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• CLINICAL RESEARCH •

Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: Results of a 25-year follow-up study

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Abstract

AIM: IBD is a systemic disease associated with a large number of extraintestinal manifestations (EIMs). Our aim was to determine the prevalence of EIMs in a large IBD cohort in Veszprem Province in a 25-year follow-up study.

METHODS: Eight hundred and seventy-three IBD patients were enrolled (ulcerative colitis/UC/: 619, m/f: 317/302, mean age at presentation: 38.3 years, average disease duration: 11.2 years; Crohn's disease/CD/: 254, m/f: 125/129, mean age at presentation: 32.5 years, average disease duration: 9.2 years). Intestinal, extraintestinal signs and laboratory tests were monitored regularly. Any alteration suggesting an EIMs was investigated by a specialist.

RESULTS: A total of 21.3 % of patients with IBD had EIM (UC: 15.0 %, CD: 36.6 %). Age at presentation did not affect the likelihood of EIM. Prevalence of EIMs was higher in women and in CD, ocular complications and primary sclerosing cholangitis (PSC) were more frequent in UC. In UC there was an increased tendency of EIM in patients with a more extensive disease. Joint complications were more frequent in CD (22.4 % *vs* UC 10.2 %, $P<0.01$). In UC positive family history increased the risk of joint complications (OR:3.63). In CD the frequency of type-1 peripheral arthritis was increased in patients with penetrating disease ($P=0.028$). PSC was present in 1.6 % in UC and 0.8 % in CD. Dermatological complications were present in 3.8 % in UC and 10.2 % in CD, the rate of ocular complications was around 3 % in both diseases. Rare complications were glomerulonephritis, autoimmune hemolytic anaemia and celiac disease.

CONCLUSION: Prevalence of EIM in Hungarian IBD patients is in concordance with data from Western countries. The high number of EIM supports a role for complex follow-up in these patients.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn' s disease (CD) are chronic inflammatory diseases of undetermined origin. Inflammatory bowel disease (IBD) is a multifactorial polygenic disease with probable genetic heterogeneity. In this hypothesis, the disease may develop in a genetically predisposed host as a consequence of altered mucosal barrier and disregulated immune response to environmental, in particular enteric antigens, resulting in continuous immune-mediated inflammation[1-4]. IBD predominantly affects the gastrointestinal system but it is associated with a large number of extraintestinal manifestations (EIMs)[5]. Some disorders parallel the activity of the bowel disease but for a number of these conditions, their courses run independently of the course of the intestinal disease[6,7]. Furthermore, there has been some variance in the literature as to whether these EIMs are more associated with CD or UC. In the classical study of Greenstein *et al*.[8] EIMs were classified as colitis associated, small bowel associated and none specific manifestations.

EIMs contribute significantly to morbidity and mortality. Defining specific associations of immune mediated diseases in extraintestinal sites and IBD may be helpful in the better understanding of the pathogenesis of IBD.

The pathogenesis of EIMs is also multifactorial. The role of genetic factors is supported by family and candidate (e.g. certain HLA) gene studies[9-11]. The role of humoral immunity is supported by the higher prevalence of autoantibodies in the presence of EIMs, especially pANCA in primary sclerosing cholangitis (PSC). The immunological and clinical connections between these diseases and IBD have never been fully elucidated.

In this study we aimed to define the prevalence of EIMs in a 25-year follow up study in Hungarian IBD patients. We sought to determine if any of the EIMs was more likely associated with CD or UC, with male or female gender in a follow-up study. Possible associations between EIMs and location and disease behaviour were also investigated.

MATERIALS AND METHODS

Eight hundred and seventy-three IBD patients followed-up at the Out- and Inpatient Gastroenterology Units of the Csolnoky F. Province Hospital in Veszprem Province were enrolled. This hospital is the secondary referral center for IBD patients in the province.

The data of the 619 UC patients (male/female: 317/302) are summarized in Table 1. The age at presentation varied between 9 and 80 years (average: 38.3 years). Average disease duration was 11.2 years (1-56 years). The location of UC according to the known greatest extent was proctitis in 117,

left sided colitis in 304 (including 171 patients with proctosigmoiditis), subtotal (98) and pancolitis (100) in 198 cases. Two hundred and fifty-four CD patients were included (125 males, 129 females). Average age at presentation was 32.5 years (12-80 years). According to the Vienna classification 192 patients were classified as A1, while 62 as A2. Disease duration was 9.2 years (1-40 years). Location of CD was ileal (L1) in 60, colonic (L2) in 81 and ileocolonic (L3) in 113 cases. Patients with upper GI manifestation had lower GI disease as well and they were classified according to their lower GI disease. According to the disease behavior 83 of our CD patients were defined as non-stricturing non-penetrating, 62 as stricturing and 105 as penetrating. Fifty-eight patients of the 95 penetrating cases had parallel strictures. Patients with indeterminate colitis were excluded.

Table 1 Clinical data of IBD patients

	Ulcerative colitis	Crohn's disease
Number of patients	619	254
Male / female	317 / 302	125 / 129
Mean age at diagnosis	38.3 yrs (9-80 yrs)	32.5 yrs (12-80 yrs)
Location	Proctitis: 117	L1: 60
	Left sided colitis: 304	L2: 81
	Pancolitis: 198	L3: 113
Behaviour of CD	-	B1: 87
		B2: 62
		B3: 105

In Crohn's disease (CD). Location: L1: terminal ileum, L2: colonic, L3: ileocolonic, behaviour: B1: non stricturing-non penetrating, B2: stricturing, B3: penetrating.

Patients in remission were followed-up twice per year. Patients who relapsed were followed-up or hospitalised according to the actual disease activity. Special interest was dedicated to the presence of EIM. Screening of EIMs was not performed, therefore the number of EIMs may have been underestimated. Routine follow-up consisted of assessment of patient's complaints, physical examination and laboratory testing.

Any alteration suggesting an EIMs was investigated by a specialist. In this study we did not assess the association between disease activity and the presence of EIM. Major EIMs studied in this report were axial and peripheral arthropathies (including ankylosing spondylitis), aseptic femoral head necrosis, primary sclerosing cholangitis (PSC), small duct cholangitis, autoimmune hepatitis, erythema nodosum, pyoderma gangrenosum, chronic urticaria, acute anterior uveitis, iritis, episcleritis, conjunctivitis, autoimmune hemolytic anaemia (AIHA), immune thrombocytopenic purpura (ITP), celiac disease, myositis, and glomerulonephritis.

Joint involvements were classified as peripheral and/or axial arthropathies. Peripheral arthropathies were divided into two subgroups according to the classification of Orchard *et al*[13]. Type-1 arthritis is an acute self-limiting pauciarticular (less than 5 joints) arthropathy typically affecting large joints. It is associated with other EIMs and its course parallels with the activity of the bowel disease. In contrast, type 2 arthritis is a chronic bilateral, symmetrical polyarticular arthropathy affecting five or more small joints. Its course runs independently of the course of the intestinal disease. Axial arthropathies are divided into sacroileitis and ankylosing spondylitis (SPA). Its incidence is 20-times higher than that in the normal population[14]. Rheumatologists investigated sacroileitis and ankylosing spondylitis cases. Laboratory testing (rheumatoid factor), X-ray and since 1997 MRI examinations were done.

Patients with elevated liver function tests (LFT, aminotransferases, cholestatic enzymes) were followed-up more cautiously. In patients with chronic or progressive elevation of enzyme levels liver biopsy and/or endoscopic retrograde cholangiopancreatography (ERCP) examination was done if patient gave informed consent. The diagnosis of PSC was based on elevated liver function tests, ERCP and consistent histology findings. Small duct PSC was diagnosed if histology suggested PSC, but ERCP could not verify the diagnosis[15,16]. Cholelithiasis, cirrhosis and focal nodular hyperplasia (FNH) were excluded from hepatobiliary manifestations.

In patients with verified thrombosis, blood samples were examined for hypercoagulability including in almost all cases analysis of plasminogen, proteins C and S activity and factor V Leiden mutation.

Patients with glomerulonephritis were followed-up by nephrologists as well. Diagnosis was based on clinical and chemical data and congruent histology findings. Ureteral obstruction was diagnosed by cystoscopy and urography, CT or MRI. If the alteration suggested fistulae in the urinary tract, cytography was also performed.

Statistical analysis

For statistical comparison of the data, Statistica 6.0 (Statsoft Inc, USA) was used. Normality was tested by Shapiro-Wilk's W test. χ^2 test with Yates correction was used to compare groups and odds ratios were calculated.

RESULTS

The prevalence of major (joint, hepatobiliary, ocular and cutaneous) and all EIMs determined in this study are shown in Table 2. Major EIMs were apparent more frequently in CD than in UC (36.6 % *vs* 15.0 %, $P<0.001$). EIMs were more frequent in patients with a disease duration for more than 10 years in both CD (22.1 % *vs* 48.9 %, $P=0.003$) and UC (22.1 % *vs* 10.4 %, $P<0.001$).

Table 2 Prevalence of extraintestinal manifestations (EIM) in IBD

	Total *n* (%)	Disease duration	
		⩽ 10 yrs *n* (%)	> 10 yrs *n* (%)
IBD	873	511	352
Major EIMs	186 (21.3)	86 (16.8)	102 (30.0)
All EIM signs	547 (62.7)	278 (54.4)	269 (76.4)
Ulcerative colitis	619	357	262
Major EIMs	93 (15.0)	37 (10.4)	58 (22.1)
All EIM signs	360 (58.2)	167 (46.8)	193 (73.7)
Crohn's disease	254	164	90
Major EIMs	93 (36.6)	49 (29.9)	44 (48.9)
All EIM signs	187 (73.6)	111 (67.7)	76 (84.4)

The prevalence of EIMs was higher in CD except ocular complications and PSC ($P<0.001$ for joint, hepatobiliary and cutaneous manifestations, Tables 3 and 4). In general, EIMs were more frequent in women except hepatobiliary manifestations and arthropathies in UC patients.

All major EIMs were more prevalent in more extensive UC (Table 5). There was a tendency of increased frequency of joint manifestations in CD patients with colonic involvement (L2 and L3: 23.7 %) compared to patients with only ileal disease (18.3 %, P=NS, Table 5). The prevalences of hepatobiliary, ocular and cutaneous manifestations were not different according to disease location.

Table 3 Age at presentation and prevalence of major extraintestinal manifestations in patients with IBD

	A1 *n* (%)	A2 *n* (%)
UC (*n*: 619)	369	250
Joint	32 (8.7)	20 (8.0)
Hepatobiliary	49 (13.3)	28 (11.2)
Cutaneous	17 (4.6)	7 (2.8)
Ocular	11 (3.0)	8 (3.0)
CD (*n*: 254)	192	62
Joint	48 (25.0)	9 (14.5)
Hepatobiliary	48 (25.0)	9 (14.5)
Cutaneous	20 (10.4)	6 (9.7)
Ocular	5 (2.6)	3 (4.8)

A1: age at presentation <40 yrs, A2: age at presentation ⩾40 yrs.

Table 4A Familial IBD and association with extraintestinal manifestations

	Total	First degree relative	Second degree relative
Ulcerative colitis	24/619 (3.9 %)	18 (14 UC+4 CD) (2.9 %)	6 (5 UC+1 CD) (1.0%)
Crohn's disease	31/254 (12.2 %)	20 (3 UC+17 CD) (7.9%)	11 (2 UC+9 CD) (4.3%)

Table 4B Familial IBD and association with extraintestinal manifestations

	Ulcerative colitis	Familial IBD
Number of patients	619	24
Joint	52 (8.4 %)	6 (25.0 %)
Hepatobiliary	77 (12.4 %)	3 (12.5 %)
Cutaneous	24 (3.9 %)	1 (4.2 %)
Ocular	19 (3.0 %)	2 (8.3 %)
	Crohn's disease	Familial IBD
Number of patients	254	31
Joint	57 (22.4 %)	11 (35.5 %)
Hepatobiliary	57 (22.4 %)	4 (12.9 %)
Cutaneous	26 (10.2 %)	2 (6.5 %)
Ocular	8 (3.1%)	0

Table 5 Prevalence of extraintestinal manifestations in ulcerative colitis and Crohn's disease according to location and disease behaviour

	Joint *n* (%)	Hepatobiliary *n* (%)	Cutaneous *n* (%)	Ocular *n* (%)
Location		Ulcerative colitis		
Proctitis (*n*=117)	5 (4.3)	9 (7.7)	1 (0.9)	1 (0.9)
Left sided colitis (*n*=304)	14 (4.6)	32 (15.7)	8 (2.6)	7 (2.3)
Pancolitis (*n*=198)	33 (16.7)	36 (18.2)	15 (7.6)	12 (6.1)
Location		Crohn's disease		
L1 (*n*=60)	11 (18.3)	14 (23.3)	6 (10.0)	2 (3.3)
L2 (*n*=81)	17 (21.0)	17 (21.0)	10 (12.3)	3 (3.7)
L3 (*n*=113)	29 (25.7)	26 (23.0)	10 (8.8)	3 (2.7)
Behaviour				
B1 (*n*=87)	13 (14.9)	22 (25.3)	11 (12.6)	1 (1.1)
B2 (*n*=62)	16 (25.8)	11 (17.7)	5 (8.1)	0
B3 (*n*=105)	28 (27.6)	24 (22.9)	10 (9.5)	7 (6.7)

Age at presentation (A1: <40 years, A2: =40 years) did slightly affect the prevalence of EIMs (Table 3). Joint manifestations were more prevalent in CD patients with earlier disease onset (OR: 1.96, 95 % CI: 1.01-4.21). The same tendency was observed for cutaneous manifestations.

Familial disease was seen in 3.9 % of patients with UC and 12.2 % of patients with CD (Tables 4A-B). Joint manifestations were more frequent in UC patients with familial disease (OR: 3.63, 95 % CI: 1.43-9.31) than without. The same tendency was seen in UC patients (OR: 1.9, 95 % CI: 0.87-4.14) and ocular manifestations were found in familial UC cases.

Table 6A Joint manifestations in IBD patients

	Total *n* (%)	Axial arthritis *n* (%)	Type-1 arthritis *n* (%)	Type-2 arthritis *n* (%)
Ulcerative colitis				
Total (*n*=619)	52 (8.4)	20 (3.2)	17 (2.7)	13 (2.1)
Male (*n*=317)	24 (7.6)	10 (3.2)	7 (2.2)	7 (2.2)
Female (*n*=302)	28 (9.3)*	10 (3.4)	10 (3.3)	6 (2.0)
Crohn's disease				
Total (*n*=254)	57 (22.4)	26 (10.2)	29 (11.4)	8 (3.1)
Male (*n*=125)	23 (18.4)	11 (8.8)	12 (9.6)	3 (2.4)
Female (*n*=129)	34 (26.4)	15 (11.6)	17 (13.2)	5 (3.9)

*Two female patients with ulcerative colitis had rheumatoid arthritis.

Table 6B Joint manifestations in IBD according to location and disease behaviour

	Total *n* (%)	Axial arthritis *n* (%)	Type-1 arthritis *n* (%)	Type-2 arthritis *n* (%)
Location		Ulcerative colitis		
Proctitis (*n*=117)	5 (4.3)*	1 (0.9)	2 (1.8)	1 (0.9)
Left sided colitis (*n*=304)	14 (4.6)	4 (1.3)	5 (1.6)	5 (1.6)
Pancolitis (*n*=198)	33 (16.7)*	15 (7.6)	10 (5.0)	7 (3.5)
Location		Crohn's disease		
L1 (*n*=60)	11 (18.3)	5 (8.3)	4 (6.7)	2 (3.3)
L2 (*n*=81)	17 (21.0)	7 (8.6)	10 (12.3)	3 (3.7)
L3 (*n*=113)	29 (25.7)	14 (12.4)	15 (13.3)	3 (2.7)
Behaviour				
B1 (*n*=87)	13 (14.9)	8 (9.2)	5 (5.7)	2 (2.3)
B2 (*n*=62)	16 (25.8)	8 (12.9)	6 (9.7)	3 (4.8)
B3 (*n*=105)	28 (27.6)	10 (9.5)	18 (17.1)	3 (2.9)

*One patient with proctitis and one with pancolitis had rheumatoid athritis.

Joint manifestations were more frequent in CD than in UC ($P<0.001$, Tables 6A-B.). There was a tendency of increased frequency of joint manifestations in women with CD (26.4 % *vs* 18.4 %, OR: 1.58, 95 % CI: 0.87-2.87). Axial arthritis (10.2 % *vs* 3.2 %, $P=0.0001$) and type 1(11.4 % *vs* 2.7 %, $P=0.0001$) arthritis were more frequent in CD, with equal prevalence of type-2 arthritis. In UC joint manifestations were almost three-fold more frequent in patients with pancolitis compared to proctitis and left sided colitis cases ($P<0.002$ for both, Table 5). In CD a tendency of increased frequency of joint manifestations was observed in patients with colonic involvement (L2 and L3: 23.7 %) or stricturing/penetrating disease (26.3 %) compared to patients with ileal only disease (18.3 %) or non-stricturing non-penetrating disease behavior

(14.9 %, Table 6B). An increased frequency of type 1 arthritis was observed in patients with penetrating compared to non-stricturing non-penetrating disease (P=0.028), the same tendency was observed in patients with or without colonic involvement. Type-1 arthritis affected more frequently the joints of the lower extremities (most frequently the knee and ankle), while type-2 arthritis was more common in the joints of the upper extremities.

Hepatobiliary manifestations are summerised in Table 7. PSC was diagnosed in 10 patients with UC and only 2 patients with CD. Small duct PSC was diagnosed in 8 and 6 cases, respectively. Non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH) was diagnosed in 9.4 % of UC patients and 19.3 % of CD patients (P<0.0001). These patients had unexplained abnormal liver function tests (viral hepatitis, autoimmune, drug or alcohol induced disease, extrahepatic obstruction excluded). Liver biopsy was performed in 22/107 cases, which identified NAFLD or NASH in almost all cases. US proved hepatomegaly in 13/107 (12.1 %). Progression to cirrhosis was not observed in these patients during follow-up.

Table 7 Hepatobiliary manifestations in IBD patients

	Total *n* (%)	PSC *n* (%)	Small duct PSC *n* (%)	NAFLD / NASH *n* (%)
Ulcerative colitis				
Total (*n*=619)	77* (12.4)	10 (1.6)	8 (1.3)	58 (9.4)
Male (*n*=317)	39 (12.3)	3 (1.0)	6 (1.9)	30 (9.5)
Female (*n*=302)	38* (12.6)	7 (2.3)	2 (0.7)	28 (9.3)
Crohn's disease				
Total (*n*=254)	57 (22.4)	2 (0.8)	6 (2.4)	49 (19.3)
Male (*n*=125)	27 (21.6)	2 (1.6)	6 (4.8)	19 (15.2)
Female (*n*=129)	30 (23.3)	0	0	30 (23.3)

*One female patient had autoimmune hepatitis. NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis.

Cutaneous manifestations were seen in 10.2 % of the patients with CD and 3.9 % of the patients with UC (Tables 8A-B). Cutaneous manifestations were more common in women in both UC (male/female: 5.0 %/2.8 %) and CD (13.2 %/7.2 %, OR: 1.95, 95 % CI: 0.85-4.48). Erythema nodosum and pyoderma gangrenosum were the most frequent manifestations. In UC cutaneous manifestations were more frequent in more extensive disease (7.6 % in pancolitis *vs* 2.1 % in proctitis or left sided colitis, P=0.002).

Ocular manifestations were apparent in approximately 3.0 % of UC and CD patients (Table 9). The prevalence was more frequent in women in both UC (P=0.009, OR: 4.37, 95 % CI: 1.51-12.6) and CD (OR:3.0, 95 % CI=0.67-8). Conjunctivitis, acute anterior uveitis and scleritis were the most frequent manifestations. Ocular manifestations developed mostly during the early years of the disease. In UC more than half of the patients with ocular complication had pancolitis (6.1 % in pancolitis *vs* 1.9 % in left sided colitis or proctitis, P=0.01).

Iron deficiency anaemia was seen in 35.8 % of CD patients and in one fourth of UC patients (Tables 10A-C). It was more frequent in women in UC (32.1 % *vs* 19.6 %, P<0.001, OR=1.95, 95 % CI: 1.35-2.81). Chronic anaemia was more frequent in patients with CD (9.6 % *vs* 17.7 %, P<0.001). The prevalence of macrocytic anaemia was around 4 % in both diseases. It was also observed more frequently in patients with ileocolonic disease than without it (P=0.03). The same tendency was observed according to disease behaviour; chronic anaemia tended to be more frequent in patients with stricturing or penetrating disease (P=0.06, Table 10C). AIHA developed in four UC patients.

Table 8A Cutaneous manifestations in patients with ulcerative colitis (*n*=619)

	Total *n* (%)	Male *n* (%)	Female *n* (%)
Erythema nodosum	8 (1.3)	2 (0.6)	6 (2.0)
Pyoderma gangrenosum	3 (0.5)	1 (0.3)	2 (0.6)
Chronic urticaria	6 (1.0)	2 (0.6)	4 (1.3)
Psoriasis	3 (0.5)	2 (0.6)	1 (0.3)
Aphthous stomatitis	3 (0.5)	1 (0.3)	2 (0.6)
Herpes zoster	2 (0.3)	1 (0.3)	1 (0.3)
Cellulitis	2 (0.3)	0	2 (0.6)
Recurrent dermatitis	2 (0.3)	1 (0.3)	1 (0.3)
Lichen ruber planus	1 (0.2)	1 (0.3)	0
Total	24 (3.9)	9 (2.8)	15 (5.0)

Table 8B Cutaneous manifestations in patients with Crohn's disese (*n*=254)

	Total *n* (%)	Male *n* (%)	Female *n* (%)
Erythema nodosum	14 (5.5)	4 (3.1)	10 (7.8)
Pyoderma gangrenosum	4 (1.6)	3 (2.4)	1 (0.8)
Erythema exsudativum multiforme	2 (0.8)	1 (0.8)	1 (0.8)
Erythroderma	2 (0.8)	1 (0.8)	1 (0.8)
Stevens Johnson syndrome	1 (0.4)	0	1 (0.8)
Psoriasis	1 (0.4)	0	1 (0.8)
Eczema	1 (0.4)	0	1 (0.8)
Recurrent dermatitis	1 (0.4)	0	1 (0.8)
Total	26 (10.2)	9 (7.2)	17 (13.2)

Table 9 Ocular manifestations in IBD patients

	Total *n* (%)	Anterior uveitis *n* (%)	Conjunctivitis *n* (%)	Scleritis *n* (%)
Ulcerative colitis				
Total (*n*=619)	20* (3.2)	6 (1.0)	9 (1.5)	4 (0.7)
Male (*n*=317)	4 (1.3)	1 (0.3)	3 (1.0)	1 (0.3)
Female (*n*=302)	16 (5.3)	5 (1.7)	6 (2.0)	3 (1.0)
Crohn's disease				
Total (*n*=254)	8 (3.1)	4 (1.6)	4 (1.6)	1 (0.4)
Male (*n*=125)	2 (1.6)	1 (0.8)	0	1 (0.8)
Female (*n*=129)	6 (4.7)	3 (2.3)	4 (3.1)	0

*One orbital pseudotumor was observed in a young female UC patient.

Table 10A Hematological manifestations in patients with ulcerative colitis

	Total *n* (%)	Male *n* (%)	Female *n* (%)
Iron deficieny anaemia	159 (25.9)	62 (19.6)	97 (32.1)
Chronic anaemia	59 (9.6)	34 (10.7)	25 (8.3)
Macrocytic anaemia	24 (3.9)	15 (4.7)	9 (3.0)
AIHA	4 (0.6)	2 (0.6)	2 (0.6)
Non-Hodgkin lymphoma	1 (0.2)	1 (0.3)	0
CML	1 (0.2)	1 (0.3)	0
Chronic myeloproliferative disease	1 (0.2)	0	1 (0.3)
Leukemoid reaction	1 (0.2)	0	1 (0.3)
Methaemoglobinaemia	1 (0.2)	0	1 (0.3)
Total	260 (42.0)	90 (28.4)	170 (56.3)

AIHA: autoimmune hemolytic anaemia, CML: chronic myeloid leukaemia.

Table 10B Hematological manifestations in patients with Crohn's disease

	Total *n* (%)	Male *n* (%)	Female *n* (%)
Iron deficieny anaemia	91 (35.8)	40 (32.0)	51 (39.5)
Chronic anaemia	45 (17.7)	23 (18.4)	22 (17.1)
Macrocytic anaemia	11 (4.3)	6 (4.8)	5 (3.9)
Chronic myeloproliferative disease	1 (0.4)	0	1 (0.8)
Leukopenia	1 (0.4)	0	1 (0.8)
ITP	1 (0.4)	0	1 (0.8)
Total	150 (59.1)	69 (55.2)	81 (62.8)

ITP: immune thrombocytopenic purpura

Table 10C Association between hematological complications and location and disease behaviour in Crohn's disease patients

	Iron deficieny anaemia *n* (%)	Chronic anaemia *n* (%)	Macrocytic anaemia *n* (%)
Location			
L1 (*n*=60)	17 (28.3)	9 (15.0)	3 (5.0)
L2 (*n*=81)	22 (27.2)	9 (11.1)	2 (2.5)
L3 (*n*=113)	42 (37.2)	27 (23.9)	6 (5.3)
Behaviour			
B1 (*n*=87)	27 (31.0)	10 (11.4)	2 (2.3)
B2 (*n*=62)	23 (37.1)	12 (19.4)	3 (4.8)
B3 (*n*=105)	41 (39.0)	23 (21.9)	6 (5.7)

Thromboembolic complication was observed in 11 CD and 8 UC patients (Table 11.). Male predominance was observed in UC, while it was more frequent in women with CD, 1/15 (6.3 %) patient was positive for factor V Leiden mutation.

4.5 % of all IBD patients had multiple major extraintestinal diseases, three-fold more frequent in patients with CD than in patients with UC (9.1 % *vs* 3.1 %, $P<0.001$, Table 12.). Rare complications are summarized in Table 13. A relatively high number of glomerulonephritis was worth mentioning.

Table 11 Thromboembolic complications in patients with IBD

	Ulcerative colitis	Crohn's disease
Number of patients (%)	11/619 (1.8)	8/254 (3.1)
Male/female	9/2	2/6
Location	Proctitis: 0	L1: 3
	Left sided colitis: 6	L2: 1
	Pancolitis: 5	L3: 4
Behaviour of CD	-	B1: 0
		B2: 2
		B3: 6
Place of thromboembolism		
Lower extremity thrombosis	8	4
Pulmonary embolism	1	0
Lower extremity thrombosis complicated by pulmonary embolism	2	3
Splenic vein thrombosis	0	1

Table 12 Prevalence of multiple extraintestinal diseases

	Total *n*	Ulcerative colitis *n*	Crohn's disease *n*
Two	27	14	13
Three	14	5	9
Four	1	0	1
Total	42/873 (4.5%)	19/619 (3.1%)	23/254 (9.3%)

Table 13 Extraintestinal manifestations in IBD affecting other organ systems

	Total *n* (%)	Ulcerative colitis *n* (%)	Crohn's disease *n* (%)
Glomerulonephritis	3 (0.4)	1 (0.2)	2 (0.8)
Asthma bronchiale	7 (0.8)	4 (0.6)	3 (1.2)
Chronic pancreatitis	4 (0.5)	3 (0.5)	1 (0.4)
Acute pancreatitis	2 (0.2)	1 (0.2)	1 (0.4)
Celiac disease	2 (0.2)	1 (0.2)	1 (0.4)
Thyreoiditis	2 (0.2)	2 (0.3)	0
SLE	2 (0.2)	1 (0.2)	1 (0.4)

SLE: systemic lupus erythematodes.

DISCUSSION

It is difficult to define the true prevalence of EIMs in IBD. If one was counting only major EIMs with common immunogenetic background the prevalence was about 20-25 %[1,5,8,17,18]. However, if all possible secondary systemic effects and/or complications of therapy are also included, then almost all patients will have "extra-intestinal manifestations". Prevalence may vary depending on the actual geographic area, IBD population, location and duration of the disease, medication and diagnostic accuracy.

Only few large cohort follow-up data are available on the prevalence of EIMs in IBD. The study of Greenstein *et al*. was one of the first reports[8]. Farmer *et al*.[19] reported a prevalence of 16.7 % during a 13-year follow-up study. EIMs were more prevalent in patients with colonic involvement or previous operations. In the Swedish epidemiology study Monsen *et al*.[20] excluded arthralgia, stomatitis and episcleritis from the EIMs. More recently, Jiang and Cui[21] analyzed the data of 10218 ulcerative colitis cases in China. The frequency of EIMs was 6.1 %, however no further data were available about the type of EIM. Bernstein *et al*.[22] investigated the prevalence of five "major" EIMs (iritis/uveis, PSC, pyoderma gangrenosum, erythema nodosum and ankylosing spondylitis) with the help of the University of Manitoba IBD Database in IBD patients with a disease history of at least 10 years. They found a single EIM prevalence of 6.2 %, which was one of the lowest rates reported. However, peripheral arthropathies were excluded from their study. There is undoubtedly a debate with the diagnosis of peripheral arthopathy, as it is sometimes difficult to distinguish arthropathy from arthralgia, especially in retrospective studies. In contrast, it is one of the most typical EIMs, observed in a high frequency of the patients. Excluding peripheral arthropathy from EIMs in one study and including it in another make the data difficult to compare. The reported overall EIM prevalence of 21.3 % in our study is in concordance with previous studies. The overall prevalence of EIMs was higher in patients with a longer disease history, but age at presentation did not affect the prevalence of EIMs.

There were gender predilections. EIMs were more frequent in femal pateints compared to males, which may support the hypothesis that autoimmune diseases are more common in female subjects.

The role of genetic factors has been implicated in the pathogenesis of IBD and EIMs[8-11]. In our study we investigated the familial occurrence in IBD. Positive family history was four times more frequent in CD compared to UC. The frequencies of joint and ocular manifestations were higher in patients with familial UC. Others have suggested high concordance of the occurrence of EIMs in affected siblings with IBD[23].

Previous studies have suggested multiple extraintestinal diseases[8,22] with certain genetic associations[10,23]. We found multiple extraintestinal diseases in 4.5 % of IBD patients, more

common in patients with CD. The most frequent associations were co-existing ocular, cutaneous and joint (type 1 arthritis) manifestations. The Canadian study reported multiple extraintestinl disease in only 0.3 % of all patients[22], however the rate of multiple EIMs was comparable to our results in most studies[17, 19].

Relation of EIMs with type, location and behaviour of IBD

Type of IBD Overall EIMs were more frequent in patients with CD than in patients with UC, in concordance with previous studies[8,24] with the exception of ocular manifestations and PSC. These two EIMs were equally prevalent in CD and UC (both occurred approximately in 3 % of the patiens) in concordance with previous data[10,16,25].

Location of IBD In UC EIMs were thought to be more prevalent in extensive disease[5], but there were some contradiction in the literature[13]. In our study the rate of EIMs increased with the increasing extent of the disease. In CD it was generally accepted, that some EIMs were associated with colonic (e.g. peripheral arthropathy) others with small bowel (e.g. cholelithiasis) location[8,19]. We also found that type-1 arthritis was twice as frequent in patients with colonic or ileocolonic disease compared to patients with only ileal disease. The difference was smaller compared to patients with axial arthritis and disappeared in patients type 2 arthritis. The prevalences of cutaneous, ocular and hepatobiliary manifestations were not associated with location.

Behaviour of CD We did not find data in the literature about the relation of EIMs and the behaviour of CD, according to the Vienna classification. Earlier studies have suggested that EIMs tended to associate with perianal (=penetrating) disease[26]. We found a higher rate of joint complications in stricturing and penetrating disease than in non-stricturing non penetrating form. All but one ocular disease developed in patients with penetrating disease, but the rate of other complications was similar in the three groups.

Extraintestinal manifestations according to affected organs

Arthritis is the most common EIM in IBD IBD related arthropaties were originally classified as axial and peripheral arthritides. Orchard *et al*. subdivided the peripheral disease into type 1 (large joint, pauciarticular, parallels with the course of IBD) and type-2 (small joint, polyarticular, the course independent of IBD) arthritides[13]. In our study joint manifestations were more frequently seen in patients with CD, first of all with the higher prevalence of axial and type-1 arthritis in these patients. Type-1 arthritis was more frequent in patients with stenosing and penetrating disease compared to patients with non-stenosing non-penetrating disease behaviour. In patients with penetrating disease bacterial infections could explain the high prevalence, the reason for the high prevalence in patients with stenosing disease is not clear, perhaps it has a genetic background.

Hepatobiliary complications PSC was diagnosed in 1.6 % in UC and even more infrequently in CD. When small duct PSC was included, the overall prevalence was 2.9-3.2 % in both diseases, in concordance with the majority of previous reports (2.4-11 %)[15,16,27]. PSC was a precancerosus condition with increased risk for cholangiocarcinoma and colorectal cancer[28]. In this study 3 patients with PSC and one patient with small duct cholangitis developed colorectal cancer and one PSC patient developed cholangiocarcinoma, which supports a role for more intensive follow-up in these subgroups of patients.

The cause of elevated LFT was found to be steatosis and/or steatohepatitis, reported in 6.3 % in UC and in 4 % in CD in previous studies[29,30]. An Italian study found that 12 % of the 474 asymptomatic IBD patients had hepatobiliary disease[31]. In non-selected or operated UC patients the prevalence of steatosis could be as high as 15-45 %[16,32,33]. In our study the rate of NAFLD was twice as high in CD than in UC, otherwise our data are in concordance with the data of previous studies. Several cutaneous diseases were diagnosed, 14 were classified as EIM. Cutaneous manifestations were more frequent in CD and in female patients. The prevalence of erythema nodosum and pyoderma gangrenosum was in the range previously reported[10,34,35] with very few psoriasis cases.

Ocular complications were equally frequent in both diseases with increased prevalence in women. Anterior uveitis was found at a frequency as previously reported[8,10,22]. We found one orbital pseudotumour in a young woman with severe ulcerative pancolitis. Ocular manifestations occurred mostly in the early few years after diagnosis. Pancolitis patients with UC were more liable to develop ocular manifestations compared to other locations. Ocular manifestations did frequently occur together with other (joint or cutaneous) extraintestinal diseases.

Haematological complications Iron deficiency anaemia is the most frequent hematological manifestation. In most of the cases its course ran parallel to the course of the intestinal disease. "Chronic anaemia" that occurs in inflammatory conditions and tumours was mostly apparent in severe, refractory cases and resolved only slowly after remission. Macrocytic anaemia was more frequent in patients with ileal and penetrating/stricturing disease than in patients with colonic involvement or non-stricturing non-penetrating disease. It was less frequent since preventive folate supplementation has been introduced in patients receiving sulfasalazine treatment.

Autoimmune haemolytic anaemia (AIHA) rarely complicates IBD, the reported prevalence rates were between 0.2 % and 1.7 %. Our observed rate (0.6 %) correlated with the previous data. In concordance with other studies AIHA occurred in patients with extensive colitis. In most of the cases AIHA could be treated successfully with steroids and/or immunosuppressive drugs[36]. In our study one patient required splenectomy, and in another case haemolysis subsided only after colectomy.

Increased risk of lymphoma has been reported in IBD, especially in patients receiving immunosupressives, but data were conflicting[37,38]. Our data do not support the notion of increased risk in these patients. In our series one 76-year old male UC patient with left sided colitis developed a high grade B-cell lymphoma in the rectum, but he did not receive immunosuppressive therapy. ITP might be true EIM, methaemoglobinaemia was associated with high dose sulfasalazine treatment, leukaemoid reaction was seen in a fulminant relapse.

Hypercoagulability was thought to be involved in the pathogenesis of IBD[39-41], and increased risk of thromboembolic complications (1-6 %) has been reported in IBD[42]. The prevalence of prothrombotic inherited and/or acquired coagulation abnormalities in patients with IBD remains controversial. Genetic thrombophilia with deficiencies in some coagulation inhibitors (antithrombin, proteins C and S), acquired thrombophilia due to inflammation, antiphospholipid syndrome and mutations of factor V Leiden and recently other genes involved in thrombogenesis (prothrombin mutation 20210A or factor V fV4070G polymorphism) have been described[39,43]. The most common cause of hypercoagulability status in Europe is resistance to activated protein C (APC). Resistance to APC and mutations that cause APC resistance (mainly factor V Leiden) have been of particular interest[42,43]. Some studies reported increased frequency of Leiden mutation in IBD[42], however others found that Leiden mutation was associated with thromboembolism with (14.3 %) or without IBD (15.5 %) but not with IBD (0 % and controls 3.6 %) itself [39,44]. In our study Leiden mutation was infrequent in IBD patients with thrombosis. The frequency was the same

that as observed in normal Hungarian population without thrombosis (5.26 %)[45]. Most thromboembolic episodes developed in the lower extremities, in some patient with pulmonary embolism as a complication. Thrombosis of the splenic vein occurred in one young female CD patient with ileocolonic disease.

Other EIMs Glomerulonephritis is a rare complication in IBD. Only case reports could be found in the literature[46]. Deposition of immune-complexes is thought to be involved in the pathogenesis. Finding 3 patients (1 UC and 2 CD) in this series was an unexpected high number. Histology revealed IgA nephropathy, membranous glomerulonephritis and focal glomerulosclerosis. Ductal changes suggesting chronic pancreatitis were common in IBD[47]. Our two pancreatitis cases developed in patients taking azathioprine.

In conclusion, in IBD a variety of EIMs may occur during the course of the disease affecting several organ systems. In Hungarian IBD patients, major EIMs develop in concordance with previous European data in approximately one fifth of the patients. The high number of EIMs supports a role for complex follow-up in these patients.

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