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ORIGINAL PAPER

Extraintestinal manifestations in paediatric-onset inflammatory bowel disease depending on disease location and activity

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ABSTRACT

Aim of the study: The aim of the study was to determine the prevalence and types of extraintestinal manifestations (EIMs) in paediatric-onset inflammatory bowel diseases (IBD), i.e. Crohn's disease (CD) and ulcerative colitis (UC), depending on disease activity and location, and to determine whether the presence of EIM is associated with a distinctive clinical course of IBD.

Material and methods: The medical records of 287 children with IBD with or without EIMs were retrospectively analysed, especially regarding the following characteristics: age at diagnosis, clinical symptoms, nutritional status, the Paris Classification, and IBD activity.

Results: The study population of 287 children comprised 147 patients with UC (mean age 12.9 years) and 140 patients with CD (mean age 14.1 years). EIMs were diagnosed in 60 patients (20.9%). The most frequent immune-related EIM in UC patients was primary sclerosing cholangitis (PSC); the collective proportion of PSC and PSC/autoimmune hepatitis (AIH) was 14.9%. Arthropathy was the most prevalent EIM in the subpopulation of CD participants (10%). Pancolitis was a risk factor for EIMs in the UC patients (E4/E0-3 OR 2.3, 95% CI 1.05–5.06, $p = 0.037$), and especially for PSC and AIH/PSC (OR 2.77, 95% CI 1.09–7.06, $p = 0.032$). Nevertheless, patients with EIMs presented with bloody diarrhoea less frequently (69% vs. 90%, $p = 0.011$). The CD EIM(+) and EIM(–) patients did not differ significantly regarding the symptoms at hospital admission. No correlation was revealed between disease location or behaviour and EIM occurrence. The impact of the presence of EIM on CD activity is inconclusive.

Conclusions: EIMs are a significant issue in the population of children with IBD; they developed in 20.9% of our patients. Determination of the prevalence of these manifestations and related risk factors might raise awareness of the problem and facilitate diagnosis and therapy.

KEY WORDS:

inflammatory bowel disease, extraintestinal manifestations, paediatric ulcerative colitis, paediatric Crohn's disease.

INTRODUCTION

Inflammatory bowel disease (IBD) and its major forms, i.e. Crohn's disease (CD) and ulcerative colitis (UC), have systemic implications, which, as suggested by Vavricka *et al.* [1], can be divided into extraintestinal manifestations (EIM) directly related to immune mechanisms and non-immune extraintestinal complications resulting from malabsorption [1, 2]. Extraintestinal manifestations may develop prior to or after IBD diagnosis and

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include different forms of dermatitis, subcutaneous tissue and mucous membrane disorders, erythema nodosum, oral aphthous ulcers, axial or peripheral arthropathies, primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH) and the so-called overlap syndrome, interstitial and glomerular nephritis, autoimmune haemolytic anaemia, or vasculitis, as well as ocular symptoms such as uveitis, keratitis, and conjunctivitis. The most common extraintestinal complications are: cholelithiasis, nephrolithiasis, osteoporosis, and peripheral neuropathies due to nutritional deficiencies. Adverse effects associated with IBD medication are a separate issue [1].

Jose and Heyman provided more detailed classification of extraintestinal manifestations into five categories: 1) colitis-related dermatological, ophthalmological, musculoskeletal, and oral pathologies; 2) hepatobiliary disease that is independent of the activity of the underlying intestinal problem; 3) extraintestinal manifestations secondary to complications of bowel disease: nephrolithiasis, obstructive uropathy, colovesical fistula, and gallstones; 4) iatrogenic, e.g. drug-induced bone marrow suppression and metronidazole-related myopathy; and 5) other e.g. amyloidosis or cancer [3].

We found Vavricka *et al.*'s classification to be simpler, clearer, and more consistent with the purposes of our study. The authors noted that as many as 50% of patients with IBD developed extraintestinal manifestations within 30 years of diagnosis. It has also been estimated that EIMs may precede the diagnosis in approximately 25% of IBD sufferers [1].

AIM OF THE STUDY

The aim of the study was to determine the frequency and type of EIMs in children with IBD depending on disease activity and location.

MATERIAL AND METHODS

Medical records of 287 children with inflammatory bowel disease were retrospectively analysed. The patients had been hospitalised and diagnosed in the Department of Paediatrics, Unit of Gastroenterology, Medical University of Silesia in the years 2005–2017.

The study population was subdivided, based on the type of IBD, into two subpopulations, i.e. 147 children with UC: 67 girls and 80 boys (46% and 54%, respectively) aged 2 to 18 years (mean age 12.9 years). The mean age at diagnosis was slightly lower in boys (12.2 years) compared to girls (13.8 years), but the difference was not statistically significant ($p > 0.05$). The other subpopulation consisted of 140 patients with CD: 57 girls and 83 boys (40.7% and 59.3%, respectively) aged 5 to 18 years (mean age 14.1 years). The mean age at diagnosis was slightly lower in girls (13.9 years) than in boys (14.2), but again, the difference did not reach the level of statistical significance ($p > 0.05$).

The diagnosis was made based on the Porto criteria (2005) [4] and revised Porto criteria (2014) [5]. The medical histories of patients and data obtained in physical examinations were analysed, especially the following:

- anthropometric measurements for nutritional status assessment based on percentile charts of the OLAF study [6],
- disease activity using the Paediatric Crohn's Disease Activity Index (PCDAI) and the Paediatric Ulcerative Colitis Activity Index (PUCAI) [7, 8],
- disease location and type according to the Paris classification [9].

Immune-related extraintestinal manifestations were confirmed in 60 (20.9%) out of 287 children (Table 1).

Data on the nutritional status and laboratory parameters were obtained at the time of diagnosis, while IBD extraintestinal manifestations were analysed throughout the follow-up period. The normality of data distribution was analysed with the Shapiro-Wilk test. In statistical analysis we used the U-Mann Whitney test for symptom prevalence and activity indices in the EIM(+) and EIM(–) subpopulations. The null hypothesis of the equal EIM(+) and EIM(–) group size distribution regarding disease activity indices was also tested with the χ^2 test of independence, separately for CD and UC. The Paris classification parameters were also assessed.

RESULTS

AGE AT DIAGNOSIS

Immune-related extraintestinal manifestations were seen in 33 (22.4%) out of 147 children with UC. The mean age at UC diagnosis was 13.04 (SD 3.9) years for EIM(–) and 12.5 (SD 3.49) years for EIM(+) participants ($p > 0.05$). PSC and PSC/AIH were diagnosed at younger age, i.e. 11.8 years. Altogether, early-onset UC (EO-UC, i.e. < 10 years of age) was diagnosed in 23 (20%) EIM(–) patients and eight (24%) EIM(+) patients (see also: Paris classification, Table 5). Amongst these, very early-onset UC (VEO-UC, i.e. < 6 years) was diagnosed in eight and one patient, respectively.

TABLE 1. Characteristics of the study population by sex

Patients	Total (%)	Female (%)	Male (%)
IBD patients	287	124 (43)	163 (57)
UC patients	147 (51.2)	67 (46)	80 (54)
CD patients	140 (48.8)	57 (41)	83 (59)
Total no. of patients with EIM	60 (20.9)	24 (40)	36 (60)
UC patients	33 (22.4)	12 (36)	21 (64)
CD patients	27 (19.3)	12 (44.4)	15 (55.6)

IBD – inflammatory bowel disease, UC – ulcerative colitis, CD – Crohn's disease, EIM – extraintestinal manifestations

While, as mentioned above, in general UC was diagnosed at the age of 2–18 years, the youngest patient diagnosed with EIM was a four-year-old boy (AIH/PSC).

Based on the patients' history, the information about chronological order of EIM appearance relative to UC diagnosis was available for 30 out of 33 children. Most commonly, EIM was diagnosed concomitantly with UC (in 17 out of 30 patients, 56.5%). This included all cases of arthritis and 11 out of 21 cases of PSC, PSC/AIH with known diagnosis time. In five patients EIM was diagnosed prior to UC (17%, mean time 7 months, range 1–13 months) – and all were children with PSC or PSC/AIH overlap syndrome. In eight children (26.5%) EIM appeared later, in one of the subsequent flares of IBD (mean time 21 months, range 1–72). The distinctive part of this group were patients with renal involvement: three out of four children with interstitial nephritis were diagnosed late, after 12, 58, and 72 months of UC.

Twenty-seven (19.3%) out of 140 children with CD had EIMs. The mean age at CD diagnosis was comparable for EIM(+) and EIM(–): 13.9 SD 2.95 years vs. 14.1 SD 2.96 years; $p > 0.05$. EO-CD was diagnosed in 11 (9.7%) EIM(–) patients and two (7%) EIM(+) patients. In each group only one patient complied with VEO-CD criteria, and that was a five-year-old boy without extraintestinal manifestation and a five-year-old girl with interstitial nephritis.

Based on the patients' history, the information about chronological order of EIM appearance relative to CD diagnosis were available for 25 out of 27 patients. Most commonly the first EIM occurred after CD diagnosis – in 14 out of 25 patients, 56% (mean time 12 months, range 4–24 months). This included six out of seven cases of interstitial nephritis, five out of six cases of erythema nodosum, two out of three cases of PSC or PSC/AIH, and four out of 14 cases of arthritis. In three out of 25 patients (12%) EIM was diagnosed concurrently with CD. This included two out of 14 cases of arthritis and one case of interstitial nephritis. In eight patients EIM was diagnosed prior to CD (32%, mean time 11 months, range 2–24 months) – including six cases of arthritis, one case of erythema nodosum, and one case of PSC.

TYPES OF IMMUNE-RELATED EXTRAINTESTINAL MANIFESTATIONS

The occurrence of particular types of extraintestinal manifestations differed between patients with CD and UC, it also varied between the sexes (Table 2).

A total of 60 (20.9%) out of 287 children with IBD developed EIMs. Thirty incidents of extraintestinal manifestations were noted in 27 patients with Crohn's disease (19.3%); one patient with CD was diagnosed with erythema nodosum and arthritis, while two were diagnosed with erythema nodosum and interstitial nephritis. In the UC group 33 children developed EIM – one type occurred in one patient.

The analysis did not reveal a significant difference in the prevalence of EIMs between the sexes ($p = 0.22$). It should be noted though that the most common extraintestinal manifestation of ulcerative colitis, i.e. PSC, was found almost exclusively in boys (85%); also, 75% of the UC sufferers with PSC/AIH overlap syndrome were boys. Arthritis was the most frequent extraintestinal manifestation in girls with UC.

Arthropathy turned out to be the most common extraintestinal manifestation in our participants with Crohn's disease, revealed in 14 (51.9%) out of 27 EIM(+) patients with CD (10% of all CD patients). PSC, on the other hand, developed rarely. PSC or the overlap syndrome were only seen in three children, i.e. 11% of the EIM(+) patients (2.1% of all CD patients).

CLINICAL SYMPTOMS

Clinical symptoms most frequently reported by the UC EIM(+/–) and CD EIM(+/–) patients at the time of diagnosis were analysed. Statistically significant differences were found between UC EIM(+) and UC EIM(–) patients only with respect to bloody diarrhoea ($p = 0.011$). Other differences noted between these groups did not reach statistical significance, although the tendency was seen for abdominal pain and non-bloody diarrhoea to occur more frequently in EIM(+) patients, while weight loss was seen more commonly in EIM(–) patients. No significant differences were noted in the CD group (Table 3).

TABLE 2. Extraintestinal manifestations in children with inflammatory bowel disease

Immune-related extraintestinal manifestations in paediatric-onset IBD	No. of cases	UC			CD		
		$n = 33$ (%)	Percent of patients	Male $n = 21$	$n = 27$ (%)	Percent of patients	Male $n = 18$
Arthritis	19	5 (15)	3.4	1	14 (52)	10	8
PSC	16	14 (42)	9.5	12	2 (7)	1.3	1
Overlap syndrome AIH/PSC	9	8 (24)	5.4	6	1 (4)	0.7	0
Interstitial nephritis	11	4 (12)	2.8	2	7 (26)	5	4
Erythaema nodosum	7	1 (3)	0.7	0	6 (22)	4.2	5
Haemolytic enaemia	1	1 (3)	0.7	0	0	0	0

IBD – inflammatory bowel disease, PSC – primary sclerosing cholangitis, AIH – autoimmune hepatitis, UC – ulcerative colitis, CD – Crohn's disease

TABLE 3. Clinical symptoms most frequently reported at the time of inflammatory bowel disease diagnosis

Clinical symptoms	UC			CD			IBD
	EIM(–) $n = 114$ (%)	EIM(+) $n = 33$ (%)	p	EIM(–) $n = 113$ (%)	EIM(+) $n = 27$ (%)	p	EIM(+) $n = 60$ (%)
Bloody diarrhoea	103 (90)	23 (69)	0.011	37 (33)	10 (37)	0.694	33 (55)
Abdominal pain	42 (37)	17 (51)	0.06	70 (62)	18 (67)	0.685	35 (58)
Weight loss	41 (36)	6 (18)	0.052	59 (52)	14 (63)	0.938	20 (33)
Diarrhoea without blood	11 (9.6)	7 (21)	0.07	72 (64)	20 (74)	0.326	27 (45)
Fever	11 (9.6)	1 (3)	0.191	22 (20)	5 (19)	0.894	6 (10)
Aphthous stomatitis	0	0	–	3 (3)	1 (4)	0.781	1 (2)
Perianal lesions	0	0	–	15 (13)	3 (11)	0.747	3 (5)
Fatigue, malaise	12 (10.5)	4 (12)	0.755	80 (71)	16 (59)	0.253	20 (33)

UC – ulcerative colitis, CD – Crohn's disease, IBD – inflammatory bowel disease, EIM – extraintestinal manifestations

NUTRITIONAL STATUS

The BMI (according to OLAF) was within normal range for the majority of the 147 patients with UC (67%). In one child with UC diagnosed before the age of three years, BMI was considered normal based on weight-for-age percentile charts (within the range of 25–50th percentile for both parameters). Underweight was diagnosed in 34 (23%), overweight in 11 (7%), and obesity in four (3%) of the UC participants. Twenty-three children (70%) of the UC EIM(+) patients presented with normal nutritional status, eight (24%) were underweight, and two (6%) were overweight. No statistically significant differences in BMI were found between the UC EIM(+) and UC EIM(–) patients ($p = 0.525$).

Sixty-five (46.4%) of the CD patients presented with underweight; 69 (49%) had normal body weight, while six (4.2%) were overweight. Fifteen (55.6%) children of the CD EIM(+) subgroup had normal nutritional status; 10 (37%) were underweight and two (7.4%) were overweight. No statistically significant differences in BMI were found between the CD EIM(+) and CD EIM(–) patients ($p = 0.21$).

TABLE 4. Disease activity in children with inflammatory bowel disease – different forms of extraintestinal manifestations

PUCAI/PCDAI		Disease activity			
		Inactive/remission (%)	Mild (%)	Moderate (%)	Severe (%)
UC	UC patients $n = 147$	3 (2)	44 (29.9)	84 (57)	16 (11)
	EIM(–) $n = 114$	2 (1.7)	29 (63.2)	72 (63.2)	11 (9.6)
	EIM(+) $n = 33$	1 (3)	12 (36)	12 (36)	5 (15)
	Extraintestinal manifestations				
	Arthritis $n = 5$	0	1 (20)	3 (60)	1 (20)
	Interstitial nephritis $n = 4$	0	1 (25)	1 (25)	20 (50)
	Erythaema nodosum $n = 1$	0	1 (100)	0	0
	Haemolytic enaemia $n = 22$	0	1 (100)	0	0
	PSC/AIH or PSC $n = 22$	1 (4.5)	11 (50)	8 (36)	2 (9)
CD	CD patients $n = 140$	0	7 (5)	89 (63.6)	44 (31.4)
	EIM (–) $n = 113$	0	5 (4.4)	75 (66.4)	33 (29.2)
	EIM (+) $n = 27$	0	2 (8.3)	14 (52)	11 (40.7)
	Extraintestinal manifestations				
	Arthritis $n = 14$	0	1 (1.7)	6 (42.9)	7 (50)
	Interstitial nephritis $n = 7$	0	1 (14.3)	3 (42.9)	3 (42.9)
	Erythaema nodosum $n = 6$	0	1 (16.7)	2 (33.3)	3 (50)
	PSC/AIH or PSC $n = 3$	0	0	3 (100)	0

PUCAI – Paediatric Ulcerative Colitis Activity Index, PCDAI – Paediatric Crohn's Disease Activity Index, UC – ulcerative colitis, CD – Crohn's disease, EIM – extraintestinal manifestations, PSC – primary sclerosing cholangitis, AIH – autoimmune hepatitis

DISEASE ACTIVITY

The activity of inflammatory bowel disease was assessed with respective indices, i.e. PUCAI and PCDAI [7, 8, 10].

The majority of children presented with moderate UC and CD forms. The mode PUCAI score was 40 for both UC EIM(+) and UC EIM(–) participants, while median score was 30 and 40 points, respectively.

Referring to PCDAI, the mode scores for CD EIM(+) and EIM(–) were 55 at EIM(+) and 40 in EIM(–) patients, while median was 50 and 45 points, respectively. In PCDAI assessment though, the presence of EIM itself entails admission of an additional five (1 EIM) or 10 (≥ 2 EIM) PCDAI points. Thus we also analysed modified PCDAI (mPCDAI) i.e. without the portion of points for EIM presence, to test if EIM(+) and EIM(–) patients differ regarding other qualities. The tendency was unclear: mode mPCDAI score for EIM(+) patients remained higher than in EIM(–) patients (45 vs. 40) but median mPCDAI score equaled (45).

It should be noted that at the time of diagnosis 50% of the children with PSC and the AIH/PSC overlap syndrome – the most common among extraintestinal manifestations in UC (22 out of 33 patients) – had mild disease. The respective proportion for the whole UC population approached 30%. The more common prevalence of mild UC in the EIM(+) patients did not prove to be statistically significant (χ^2 test of independence); nevertheless, such a trend was observed (45% of the EIM[+] vs. 25% of the EIM[–] patients; $p = 0.057$).

Severe CD was diagnosed in 11 of the EIM(+) patients (40.7%) – this included two out of three patients with two EIMs diagnosed: one with erythema nodosum and arthritis and one with erythema nodosum and interstitial nephritis. Altogether the percentage of severe disease activity in the EIM(–) group was lower: 29.2% ($p < 0.05$); this may be attributed to the additional 5 or 10 PCDAI points contributing to the rate of EIM(+) by definition. Nevertheless, it does not necessarily lead to high final activity rate – despite the presence of two EIMs, the second child with concomitant erythema nodosum and interstitial nephritis scored lower PCDAI points in other criteria and finally rated mild disease activity.

THE PARIS CLASSIFICATION – ULCERATIVE COLITIS

At the time of diagnosis a considerable number of our participants (57 patients, 38%) had pancolitis (E4) including seven children with macroscopic rectal sparing (MRS). Pancolitis developed in 55% of the EIM(+) and 59% of PSC and PSC/AIH (13 of 22) patients but only in 34% of the EIM(–) population. Pancolitis was also seen in three out of four patients with interstitial nephritis; however, no statistical significance was revealed ($p > 0.05$). MRS alone was slightly more prevalent among the EIM(–) participants (5.36% vs. 3.13%; $p = 0.058$). A complete analysis of disease location according to the Paris classification is presented in Table 5.

It is worth noting that patients with pancolitis had an over two-fold increase in EIM incidence compared to the remaining UC locations (E0–E3) OR 2.3, 95% CI 1.05–5.06, $p = 0.037$, and an almost three-fold increase in PSC incidence: OR 2.77, 95% CI 1.09–7.06, $p = 0.032$.

THE PARIS CLASSIFICATION – CROHN'S DISEASE

No statistically significant differences were found between the CD EIM(+) and EIM(–) groups regarding age, location, and disease behaviour.

TABLE 5. The Paris classification – inflammatory bowel disease assessment: ulcerative colitis children – different forms of extraintestinal manifestations

UC	Age at diagnosis			Extent			Growth		Linear growth impairment	
	A1a (%)	A1b (%)	A2 (%)	E0–E3 (%)	E4 (%)	MRS (%)	G0 (%)	G1 (%)	Mild (%)	Moderate (%)
$n = 147$	31 (21)	99 (67)	17 (12)	90 (63)	57 (38)	7 (5)	120 (82)	27 (18)	17 (63)	10 (37)
EIM(–) $n = 114$	23 (20)	76 (67)	15 (13)	75 (66)	39 (34)	6 (5)	95 (83)	19 (17)	12 (11)	7 (6)
EIM(+) $n = 33$	8 (24)	23 (70)	2 (6)	15 (45)	18 (55)	1 (3)	25 (73)	8 (24)	5 (15)	3 (9)
Extraintestinal manifestations										
PSC/AIH or PSC $n = 22$	6	16	0	9	13	0	15	7	5	2
Interstitial nephritis $n = 4$	1	2	1	1	3	0	3	1	0	1
Arthritis $n = 5$	1	4	0	3	2	1	5	0	0	0
Haemolytic enaemia $n = 1$	0	0	1	1	0	0	1	0	0	0
Erythaema nodosum $n = 1$	0	1	0	1	0	0	1	0	0	0

UC – ulcerative colitis, EIM – extraintestinal manifestations, PSC – primary sclerosing cholangitis, AIH – autoimmune hepatitis

TABLE 6. The Paris classification – inflammatory bowel disease assessment: Crohn's disease children – different forms of extraintestinal manifestations

CD	Age at diagnosis			Locations				Behaviour				Growth		Linear growth impairment	
	A1a (%)	A1b (%)	A2 (%)	L1 (%)	L2 (%)	L3 (%)	L4 (%)	B1 (%)	B2 (%)	B3 (%)	B2 B3 (%)	P (%)	G0 (%)	G1 (%)	Mild (%)	Moderate (%)
$n = 140$	13 (9)	106 (76)	21 (15)	75 (54)	17 (12)	46 (33)	2 (1)	89 (64)	30 (21)	17 (12)	4 (3)	34 (24)	108 (77)	32 (23)	22 (16)	10 (7)
EIM(–) $n = 113$	11 (10)	86 (76)	16 (14)	60 (53)	14 (12)	37 (33)	2 (2)	71 (63)	24 (21)	15 (13)	3 (3)	31 (27)	87 (77)	26 (23)	20 (18)	6 (5)
EIM(+) $n = 27$	2 (7)	20 (74)	5 (19)	15 (56)	3 (11)	9 (33)	0	18 (67)	6 (22)	2 (7)	1 (4)	3 (11)	21 (78)	6 (22)	2 (7)	4 (15)
Extraintestinal manifestations (30)																
Arthritis $n = 14$	0	10	4	8	3	3	0	9	4	0	1	1	12	2	1	1
Interstitial nephritis $n = 7$	2	5	0	5	0	2	0	6	1	0	0	2	6	1	0	1
Erythaema nodosum $n = 6$	0	5	1	2	0	4	0	4	1	1	0	0	4	2	0	2
PSC/AIH or PSC $n = 3$	0	3	0	2	0	1	0	2	0	1	0	0	2	1	1	0

CD – Crohn's disease, EIM – extraintestinal manifestations, PSC – primary sclerosing cholangitis, AIH – autoimmune hepatitis

Our patients mostly presented with isolated ileocecal disease. No correlation was observed between the age of the patients and lesion location; similarly, no correlation was revealed between the development of extraintestinal manifestations and the involvement of particular segments of gastrointestinal tract. The parameters assessed in the CD patients are presented in Table 6.

It should be noted that L4 location, i.e. upper GI tract, consists of two subcategories: L4a – disease proximal to ligament of Treitz, which we have not observed, and L4b, which represents the entirety of our L4 cases, i.e. upper disease distal to ligament of Treitz and proximal 2/3 of ileum.

DISCUSSION

PREVALENCE AND TYPES OF IMMUNE-RELATED EXTRAINTESTINAL MANIFESTATIONS AND THEIR CORRELATION WITH THE CLINICAL COURSE OF IBD

Literature data on extraintestinal manifestations and the effects thereof on the course of UC and CD are scarce, especially with regard to the paediatric population.

In our study the prevalence of IBD-related extraintestinal manifestations was 20.9% (22.4% for the UC and 19.5 for the CD participants). Comparable results were obtained by Ludvigsson *et al.* [11] in a group of 1432 paediatric patients with IBD, 20% of whom had at least one extraintestinal manifestation (21% of CD and 16% of UC patients) as well as by Vernier-Massouille (23%) [12]. The proportions of EIM revealed by Guariso *et al.* [13] were 14.3% for children and 7.3% for adult patients, i.e. lower than in our study. This discrepancy might have resulted from the fact that we analysed the occurrence of EIMs throughout the follow-up, and not only at IBD diagnosis.

Duricova *et al.* compared the occurrence of EIMs in paediatric and elderly patients with UC and CD from a French prospective population-based registry [EPIMAD] [14, 15]. At the time of diagnosis, EIMs were seen in 8.9% of 158 children with UC and 23.5% of 535 children with CD, while 29.8% of paediatric CD sufferers developed EIM during the follow-up. The prevalence of EIMs was three- and five-fold lower in the adult UC and CD populations, respectively.

Regarding the types of EIMs, Duricova *et al.* reported joint involvement as the most frequent in paediatric onset UC and CD (UC 15.8% and CD 11.2%) [14, 15]. In our study, arthritis was the most common EIM only in children with CD (10% of the patients vs. 3.4% of the UC participants). Interstitial nephritis and erythema nodosum were also more common in CD, occurring in 5% and 4%, respectively, of CD children, compared to 2.8% and 0.7%, respectively, in UC.

Veloso *et al.* also observed that arthritis and erythema nodosum were more common in CD compared to UC [16, 17]. They estimated that arthropathies developed in

20.2% of patients with CD and 11% of UC sufferers. The prevalence of erythema nodosum was 8.4% and 3.2%, respectively. Guariso *et al.* [13] reported that three out of four children with erythema nodosum had CD; the overall prevalence of this cutaneous pathology in IBD children (2.8%) was comparable to that revealed in our study (2.4%).

Analysing the material, we found it thought-provoking that in a group of almost 300 patients we did not observe ophthalmological manifestations – none of our participants was diagnosed with uveitis or iritis. It is consistent with the results obtained by Guariso *et al.* [13], who compared patients with childhood- and adult-onset IBD and only found uveitis in adult IBD sufferers. It seems justified to speculate that this particular EIM might be more typical for adults with IBD.

What attracts attention is also the distinctive character of PSC in patients. It is well-known that the development of PSC is especially associated with UC in comparison to CD. Faubion *et al.* [18] analysed the prevalence of PSC among children hospitalised in the Mayo Clinic and found that 89% of the paediatric patients with PSC suffered from ulcerative colitis (in our study: 87%) while 11% had Crohn's disease. This tendency was also observed in our group – 88% of IBD patients with PSC or the AIH/PSC overlap syndrome had UC. Moreover, patients with PSC or PSC/AIH tend to obtain lower PUCAI scores than UC EIM(–) patients: in our group 54.5% of children with PSC or PSC/AIH had inactive or mild disease, while in the UC EIM(–) population mild disease concerned only 27.1% of patients.

At this point it should also be noted that PSC may precede the symptoms of ulcerative colitis, resulting in earlier diagnosis of IBD and, consequently, lower initial disease activity. Such a tendency was also observed among our patients, as is shown on the above data. The mean age at IBD diagnosis was one year lower in patients suffering from PSC or PSC/AIH compared to other EIMs. Nevertheless, the difference was not statistically significant.

The mild form of clinical symptoms contrasts with the extent of colonic inflammation in PSC-IBD: nearly 60% of our PSC or PSC/AIH patients had pancolitis, while it occurred only in 34% of EIM(–) children. Also, pancolitis (E4) increased the risk for the prevalence of PSC almost three-fold compared to E0–E3. It is consistent with the finding that EIMs are more frequently present in patients with extensive UC [19].

These findings seem to confirm the observations of several authors, who concluded that PSC-IBD was a specific type of inflammatory bowel disease characterised by mild clinical course, extensive right-sided colitis, and increased risk for colorectal neoplasia [18, 20, 21]. This altogether led Faubion *et al.* to recommend endoscopic biopsy surveillance in this group [18].

Regarding location in CD, Karmiris *et al.* observed that the risk of peripheral arthropathy seems to increase with the upper GI involvement. They also noted a positive association between incidence of ankylosing spondylitis and CD ileocolitis and a reverse association between sacroiliitis and CD colitis [19].

As these observations and especially the example of PSC show, analysing the impact of EIMs on the clinical course of IBD, not only the presence of manifestation should be considered but also the type thereof, especially regarding disease location, as well as the activity stratified with the PUCAI/PCDAI scores. On this basis EIM types have been divided into dependent on and independent of intestinal disease activity [3, 19, 20].

It has to be underlined that while PUCAI is a clinical symptomatic scale assessing only altered defecation patterns, abdominal pain, and general activity level, PCDAI is more complex and the EIM presence is assessed in the index itself, contributing to the final rate. It becomes difficult to interpret how much of the observed tendency of EIM(+) patients to be classified more frequently with severe disease is due to the impact of EIM occurrence. We therefore analysed modified PCDAI (mPCDAI) as proposed by Dotson *et al.* [22], which is a reduced EIM portion of the score, and we did not confirm this tendency: while primarily 40% of EIM(+) PCDAI were rated as severe, it was only true for 15% of EIM(+) patients considering mPCDAI.

We observed no correlation between EIMs generally and CD behaviour. Karmiris *et al.* found an association between stricturing disease (B2) and episcleritis. They also observed that the B2 and B3 forms, in comparison to B1, promoted the development of EIMs [19].

CLINICAL SYMPTOMS, ANTHROPOMETRIC MEASURES – NUTRITIONAL STATUS AND GROWTH

The literature review did not provide us with a comparison of IBD symptoms reported by EIM(+) and EIM(–) patients. Nevertheless, bloody diarrhoea, fatigue, and fever have been mentioned as the most common symptoms of the disease [12, 23].

Our results revealed a statistically significant difference between the UC EIM(+) and UC EIM(–) patients with respect to bloody diarrhoea. While remaining the most common UC symptom in general, it was less frequently noted in the UC EIM(+) participants in comparison to EIM(–) patients. We also noted a tendency towards lower rate of weight loss in the EIM(+) group and higher rate of abdominal pain and non-bloody diarrhoea.

No significant differences were observed in symptom distribution between the CD EIM(+) and CD EIM(–) patients, the most common symptom being fatigue and non-bloody diarrhoea followed by abdominal pain and weight loss. The latter was noted in over 50% of CD patients.

While growth retardation was in general equally frequent in our CD EIM(+) and EIM(–) group (20%),

those of children who exhibited growth retardation in the EIM(+) group more frequently presented with severe growth impairment, while most of the CD EIM(–) patients with growth retardation had its mild presentation. In UC, although a noticeable group of patients also presented with growth impairment, no significant differences between EIM(+) and EIM(–) groups were observed.

We did not find any literature reports specifically concerned with short stature of IBD children with or without immune-related extraintestinal manifestations.

CONCLUSIONS

EIMs are an important issue for patients with inflammatory bowel disease. Determination of the prevalence of these manifestations and related risk factors might raise awareness of the problem and facilitate diagnosis and therapy. The presence of EIMs at diagnosis might indicate more severe disease and mandate more aggressive treatment. Our study aimed at identifying features that might help distinguish EIM(+) children from other paediatric patients with IBD. The UC EIM(+) patients seem to have distinctive IBD symptom pattern. Children with pancolitis were at a significantly higher risk of developing extraintestinal manifestation and especially PSC/AIH. Our IBD EIM(+) participants were slightly younger than EIM(–) individuals; this mostly referred to boys – but it should be confirmed in a larger group. The distribution of growth impairment and disease behaviour parameters was inconclusive and also requires further investigations. We believe the effect of EIMs on the clinical condition, prognosis, laboratory findings, and treatment of children with IBD is an interesting subject for further research.

DISCLOSURE

The authors declare no conflict of interest.

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