraintestinal Manifestations in Children Diagnosed with Inflammatory Bowel Disease

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Abstract

Objectives: We aimed to evaluate the frequency of extraintestinal manifestations (EIM) in children with inflammatory bowel disease (IBD) and the correlation of EIM with disease activity index, disease type and disease age.

Methods: Records of patients who were under the 18 years of age and followed up with the diagnosis of IBD were included in the study. The demographic characteristics of the patients, the age of the patients, the sex of the patients, the type of disease and the age of the disease were recorded. When patients were enrolled in the study disease activity indexes were calculated by examining the physical examination and laboratory values of the patients in their last visits, by using the Pediatric Ulcerative Colitis Activity Index (PUCAI) in Ulcerative Colitis (UC) and the Pediatric Crohn's Disease Activity Index (PCDAI) in Crohn's Disease (CD).

Results: It was conducted with a total of 44 patients, 40.9% (n=18) females and 59.1% (n=26) males diagnosed with IBD. The ages of the patients participating in the study ranged from 8 to 19 and the mean was found to be 14.64±3.19 years. According to the type of disease; 27.3% of the patients were CD and 72.7% were UC. When the disease activity is examined; 37.2% were in remission, 37.2% were mild, 16.3% moderate and 9.3% severe. The incidence of EIM in females is 77.8% and 65.4% in males. The incidence of EIM is 75% in CD and 68.8% in UC. Hepatobiliary involvement was detected in 41.5% (n=17) of the patients, joint involvement in 29.5% (n=13), osteopenia in bone in 16.3% (n=7), osteoporosis in 7% (n=3), ocular involvement (uveitis) in 2.3% (n=1) and skin involvement (erythema nodosum) in 2.3% (n=1).

Conclusion: EIM are common in childhood IBD patients. It should be kept in mind that EIM are as common in UC as CD.

Keywords: Extraintestinal manifestations, pediatric inflammatory bowel disease, pediatric ulcerative colitis, pediatric crohn's disease

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Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition characterized with alternating periods of flares and remissions and mainly affecting gastrointestinal tract sometimes accompanied by possible extraintestinal manifestations (EIM).[1] IBD patients are classified as Ulcerative Colitis (UC), Crohn's Disease (CD) and indeterminate IBD (IBD-I). IBDs have a significantly negative effect on the quality of life, are associated with high morbidity, require frequent hospitalization, and may be characterized with complications which may sometimes require surgical intervention.[2] While the etiology and pathogenesis of IBD are yet to be completely elucidated, the effects of genetic and

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environmental factors are widely accepted.[3] CD and UC are seen more frequently in developed countries compared to developing countries, and they are one of the most common chronic gastrointestinal tract diseases in children living in developed countries.[4] A study in our country found the incidence of IBD to be lower than North and West Europe and similar to Middle East with the incidence of UC being determined to be 4.4/100.000 and CD to be 2.2/100.000.[5] Both CD and UC commonly manifest with abdominal pain and diarrhea. Rectal bleeding is more common in UC (83-95%) compared to CD (40%).[6] There might be delays in diagnosis as children with IBD have different clinical presentations and sometimes non-specific symptoms. While growth retardation is the first and only manifestation in 5% of the patients, EIMs are the presenting complaint in 6-35%.[7] While IBDs may involve all organ systems, the most commonly involved extraintestinal systems include skin, eye, skeletal system, joints, liver and biliary tract. EIM associated with skin include erythema nodosum, pyoderma gangrenosum, psoriasis and aphthous stomatitis. Other EIM include peripheral arthritis, axial arthropathy, primary sclerosing cholangitis (PSC), pancreatitis, chronic active hepatitis and uveitis.[8] As about 35% of the pediatric IBD patients may present with EIM preceding intestinal symptoms, IBD should always be considered and included in differential diagnosis in children with symptoms and signs consistent with EIM.[9] The most common EIM in children with IBD is arthritis (8-26%) and aphthous stomatitis (7-21%). The same study showed that the most common EIM developing after the diagnosis is arthritis (17%) and osteopenia/osteoporosis (15%).[7] Bone remodelling and growth is inhibited in pediatric IBD patients. IBD has been found to be associated with autoimmune cutaneous diseases (e.g., psoriasis, vitiligo, polymyositis, lupus and scleroderma). In particular, while psoriasis is seen in 1-2% of the general population, its prevalence is 7-11% in patients with IBD.[10] The severity of the disease is associated with EIMs. We aimed to evaluate the frequency of EIM in children with IBD and the correlation of EIM with disease activity index, disease type and disease age.

Methods

The study included 44 patient records consisting of patients of both sexes younger than 18 years who were being followed up for IBD in Dr. Sadi Konuk Training and Research Hospital, Pediatric Gastroenterology Outpatient Clinic between 01.01.2017 and 31.12.2019. This retrospective study was initiated after approval from Dr. Sadi Konuk Training and Research Hospital, Ethics Committee for Non-Drug and Non-Medical Device Studies with the decision no. 2020/277 dated 22.06.2020. The study was carried out in accordance with the Helsinki Declaration. When the medical records were reviewed, it was observed that IBD was diagnosed based on The European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) revised porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents, original porto criteria and Paris classification of pediatric IBD. Intestinal involvement areas and involvement characteristics were reviewed from the colonoscopy reports of all of the patients who were followed up. Demographic characteristics, age, sex, disease duration and disease type of the patients were recorded. The patients' disease activity indices were calculated based on the physical examination and laboratory findings during their last clinic visit before the study using PUCAI (Pediatric Ulcerative Colitis Activity Index) in UC and PCDAI (Pediatric Crohn's Disease Activity Index) in CD. PUCAI is a non-invasive, valid, highly reliable and sensitive index to assess the disease activity in pediatric UC. PUCAI is a non-invasive disease activity index consisting of 6 items with a score of 0 to 85 to be used in pediatric UC clinical trials. According to PUCAI, a score of <10 indicates remission, a score of 10 to 34 mild disease activity, a score of 35 to 64 moderate disease activity and a score of >65 severe disease activity. PCDAI is a scoring system to measure the disease activity by also including laboratory markers. PCDAI is scored on a scale of 100. According to PCDAI, a score of <10 indicates remission, a score of 10 to 27.5 mild disease activity, a score of 30 to 37.5 moderate disease activity and a score of >40 severe disease activity. Height, weight, skin signs, joint signs, eye signs, hepatosplenomegaly, jaundice, perianal inspection and all other systemic signs were evaluated in the physical examination during the patients' last clinic visit. Eye examination findings were noted from the patients' medical records. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamine transferase (GGT), alkaline phosphatase (ALP) and albumin levels of the patients during their last visit were assessed. Their bone densitometry measurements were evaluated. HbsAg, Anti Hbs, Anti HAV IgM, Anti HAV IgG, Anti HCV and autoimmune hepatitis workup which were requested to rule out other liver disorders from patients detected to have asymptomatic hypertransaminasemia which may occur in IBD were assessed. Ultrasonography (USG) and Magnetic resonans cholangioportography (MRCP) imaging results were assessed. The results of Dual Enerji X - ray Absorpsiyometri (DEXA) scans performed during the patients' follow-up were recorded. L1-L4 DEXA SDS of -1 to -2.5 was considered to be osteopenia, and less than -2.5 to be osteoporosis. The demographic characteristics, the incidence and characteristics of EIMs, and the correlation of these findings with disease activity index, disease type and disease duration were examined in children diagnosed with IBD.

Statistical Analysis

The Number Cruncher Statistical System (NCSS) software was used for the statistical analysis of the data. Categorical data were expressed as numbers and percentages, while continuous data were expressed as mean and standard deviation (median, and minimum-maximum values, where required). The chi-square test and Fisher's exact test, Fisher-Freeman-Halton exact test were applied for the comparison of categorical variables. Mann Whitney u-test is used to compare the continuous variables in paired groups with normal distrubution. The level of statistical significance was accepted as 0.05 for all analyses.

Results

The study included 44 patients. The patients' ages varied from 8 to 19 years with a mean age of 14.64±3.19 years. 40.9% of the patients (n=18) were females, and 59.1% (n=26) were males. With regards to disease type, 27.3% of the patients had CD and 72.7% had UC. Disease duration varied from 8 to 115 months with a median disease duration of 26 months. With regards to disease activity, 37.2% of the patients were in remission, 37.2% had mildly active disease, 16.3% had moderately active disease and 9.3% had severely active disease. Comorbidities were detected in 25% of the patients (Table 1).

According to the analysis based on the presence of EIMs, there was no statistically significant difference between the ages of the patients (p>0.05). With regards to sex, EIMs was detected in 77.8% of the female patients and in 65.4% of the male patients. No statistically significant difference was detected between the rates of occurrence of EIMs by sex (p>0.05). With regards to disease type, EIMs were detected in 75% of the CD patients and in 68.8% of the UC patients. No statistically significant difference was detected between the rates of occurrence of EIMs occurrence by disease type (p>0.05). With regards to EIMs, no statistically significant difference was detected between the disease activity indices of the patients at study entry (p>0.05). EIMs were detected in 57% of the patients with moderate disease activity (n:7), 75% of the patients with mild disease activity (n:16) and 62% of the patients who were in remission (n:16) (p>0.05). No statistically significant difference was detected between the rates of occurrence of EIMs by disease activity (p>0.05). No statistically significant difference was detected between the rates of occurrence of EIMs by the presence of comorbidities (p>0.05) (Table 2). The ages of the patients with severe disease activity and EIMs vary between 8 and 17 years with a mean of 13.00±3.74. 50% of the patients with severe disease activity (n:4) were males, and 50% were females. All of the patients with severe disease activity (n:4) had the diagnosis of CD with EIMs. Approximately 41.5% of the patients (n=17) were observed to have hepatobiliary involvement, 16.3% (n=7) to have osteopenia, 7% (n=3) to have osteoporosis, 2.3% (n=1) to

Table 1. The Evaluation of the Descriptive Characteristics of the Inflammatory Bowel Diseases

	n (%)
Sex	
Female	18 (40.9)
Male	26 (59.1)
Disease Type	
Crohn's Disease	12 (27.3)
Ulcerative Colitis	32 (72.7)
Disease Activity	
In remission	16 (37.2)
Mild	16 (37.2)
Moderate	7 (16.3)
Severe	4 (9.3)
Comorbidity	
No	33 (75.0)
Yes	11 (25.0)

Table 2. The Evaluation of the Descriptive Characteristics by Extraintestinal Manifestations

	Extraintestinal Manifestations		
	No (n=13)	Yes (n=31)	p
Age			
Mean±SD	15.23±3.00	14.39±3.28	
Sex			
Female	4 (22.2)*	14 (77.8)*	[b]0.376
Male	9 (34.6)*	17 (65.4)*	
Disease Type			
Crohn's Disease	3 (25.0)*	9 (75.0)*	[c]1.000
Ulcerative Colitis	10 (31.3)*	22 (68.8)*	
Disease Duration (months)			
Min-Max (Median)	8-96 (22)	8-115 (28)	[a]0.132
Disease Activity Index			
Min-Max (Median)	0-35 (12.5)	0-55 (15)	[a]0.379
Disease Activity			
In remission	6 (37.5)*	10 (62.5)*	[d]0.424
Mild	4 (25.0)*	12 (75.0)*	
Moderate	3 (42.9)*	4 (57.1)*	
Severe	0 (0.0)*	4 (100.0)*	
Comorbidity			
No	8 (24.2)*	25 (75.8)*	[c]0.256
Yes	5 (45.5)*	6 (54.5)*	

[a]Mann Whitney U Test; [b]Pearson Chi-Square Test; [c]Fisher Freeman Halton Test; [d]Fisher's Exact Test; *n (%).

have eye involvement (uveitis), 29.5% (n=13) to have joint involvement and 2.3% (n=1) to have skin involvement. USG finding was observed in 39% of the patients (n=16), and MRCP finding was observed in 25% of CD patients with severe disease activity (n=1) (Fig.1).

Discussion

In a study based on the data obtained from multi-center pediatric IBD records, the mean age of the pediatric IBD patients at diagnosis was 10 years. 15% of the patients were diagnosed before the age of 6 (6% before the age of 3), 48% were diagnosed between the ages of 6 and 12, and 37% were diagnosed between the ages of 13 and 17.[11] In our study, the ages of the pediatric patients varied from 8 to 19 years with a mean age being detected to be 14 years. Small differences have been reported in the incidence of IBD by sex. In their study in 17 different cohorts from 16 different regions of Europe, North America, Australia and New Zealand comparing the differences of IBD by sex, Shah et al. reported that there is a male dominance in the incidence of CD during middle-to-late childhood and early adolescence (ages 5 to 14), however, the risk of CD is increased in females with advancing age; and they detected that the incidence of UC is higher in females of ages 5 to 9 years, there is no significant difference until age of 45 years and there is a male dominance after the age of 45 years.[12] In their retrospective multi-center study in 2015 involving Turkish children diagnosed with IBD, Cakir et al.[13] determined that 51.4% of the patients were females. There was a slight male dominance in our study. In the same study, 70.9% of the patients were detected to have UC, 22.8% to have CD and 6.3% to have IBD-I.[13] With regards to disease type in our study; 27.3% of the patients had CD and 72.7% had UC. Differently from the literature, there was no patient with IBD-I colitis in our study.[14] In their study, Datson et al.[15] found close correlation between disease type, and the presence and incidence of extraintestinal manifestations. Statistically significant difference was detected in the incidence of aphthous stomatitis, primary sclerosing cholangitis and erythema nodosum between UC and CD.

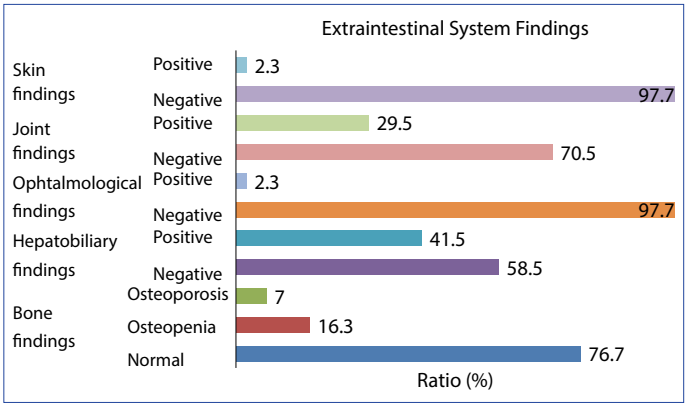

Figure 1. The Evaluation of the Descriptive Characteristics by Extraintestinal Manifestations.

In the literature, in their retrospective study in 329 patients, Greuter et al.[16] reported that EIMs are more frequent in CD compared to UC and IBD-I. In their cohort study involving 1649 pediatric patients with IBD who were followed up for 15 years, Jose et al. stated that the incidence of EIM is higher in children compared to adults and it may be as high as 28%, and reported that these manifestations are independent from the disease type (e.g., CD or UC).[7] While there was no statistically significant difference detected in terms of EIMs between UC and CD in our study, it was detected that EIMs in children diagnosed with UC were as frequent as EIMs in CD consistent with study by Jose et al.[7]

Cohort studies in the literature indicate that the incidence of EIMs increases with the increasing disease duration during the follow-up period after diagnosis.[17] This is consistent with the fact that data obtained from Pediatric IBD Consortium Registry involving 1649 children with IBD indicated that the cumulative incidence of EIMs is 9% at 1 year, 19% at 5 years and up to 29% at 15 years after the diagnosis. Developing an EIM increases the likelihood of developing other EIMs.[11]

There was no statistically significant difference between disease duration and EIMs in our study. Given the fact that the median disease duration of our study population is 26 months, different results may be obtained with studies with longer follow-up periods or larger samples.

Studies have detected that increased disease activity index is correlated with EIMs.[15] In their cohort study involving 301 children diagnosed with IBD, Nir et al.[18] detected that disease severity and the frequency of disease relapses are correlated with EIMs. The present study did not detect a statistically significant difference between disease activity index and EIMs. This finding was associated with fact that our sample being small.

In their retrospective study in 2019, Shan et al.[19] demonstrated that the incidence of EIM is higher in CD compared to UC, and the risk of developing EIM is higher in CD with moderate-to-severe disease activity. In their cohort study involving 1009 children with IBD, Dotson et al.[15] found a significant correlation between the severity of IBD and the likelihood of developing EIMs and detected that this correlation is stronger in CD compared to UC. In our study, the disease type of all patients with severe disease activity index and EIMs was detected to be CD.

In the trial by Kucharska et al.[20] to examine the presence of hepatobiliary disease associated with pediatric IBD, while

PSC was the most commonly detected condition, abnormal liver enzymes were also found to be frequent. It was found that idiopathic chronic cholestatic hepatitis diseases characterized with inflammation and fibrosis such as PSC is associated with UC, and the likelihood of developing PSC in children with IBD is 3-fold higher than CD.[15] In our study, hepatobiliary involvement was the most common EIM. The most common hepatobiliary manifestation was abnormal hypertransaminasemia.

Inflammatory arthropathies are one of the most common EIMs seen in IBD patients with an incidence varying from 7 to 15%.[8] They are typically pauciarticular and asymmetric migratory, and they usually do not lead to joint deformation. Axial involvement is usually asymptomatic or seen as sacroiliitis, and less often as progressive ankylosing spondylitis.[21] Perianal involvement in IBD may present as perianal erythema, abscess, fistula, perianal fissure. The incidence of perianal involvement in CD is around 50%.[22]

In their retrospective study in 2017, Guz-Mark et al.[23] showed that osteopenia and osteoporosis is higher in adult IBD patients with pediatric onset and associated with low Z-score at diagnosis. In their study in 40 children diagnosed with IBD, Lopez et al. found that bone mineral density was measured to be low in 25% of the patients.[24] Consistent with the literature, DEXA assessments of our study population showed osteopenia findings in 16.3% of the patients and osteoporosis findings in 7%. In the literature, in their retrospective study involving 301 patients in 2017, Nir et al.[18] found that the rate of joint involvement was 26.9%, and higher in female patients. Consistent with the literature, in the present study, joint involvement was detected in 29.5% of our patients and to be higher in females.

In their study published in 2017, Naviglio et al.[25] reported 1.06% as the prevalence of uveitis. Eye manifestations of IBD are seen in 10% of the patients and include episcleritis, scleritis, uveitis and corneal findings associated with eye involvement, and cataract and glaucoma associated with treatment. Consistent with the literature, the rate of uveitis was detected to be 2.3% in our study.

In the literature, the incidence of skin involvement in IBD varies from 10 to 15%. In their study in 1009 children with IBD, Dotson et al.[15] reported the incidence of erythema nodosum to be 2.8% and the incidence of pyoderma gangrenosum to be 0.3%. In our study, erythema nodosum was detected 2.3% of the patients. Pyoderma gangrenosum was not observed in any of our patients during the follow-up period.

In the present study, the majority of the patients were diagnosed with UC, and there was a slight male dominance. It was observed that EIMs are as frequent in the patients diagnosed with UC as CD. EIMs were not found to be correlated with disease type, disease duration and disease activity index. With regards to disease activity index, patients with severe disease activity and EIM had CD. While osteopathy, joint, skin and eye manifestations were consistent with the literature, differently from the literature, the most common hepatobiliary manifestation was detected to be abnormal hypertransaminasemia. The limitation of the study is the small sample size.

Conclusion

It would be beneficial for pediatric gastroenterology clinics treating patients diagnosed with inflammatory bowel diseases to remember that extraintestinal manifestations are common in pediatric IBD patients and these manifestations may be as frequent in UC as CD. The present study did not find a statistically significant correlation between extraintestinal manifestations, and disease type, disease duration and disease activity index in children diagnosed with IBD. We believe it was caused by the short follow-up period and small sample size.

Disclosures

Ethics Committee Approval: This retrospective study was initiated after approval from Dr. Sadi Konuk Training and Research Hospital, Ethics Committee for Non-Drug and Non-Medical Device Studies with the decision no. 2020/277 dated 22.06.2020.

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Conflict of Interest: None declared.

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