

Smoking increases the risk of extraintestinal manifestations in Crohn's disease

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Abstract

AIM: To demonstrate a high prevalence of extraintestinal manifestations (EIMs) in a prospective population-based cohort of inflammatory bowel disease (IBD) patients at first diagnosis as well as during the early course of the disease.

METHODS: EIMs are common in patients with IBD. Data on the frequency of EIMs have mostly been assessed in patients from tertiary centers; however, data about the prevalence of EIMs at first diagnosis as well as factors influencing their incidence during the early course of disease from prospective population-based cohorts are scarce. We present data of patients of our population-based "Oberpfalz cohort" (Bavaria, Germany) from first diagnosis (up to 3 mo after first diagnosis) as well as during the early course of the disease. Possible risk factors were assessed by calculating the relative risk (RR) as well as using logistic regression analysis.

RESULTS: In total, data of 257 newly diagnosed pa-

tients with IBD were evaluated [161 Crohn's disease (CD), 96 ulcerative colitis (UC)]. Median duration of follow-up was 50 mo after first diagnosis. In 63.4% of all patients ($n = 163$), an EIM was diagnosed at any point during the observation period. At first diagnosis, patients with CD had a significantly increased risk of an EIM [$n = 69$ (42.9%)] compared with UC patients [$n = 21$ (21.9%); $P < 0.001$; RR = 1.96; 95%CI: 1.30-2.98]. Active smoking increased the risk of CD patients developing an EIM during the early course of the disease, but notably not of UC patients ($P = 0.046$; RR = 1.96; 95%CI: 1.01-3.79). In addition, using logistic regression analysis, the need for IBD-related surgery and a young age at first diagnosis were identified as risk factors for the development of an EIM in CD patients. No association with EIMs was found for the factors sex, localization of the disease and positive family history of IBD. In contrast, no key factors which increased the risk of development of an EIM could be identified in UC patients.

CONCLUSION: We found a high prevalence of EIM in this cohort at first diagnosis and during the early course of the disease. In patients with CD, smoking, need for surgery and younger age at first diagnosis were risk factors for the development of an EIM.

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Key words: Extraintestinal manifestations; Crohn's disease; Ulcerative colitis; Smoking; Surgery; Age at onset

Core tip: Owing to the high prevalence of extraintestinal manifestations (EIM) in patients with inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis have to be considered as systemic diseases. However, prospective data on the prevalence of EIM at first diagnosis from population-based cohorts are lacking. We found a high prevalence of EIMs in our population-based cohort of IBD patients at first diagnosis, with an increased risk in patients with CD. More than 60%

of patients developed an EIM during the early course of disease. Smoking, young age at disease onset and the need for IBD-related surgery were identified as risk factors for developing an EIM in CD.

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INTRODUCTION

Given that many patients with inflammatory bowel diseases (IBD) are affected by extraintestinal manifestations (EIMs) at any point during their disease course, Crohn's disease (CD) and ulcerative colitis (UC) have to be considered as systemic diseases. In general, EIMs and complications can be divided into three different groups. The first group includes IBD-related diseases, which mainly correlate with intestinal disease activity and which are ameliorated by treatment of the underlying disease (*e.g.*, peripheral arthritis, erythema nodosum). The second comprises EIMs, which are activity-independent such as primary sclerosing cholangitis (PSC) and ankylosing spondylitis. Finally, in the third group, IBD-related extraintestinal complications have to be considered which are caused by the disease itself due to the loss of function of diseased or resected bowel (*e.g.*, micronutrient deficiencies) and those due to specific treatments (*e.g.*, peripheral neuropathy, drug-induced fatty liver disease)^[1].

In different studies, the prevalence of EIMs in patients with IBD varied between 6% and 53%, depending on the study design and criteria used^[2-8]. The most common EIMs include arthralgias/arthritis, and cutaneous, ophthalmologic and hepatobiliary manifestations, but less frequent manifestations such as pulmonary or neurologic involvement have to be considered in IBD patients. Of clinical importance, extraintestinal symptoms might appear prior to first diagnosis of an IBD, simultaneously with the occurrence of intestinal symptoms or even after resection of affected bowel segments.

Most studies on the prevalence of EIMs in IBD patients have been conducted in tertiary centers including consecutive patients at any time point during their disease course. There are only a few studies focusing on the prevalence of EIMs at the time of first diagnosis^[9]. Two are retrospective studies from tertiary centers in Iran and China, and there is just one population-based cohort study using data from a Medicaid database to conduct a retrospective matched-cohort study^[10-12]. However, prospective studies on the prevalence of EIM at first diagnosis from population-based cohorts are lacking. Therefore, the aim of our study was to assess the prevalence of different EIMs in patients with IBD at onset of the disease and during the early course. Furthermore, we aimed to

identify possible risk factors for the development of an EIM during the first years of the disease.

MATERIALS AND METHODS

Patients

We established a prospective population-based cohort in the rural region of Oberpfalz (Bavaria, Germany) by setting up a network of reporting clinicians and general practitioners including internists, gastroenterologists, surgeons and pediatricians, in hospitals as well as in private practice as described elsewhere^[13]. This study was approved by the institutional ethics committee on human studies according to criteria of the modified Helsinki Declaration of 1983.

Patients were included in this study if they presented with a first diagnosis of IBD between January 1, 2004 and December 31, 2008. For each patient, a standardized data form was completed at the time of first diagnosis by the attending physician including demographic data (date of birth, sex, place of residence), date of diagnosis, extent of disease, family history of IBD, EIMs, and actual laboratory tests. After informed consent, all patients were contacted by the study center personnel. During follow-up, information on the course of disease, appearance of different EIMs, need for IBD-related surgery (resections in CD, colectomy in UC), medical therapies and risk factor exposure were collected using pretested standardized questionnaires.

The prevalence of an EIM at first diagnosis as well as during the early course of the disease was assessed. Possible risk factors for the development of an EIM during the early course of the disease were evaluated, including sex, age at disease onset, colonic involvement in CD patients, pancolitis in UC patients, active smoking at first EIM occurrence, positive family history of IBD, need for IBD-related surgery, the presence of perianal fistula in CD, reaction to systemic corticosteroid therapy, and the need of immunosuppressants or anti-tumor necrosis factor (TNF) therapies.

Definitions of EIMs

We evaluated the main EIMs including peripheral arthropathies, ophthalmologic manifestations (conjunctivitis, episcleritis, uveitis), erythema nodosum, pyoderma gangrenosum, sacroiliitis and PSC.

Peripheral arthropathies were divided into peripheral arthralgias in patients with painful joints without obvious swelling, but with decreased range of motion, and peripheral arthritis (type I or II) in patients with pain and swelling. Patients with ocular and cutaneous manifestations were diagnosed by specialists in our center. The diagnosis of sacroiliitis with typical clinical symptoms and characteristic findings in X-ray or magnetic resonance imaging was solely made by a rheumatologist. For the diagnosis of PSC, a magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography had to be performed to visualize the typical

Table 1 Patient characteristics at first diagnosis and during follow-up *n* (%)

		All patients <i>n</i> = 257	Crohn's disease <i>n</i> = 161 (62.6)	Ulcerative colitis <i>n</i> = 96 (37.4)	<i>P</i> value RR (95%CI)
Sex: male/female		121 (47.1)/136 (52.9)	71 (44.1)/90 (55.9)	50 (52.1)/ 46 (47.9)	0.22
EIM at first diagnosis	At least 1 EIM	91 (35.4)	69 (42.9)	21 (21.9)	< 0.001; RR = 1.96 (1.30-2.95)
New EIM during follow-up	At least 1 EIM	115 (44.7)	79 (49.1)	36 (37.5)	0.07
EIM at any point of observation	At least 1 EIM	163 (63.4)	114 (69.9)	49 (30.1)	0.001; RR = 1.39 (1.11-1.73)
	> 1 EIM	24 (14.5)	18 (15.5)	6 (12.2)	0.39
New EIM during follow-up		94 (36.6)	64 (39.8)	30 (31.3)	0.17
EIM resolved during follow-up		64 (66.0)	47 (64.4)	17 (70.8)	0.63
Disease phenotype at first diagnosis	Crohn's disease		Terminal ileum (L1) 56 (34.8) Colon (L2) 40 (24.8) Terminal ileum and colon (L3) 61 (37.9) Upper GI tract (L4) 2 (1.2)	Proctitis 36 (37.5) Left-sided colitis 23 (24.0) Pancolitis 29 (30.2) ¹	
	Ulcerative colitis				

¹Not applicable in 8 patients. EIM: Extraintestinal manifestation; GI: Gastrointestinal.

irregular bile ducts with multifocal strictures.

Statistical analysis

Statistical analysis was performed using SPSS 21.0 software (IBM Corp., Armonk, NY, United States). Data are given as numbers, percentages and relative risk (RR) with 95%CI.

Univariate analyses were performed using the chi-square test based on a 95% confidence level (two sided) or Fisher's exact test as appropriate. The association of possible risk factors for developing an EIM during the observation period was analyzed using a binary logistic regression model with EIM being the dependent (outcome) variable (yes *vs* no). Independent variables in the regression model were age at disease onset (≤ 40 years *vs* > 40 years), colonic involvement in CD (yes/no), pancolitis in UC (yes/no), active smoking at the time, EIM occurring for the first time (yes/no), positive family history of IBD (yes/no), need for IBD-related surgery (yes/no), the presence of a perianal fistula in CD (yes/no) and the use of immunosuppressants or anti-TNF-therapies (yes/no). *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 257 patients with newly diagnosed IBD were included in this study. CD was diagnosed in 161 patients (males/females 71/90), and UC in 96 patients (males/females 50/46). The median observation period was 50 mo (min. 12, max. 101; SD: 19.3 mo). At first diagnosis, significantly more patients with CD suffered from an EIM [$n = 69$ (42.9%)] compared with UC patients [$n = 21$ (21.9%); $P < 0.001$; RR = 1.96; 95%CI: 1.30-2.98]. During the

whole observation period, 163 patients (63.4%) presented at least one EIM, 24 patients were affected by more than one EIM (14.5%). A new or further EIM during the early course of the disease occurred in 115 patients (44.7%; 79 CD, 36 UC; $P = 0.07$). In 64 patients, the EIM present at first diagnosis resolved during the early disease course (66%; 47 CD, 17 UC; $P = 0.63$) (Table 1). The risk of developing more than one EIM did not differ between CD and UC patients (18 CD, 6 UC; $P = 0.57$).

Frequency of different EIMs

Details on the prevalence of the different EIMs at first diagnosis are given in Table 2. Arthralgia was the most common EIM at first diagnosis with 17.8% in CD and 14.6% in UC patients, followed by arthritis (8.9% in CD, 5.2% in UC). No differences could be detected regarding the prevalence of arthralgias, arthritis, ocular manifestations, sacroiliitis, pyoderma gangrenosum and PSC in CD *vs* UC. In contrast, there was a significantly higher prevalence of erythema nodosum in CD patients at first diagnosis compared with UC patients ($P = 0.002$).

Of note, the EIM resolved in 64 patients during the observation period. One-hundred and fifteen patients developed a new EIM. Details of the different EIMs during the early course of the disease are presented in Table 3. Arthralgia and arthritis were still the most common EIMs in both patient groups. During the observation period, the development of specific EIMs did not differ between CD and UC patients.

Evaluation of possible risk factors in Crohn's disease

In univariate analysis, no sex-related preponderance for development of an EIM was found, neither at first diagnosis (47.6% in males *vs* 52.4% in females; $P = 0.64$), nor

Table 2 Different extraintestinal manifestations at first diagnosis *n* (%)

	All patients <i>n</i> = 257	Crohn's disease	Ulcerative colitis	<i>P</i> value
Arthralgia	40 (16.3)	26 (17.8)	14 (14.6)	0.60
Arthritis	18 (7.3)	13 (8.9)	5 (5.2)	0.50
Ocular manifestation	5 (2.1)	2 (1.4)	3 (3.1)	0.63
Active sacroiliitis	12 (4.9)	11 (7.6)	1 (1.0)	0.06
Pyoderma gangrenosum	2 (0.8)	1 (0.7)	1 (1.0)	0.95
Erythema nodosum	7 (2.7)	7 (4.9)	0	0.002
PSC	1 (0.4)	0	1 (1.0)	0.4

PSC: Primary sclerosing cholangitis.

during follow-up (53.3% in males *vs* 51.1% in females; *P* = 0.87) in CD patients.

In patients aged 40 or less at the onset of CD, the risk of developing an EIM during the early course of the disease was significantly increased (*P* = 0.026; RR = 2.4; 95%CI: 1.01-5.23).

As colonic disease in CD patients is described to increase the risk for EIMs, we evaluated all EIMs according to disease localization. In our population, no correlation between colonic disease and any type of EIM was found (EIM at any point and colonic involvement: *P* = 0.83; RR = 1.1; 95%CI: 0.5-2.2).

In 35 patients with CD (21.7%), at least one first-degree relative was also affected with IBD, which was defined as a positive family history. The variable "positive family history" showed no correlation with the diagnosis of an EIM (*P* = 1.0; RR = 1.0; 95%CI: 0.45-2.40).

Smoking was defined as "yes", if the patient was an active smoker at the time the EIM was diagnosed for the first time. At first diagnosis, 45 patients (24.9%) were active smokers. At the time the EIM became obvious, 55 patients (34.2%) were active smokers. In our cohort of CD patients, an association of active smoking with the risk of developing an EIM became obvious (*P* = 0.046; RR = 1.96; 95%CI: 1.01-3.79). Moreover, active smoking was strongly associated with the occurrence of arthralgias (*P* = 0.021; RR = 3.6; 95%CI: 1.17-11.04).

At first diagnosis, 19 patients were diagnosed with perianal fistula (12.8%), 10 patients had fistulas other than perianal (*e.g.*, entero-enteric, 6.7%). In 26 patients, an abscess was found at first diagnosis (17.4%). In total, 27 patients (16.8%) with CD had to undergo IBD-related surgery, mainly due to a fistula or abscess. If the patient needed surgery for his disease, the risk of suffering from an EIM was significantly increased (*P* = 0.015; RR = 2.93; 95%CI: 1.2-7.16). In contrast, the presence of perianal fistulas had no influence on the development of EIMs (*P* = 0.72; RR = 1.2; 95%CI: 0.40-3.84).

According to disease specific therapies at first diagnosis, 69 patients with CD were treated with systemic corticosteroids (46.3%), 28 patients with budesonide (18.8%), 24 (16.1%) with mesalamine, 2 patients (1.3%) with azathioprine monotherapy, and 6 patients with systemic steroids and azathioprine (4.0%). In 63.1% of patients with steroid therapy, the EIM present at first

Table 3 Different extraintestinal manifestations during the observation period *n* (%)

	All patients <i>n</i> = 257	Crohn's disease	Ulcerative colitis	<i>P</i> value
Arthralgia	89 (34.6)	56 (34.8)	33 (34.4)	1.0
Arthritis	23 (8.9)	13 (8.1)	10 (10.4)	0.65
Ocular manifestation	19 (7.4)	13 (8.1)	6 (6.2)	0.81
Active sacroiliitis	7 (2.7)	5 (3.1)	2 (2.1)	1.0
Pyoderma gangrenosum	0	0	0	1.0
Erythema nodosum	1 (0.4)	1 (0.6)	0	1.0
PSC	1 (0.4)	0	1 (1.0)	0.4

PSC: Primary sclerosing cholangitis.

diagnosis resolved during the observation period. During the early course of the disease, 27 patients never received systemic corticosteroids (17.1%), whereas 76 patients (47.2%) were treated with an immunosuppressive therapy [azathioprine or methotrexate *n* = 55 (74.3%), anti-TNF-therapy *n* = 19 (25.7%)]. There was no correlation between development of an EIM and the specific response towards corticosteroid therapy, including induction of remission (46.3%), steroid-dependency (35.8%), or steroid-refractory course (17.9%) (steroid-dependent: *P* = 0.30; RR = 0.5; 95%CI: 0.1-1.8; steroid-refractory: *P* = 1.0; RR = 1.0; 95%CI: 0.3-3.8).

In addition, patients with EIMs, either suffering from disease activity-dependent EIM or disease activity-unrelated EIM, were not treated more frequently with immunosuppressive agents (azathioprine, methotrexate) or anti-TNF-therapy (infliximab, adalimumab) compared with patients without an EIM (*P* = 0.82; RR = 1.1; 95%CI: 0.6-2.0). Rates of clinical remission were not different in patients with or without EIMs. Patients with an EIM during the observation period achieved remission in 78.1% of cases, while 76.6% of patients without an EIM were in remission with an average duration of remission of 19 and 28 mo, respectively (*P* = 0.84; RR = 1.1; 95%CI: 0.49-2.44).

Logistic regression model evaluating risk factors for an EIM in CD

The results of the binary logistic regression model with EIM being the dependent (outcome) variable are given in Table 4. The multivariable model suggests an increased risk of developing an EIM in patients needing surgery for IBD, active smoking patients and patients with younger age at first diagnosis.

Evaluation of possible risk factors in ulcerative colitis

We also evaluated these risk factors in patients suffering from UC. No relationship was identified according to the development of an EIM, and the variables sex, diagnosis of pancolitis, positive family history, active smoking, younger age at first diagnosis, the need of immunosuppressive therapy/anti-TNF-therapy or the reaction to corticosteroid therapy. In detail, 52 patients with UC received systemic corticosteroids at first diagnosis (49.5%), 23 patients (21.9%) were treated with mesalamine and no

Table 4 Univariate analysis and logistic regression model (outcome variable = extraintestinal manifestation during observation period) for Crohn's disease *n* (%)

Variable	Category (<i>n</i>)	With EIM	Univariate analysis		Logistic regression analysis	
			<i>P</i> value	RR (95%CI)	<i>P</i> value	RR (95%CI)
Surgery	Yes (27)	19 (70.4)	0.015	2.93 (1.20-7.16)	0.015	3.19 (1.26-8.02)
	No (134)	60 (44.8)				
Smoking	Yes (55)	33 (60.0)	0.046	1.96 (1.01-3.74)	0.023	2.36 (1.13-4.93)
	No (106)	46 (43.4)				
Age	≤ 40 yr (126)	62 (49.2)	0.026	2.40 (1.01-5.23)	0.011	2.94 (1.28-6.76)
	> 40 yr (35)	22 (62.9)				
Family history	Yes (35)	20 (57.1)	0.510	1.29 (0.61-2.75)	0.260	1.59 (0.71-3.55)
	No (126)	64 (50.8)				
Sex	Female (90)	46 (51.1)	0.870	0.9 (0.49-1.69)	0.070	0.52 (0.25-1.05)
	Male (71)	38 (53.3)				

EIM: Extraintestinal manifestation.

Table 5 Univariate analysis for ulcerative colitis *n* (%)

Variable	Category (<i>n</i>)	With EIM	Univariate analysis	
			<i>P</i>	RR (95%CI)
Sex	Female (46)	17 (37.0)	0.92	0.96 (0.42-2.20)
	Male (50)	19 (38.0)		
Pancolitis ¹	Yes (29)	12 (41.4)	0.49	1.38 (0.55-3.44)
	No (59)	20 (33.9)		
Surgery	Yes (6)	5 (83.3)	0.03	9.52 (1.06-85.08)
	No (90)	31 (34.4)		
Family history	Yes (5)	1 (20.0)	0.65	0.39 (0.04-3.66)
	No (90)	25 (38.9)		
Smoking	Yes (19)	7 (36.8)	0.80	1.14 (0.42-3.13)
	No (77)	29 (37.7)		
Age	≤ 40 y (67)	27 (40.3)	0.39	0.67 (0.26-1.68)
	> 40 y (29)	9 (31.0)		
Immunosuppressive therapy	Yes (27)	11 (40.7)	0.71	1.18 (0.48-2.95)
	No (68)	25 (36.8)		

¹Not applicable in 8 patients. EIM: Extraintestinal manifestation.

patient had immunosuppressive therapy. Corticosteroid therapy induced remission in 44.1% of patients, 33.8% became steroid-dependent, and 22.1% of patients had a steroid-refractory course of their disease. During the observation period, 23 patients (24.2%) never had corticosteroids and 27 patients (28.4%) needed immunosuppressive therapy [azathioprine or methotrexate, *n* = 23 (85.2%); anti-TNF-therapy, *n* = 4 (14.8%)].

In 76.5% of patients with UC receiving corticosteroids, the EIM present at first diagnosis resolved during the observation period. However, no correlation was found with the reaction to corticosteroid therapy and the development of an EIM during the observation period (steroid-dependent: *P* = 0.67; RR = 1.3; 95%CI: 0.4-4.5; steroid-refractory: *P* = 0.16; RR = 2.6; 95%CI: 0.7-10.1).

As presented in Table 5, only the need for surgery (colectomy in all cases) significantly increased the risk of a concomitant EIM (*P* = 0.03; RR = 9.52; 95%CI: 1.06-85.08). However, as expected, the number of affected patients was rather small (*n* = 6 needing surgery).

Relationship of different EIMs

We finally assessed the relationship of different EIMs

in patients suffering from more than one EIM. The presence of arthralgias was significantly associated with an ocular manifestation (*P* < 0.001; RR = 6.1; 95%CI: 2.11-17.51). In addition, patients suffering from arthritis had an increased risk of developing ocular manifestations (*P* = 0.001; RR = 5.64; 95%CI: 1.92-16.61) and sacroiliitis (*P* = 0.12; RR = 5.41; 95%CI: 1.26-23.19).

DISCUSSION

Several studies, mostly retrospective or case-control from tertiary centers have shown a high prevalence of EIMs in patients with IBD, ranging from 6% to 53%. However, prospective data focusing on the presence of EIMs at first diagnosis and during the early course of the disease from a population-based cohort are lacking. Therefore, owing to the high impact of EIMs on patient quality of life, this study aimed to evaluate the prevalence of EIMs in IBD patients at the onset of their disease and during the early course of disease. Additionally, we assessed factors possibly related to the development of an EIM during the first years after diagnosis of an IBD.

The wide variations in the prevalence of EIMs may on the one hand be explained by the differences in study design, inclusion criteria and the patient cohorts used. On the other hand, the development of EIMs may vary due to geographic differences, as African-Americans, for example, seem to be at higher risk of EIMs compared with Caucasians^[14-16].

One of the lowest prevalence rates of EIM was reported by Bernstein *et al*^[3], with an overall EIM rate of only 6.2% in IBD patients with a minimum 10-year course of disease. However, arthralgias and arthritis were excluded from this study, which represent the most common EIMs in several reports^[4,7,8,17,18].

In our population, the incidence of an EIM at first diagnosis was 36.2% in all patients, with a significant preponderance in CD patients (42.9% *vs* 21.9% in UC). These results are in line with the study of Greenstein *et al*^[6] (prevalence of 36% in an IBD cohort of 700 patients), and with recent data from a geographically similar cohort from Switzerland, in which 43% of CD patients

and 31% of UC patients suffered from EIMs^[4]. Nevertheless, 64.2% of patients in our study developed at least one EIM at any point during the early course of their disease, with a median observation period of 50 mo. These findings are even higher than the rate of EIMs described by Löfberg *et al*^[8] in his study on the effect of adalimumab on EIMs in CD, which was reported to be 53% in 945 patients. One may speculate that this high rate of EIMs, especially of disease activity-dependent EIMs, is related to the population-based design of our study, as in this cohort, patients are seen to some extent by general practitioners and not in tertiary centers, particularly if they have only a few abdominal symptoms and the course of the abdominal disease is relatively mild at first diagnosis and during the first years after onset.

The increased risk for patients with CD of developing an EIM has been reported in several studies^[4,6,10,19-21]. In contrast, only a few studies did not find any association of EIMs with IBD type^[3,22]. In our cohort, the prevalence of EIMs was higher in patients with CD at first diagnosis, whereas the risk of developing a new EIM during the early course of the disease was not different between CD and UC patients.

The most common EIMs in our study were arthropathies, both in CD and UC. As mentioned above, these results are in line with several studies confirming the high rates of joint involvement, with arthralgias described in up to 47.1% of patients^[8] and arthritis in about 20%-33%^[4,6,7,23].

Patients suffering from one EIM seem to be at increased risk of developing further extraintestinal symptoms, in particular if joints, the biliary tract, eyes or skin (erythema nodosum) are involved. Therefore, a common pathogenic pathway is suggested in some EIMs, as they tend to appear simultaneously in affected patients^[24].

As reported by Vavricka *et al*^[4], we also found an association of peripheral arthritis with sacroiliitis. Additionally, a relationship between arthropathies and ocular manifestations was obvious in our series.

Erythema nodosum, representing another disease activity-dependent EIM, is reported to occur more frequently in CD patients and females^[25]. In our cohort, significantly more patients with CD were found to suffer from erythema nodosum at first diagnosis, but we could not find a female predisposition. The prevalence at first diagnosis compared well with previous data, which reported rates of erythema nodosum of 2%-7.5% in CD and 0.9%-4% in UC^[6,19,26]. During the early disease course, the frequency of erythema nodosum decreased, most probably due to induction of specific treatment for the underlying IBD.

Pyoderma gangrenosum, representing the second main IBD-related cutaneous manifestation, was diagnosed less frequently at disease onset, which is in accordance with previous studies reporting a prevalence of pyoderma gangrenosum of 0.6%-2.2%^[25,26].

Our findings on the prevalence of sacroiliitis with an increased risk in CD patients were comparable to other series, with an overall prevalence rate of 1%-6%^[4,6,27].

Furthermore, the frequency of ophthalmologic manifestations in our cohort, including conjunctivitis, episcleritis and uveitis was in line with the previously described rates of 2%-12%^[4,6,7,18,19,28].

There have been few studies evaluating factors which influence the risk of suffering from EIMs. Several studies reported an increased rate of EIMs in patients with colonic CD, suggesting differences in immune tolerance mechanisms and bacterial flora being relevant for this finding^[6,17-19,29]. In contrast, the study of Vavricka *et al*^[4] could not confirm this association. In our series, neither colonic involvement in CD patients nor pancolitis in UC patients was identified to increase the risk of developing an EIM. This might be due to the fact that our cohort is studied during the early course of the disease, while disease location and extent is still limited in many patients, with a chance for progression during the later years.

In addition, a positive family history might influence the occurrence of EIM, as an association between different genetic markers and the development of EIMs has been shown^[30]. There are only two studies directly addressing the impact of positive family history on the development of EIMs. Vavricka *et al*^[4] found an increased risk of EIMs in CD patients with a positive family history of IBD, whereas Lakatos *et al*^[19] reported joint and ocular manifestations associated with familial UC. In our cohort, no relationship between a positive family history and the development of an EIM was obvious, neither in CD nor in UC patients.

Active smoking has been shown to have a negative impact on disease behavior in CD patients, resulting in higher rates of complications in several studies^[31-34]. Lakatos *et al*^[35] previously reported an association between smoking and EIMs in a Hungarian population. We clearly confirmed this variable as a risk factor for EIMs during the early course of the disease in CD patients in our population-based cohort. Manguso *et al*^[36] found a negative influence of smoking on the development of EIM in UC patients, but this phenomenon was obvious only after a disease course of about 10 years. However, as we do not have data of passive smoking history, this must be considered as a possible confounder.

Of note, the need of surgery was related to an increased risk of EIMs in both CD and UC patients in our study. In CD patients, 70.4% of patients who required surgery also suffered from an EIM. In UC, 83.3% of patients needing colectomy during the observation period presented with an EIM, although there was a limitation because of the small number of operated patients in UC. These findings were in contrast to previous reports which found no association of surgery with EIMs^[4,18,37]. One possible explanation for the association of surgery with EIMs might be the early stage of disease in our cohort, with some patients presenting with severe disease at first diagnosis and needing urgent surgery due to high activity. This high activity might also be responsible for the frequent development of disease activity-dependent EIMs in those patients.

This study, presenting a high prevalence of EIMs at

the onset of IBD, has several strengths but also limitations. The main strength is the prospective population-based design of the study, not only including patients from hospitals or tertiary centers, but also patients with milder forms of IBD, which are mainly treated by their family doctors and general practitioners. The prospective follow-up provided a favorable basis to avoid underreporting of EIMs during the early course of the disease, especially compared with retrospective results from databases. However, owing to the moderate incidence of IBD in our region, the number of patients assessed was lower than in some previous studies, which included patients at different points of their disease course.

We are well aware that the duration of follow-up, with a median of 50 mo, might be too short to identify risk factors influencing the development of EIMs later in the disease course. However, the focus of our study was to evaluate the frequency of EIMs during the early course of the disease and to identify possible risk factors at that stage, in order to increase the clinical awareness of EIMs.

In conclusion, we demonstrate a high prevalence of EIMs in a prospective population-based cohort of IBD patients at first diagnosis as well as during the early course of the disease. In patients with CD, the need of IBD-related surgery, young age at first diagnosis, and active smoking are associated with the development of EIMs, whereas in UC no key risk factors could be identified. Owing to the high impact of EIMs on the quality of life in affected patients, one goal in the care of IBD-patients is to increase the awareness of these conditions, which in some cases are more incapacitating than the intestinal disease itself. Prompt diagnosis and sufficient treatment is essential to prevent severe morbidity and mortality in patients suffering from EIMs. Of note, our data strongly confirm the negative effect of smoking on the course of the disease, especially in CD patients.

COMMENTS

Background

Crohn's disease (CD) and ulcerative colitis (UC) are chronic diseases of the digestive tract. Main symptoms are abdominal pain and diarrhea, which may be bloody in severe cases. As these diseases may also cause complications outside the gastrointestinal tract, such as arthralgias, arthritis, inflammation of the eyes and lesions of the skin (erythema nodosum, pyoderma gangrenosum), inflammatory bowel diseases (IBD) have to be considered as systemic diseases.

Research frontiers

The manifestations outside the gastrointestinal tract, so-called extraintestinal manifestations (EIMs), are in some cases more incapacitating than the intestinal disease itself. Prospective studies on the prevalence of EIMs at first diagnosis from population-based cohorts of patients with IBD are lacking. Therefore, the aim of this study was to assess the prevalence of different EIMs in patients with IBD at onset of the disease and during the early course.

Innovations and breakthroughs

A high prevalence of EIMs was found in this population-based cohort of IBD patients at first diagnosis, especially in patients with CD. Furthermore, authors were able to identify possible risk factors for the development of EIMs in patients with CD.

Applications

Owing to the high impact of EIMs on the quality of life in affected patients, early recognition and adequate treatment is necessary to prevent severe morbidity

and mortality. By demonstrating a high prevalence of EIMs, the awareness of these conditions might be increased and, as a consequence, the care of affected patients might be improved.

Terminology

IBD are chronic inflammatory conditions of the gastrointestinal tract with the two major types CD and UC. Main symptoms of these diseases are abdominal pain and diarrhea; CD: this inflammatory bowel disease can affect every part of the gastrointestinal tract from the mouth to the anus. Complications as stenosis or fistulas can occur; ulcerative colitis: in contrast to CD, ulcerative colitis is restricted to the colon and rectum; EIMs: beyond the intestinal manifestation of the disease, patients with IBD can develop complications outside the gastrointestinal tract. The most common include arthropathies, cutaneous and ophthalmologic manifestations as well as manifestations of the hepatobiliary system.

Peer review

The paper is informative and original in presenting the prevalence of extraintestinal manifestation of disease in a population of patients at first diagnosis of IBD or the early course of the disease. Undoubtedly, the clinical consequences of the findings are substantial.

REFERENCES

- Ott C, Schölmerich J. Extraintestinal manifestations and complications in IBD. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 585-595 [PMID: 23835489 DOI: 10.1038/nrgastro.2013.117]
- Su CG, Judge TA, Lichtenstein GR. Extraintestinal manifestations of inflammatory bowel disease. *Gastroenterol Clin North Am* 2002; **31**: 307-327 [PMID: 12122740]
- Bernstein CN, Blanchard JF, Rawsthorne P, Yu N. The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001; **96**: 1116-1122 [PMID: 11316157]
- Vavricka SR, Brun L, Ballabeni P, Pittet V, Prinz Vavricka BM, Zeitz J, Rogler G, Schoepfer AM. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011; **106**: 110-119 [PMID: 20808297 DOI: 10.1038/ajg.2010.343]
- Ricart E, Panaccione R, Loftus EV, Tremaine WJ, Harmsen WS, Zinsmeister AR, Sandborn WJ. Autoimmune disorders and extraintestinal manifestations in first-degree familial and sporadic inflammatory bowel disease: a case-control study. *Inflamm Bowel Dis* 2004; **10**: 207-214 [PMID: 15290913]
- Greenstein AJ, Janowitz HD, Sachar DB. The extra-intestinal complications of Crohn's disease and ulcerative colitis: a study of 700 patients. *Medicine (Baltimore)* 1976; **55**: 401-412 [PMID: 957999]
- Veloso FT, Carvalho J, Magro F. Immune-related systemic manifestations of inflammatory bowel disease. A prospective study of 792 patients. *J Clin Gastroenterol* 1996; **23**: 29-34 [PMID: 8835896]
- Löfberg R, Louis EV, Reinisch W, Robinson AM, Kron M, Cammez A, Pollack PF. Adalimumab produces clinical remission and reduces extraintestinal manifestations in Crohn's disease: results from CARE. *Inflamm Bowel Dis* 2012; **18**: 1-9 [PMID: 21351211 DOI: 10.1002/ibd.21663]
- Isaacs KL. How prevalent are extraintestinal manifestations at the initial diagnosis of IBD? *Inflamm Bowel Dis* 2008; **14** Suppl 2: S198-S199 [PMID: 18816779 DOI: 10.1002/ibd.20597]
- Aghazadeh R, Zali MR, Bahari A, Amin K, Ghahghaie F, Firouzi F. Inflammatory bowel disease in Iran: a review of 457 cases. *J Gastroenterol Hepatol* 2005; **20**: 1691-1695 [PMID: 16246187]
- Cao Q, Si JM, Gao M, Zhou G, Hu WL, Li JH. Clinical presentation of inflammatory bowel disease: a hospital based retrospective study of 379 patients in eastern China. *Chin Med J (Engl)* 2005; **118**: 747-752 [PMID: 15899137]
- Arora G, Singh G, Vadavkar S, Shah SB, Mannalithara A, Mithal A, Triadafilopoulos G. Incidence and risk of intestinal and extra-intestinal complications in Medicaid patients with inflammatory bowel disease: a 5-year population-based

- study. *Dig Dis Sci* 2010; **55**: 1689-1695 [PMID: 20428948]
- 13 **Ott C**, Obermeier F, Thieler S, Kempfner D, Bauer A, Schölmacher J, Rogler G, Timmer A. The incidence of inflammatory bowel disease in a rural region of Southern Germany: a prospective population-based study. *Eur J Gastroenterol Hepatol* 2008; **20**: 917-923 [PMID: 18794607 DOI: 10.1097/MEG.0b013e3282f97b33]
 - 14 **Jiang L**, Xia B, Li J, Ye M, Yan W, Deng C, Ding Y, Luo H, Hou W, Zhao Q, Liu N, Ren H, Hou X, Xu H. Retrospective survey of 452 patients with inflammatory bowel disease in Wuhan city, central China. *Inflamm Bowel Dis* 2006; **12**: 212-217 [PMID: 16534423]
 - 15 **Nguyen GC**, Torres EA, Regueiro M, Bromfield G, Bitton A, Stempak J, Dassopoulos T, Schumm P, Gregory FJ, Griffiths AM, Hanauer SB, Hanson J, Harris ML, Kane SV, Orkwis HK, Lahaie R, Oliva-Hemker M, Pare P, Wild GE, Rioux JD, Yang H, Duerr RH, Cho JH, Steinhardt AH, Brant SR, Silverberg MS. Inflammatory bowel disease characteristics among African Americans, Hispanics, and non-Hispanic Whites: characterization of a large North American cohort. *Am J Gastroenterol* 2006; **101**: 1012-1023 [PMID: 16696785]
 - 16 **White JM**, O'Connor S, Winter HS, Heyman MB, Kirschner BS, Ferry GD, Cohen SA, Baldassano RN, Smith T, Clemons T, Gold BD. Inflammatory bowel disease in African American children compared with other racial/ethnic groups in a multicenter registry. *Clin Gastroenterol Hepatol* 2008; **6**: 1361-1369 [PMID: 18848910 DOI: 10.1016/j.cgh.2008.07.032]
 - 17 **Barreiro-de Acosta M**, Domínguez-Muñoz JE, Núñez-Pardo de Vera MC, Lozano-León A, Lorenzo A, Peña S. Relationship between clinical features of Crohn's disease and the risk of developing extraintestinal manifestations. *Eur J Gastroenterol Hepatol* 2007; **19**: 73-78 [PMID: 17206080]
 - 18 **Repiso A**, Alcántara M, Muñoz-Rosas C, Rodríguez-Merlo R, Pérez-Gruoso MJ, Carrobes JM, Martínez-Potenciano JL. Extraintestinal manifestations of Crohn's disease: prevalence and related factors. *Rev Esp Enferm Dig* 2006; **98**: 510-517 [PMID: 17022700]
 - 19 **Lakatos L**, Pandur T, David G, Balogh Z, Kuronya P, Tollas A, Lakatos PL. 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. *World J Gastroenterol* 2003; **9**: 2300-2307 [PMID: 14562397]
 - 20 **Danzi JT**. Extraintestinal manifestations of idiopathic inflammatory bowel disease. *Arch Intern Med* 1988; **148**: 297-302 [PMID: 3277559]
 - 21 **Veloso FT**. Extraintestinal manifestations of inflammatory bowel disease: do they influence treatment and outcome? *World J Gastroenterol* 2011; **17**: 2702-2707 [PMID: 21734777 DOI: 10.3748/wjg.v17.i22.2702]
 - 22 **Jose FA**, Heyman MB. Extraintestinal manifestations of inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2008; **46**: 124-133 [PMID: 18223370 DOI: 10.1097/MPG.0b013e318093f4b0]
 - 23 **Salvarani C**, Vlachonikolis IG, van der Heijde DM, Fornaciari G, Macchioni P, Beltrami M, Olivieri I, Di Gennaro F, Politi P, Stockbrügger RW, Russel MG. Musculoskeletal manifestations in a population-based cohort of inflammatory bowel disease patients. *Scand J Gastroenterol* 2001; **36**: 1307-1313 [PMID: 11761022]
 - 24 **Das KM**. Relationship of extraintestinal involvements in inflammatory bowel disease: new insights into autoimmune pathogenesis. *Dig Dis Sci* 1999; **44**: 1-13 [PMID: 9952216]
 - 25 **Farhi D**, Cosnes J, Zizi N, Chosidow O, Seksik P, Beaugerie L, Aractingi S, Khosrotehrani K. Significance of erythema nodosum and pyoderma gangrenosum in inflammatory bowel diseases: a cohort study of 2402 patients. *Medicine (Baltimore)* 2008; **87**: 281-293 [PMID: 18794711 DOI: 10.1097/MD.0b013e318187cc9c]
 - 26 **Tromm A**, May D, Almus E, Voigt E, Greving I, Schwegler U, Griga T. Cutaneous manifestations in inflammatory bowel disease. *Z Gastroenterol* 2001; **39**: 137-144 [PMID: 11253504]
 - 27 **Palm O**, Moum B, Ongre A, Gran JT. Prevalence of ankylosing spondylitis and other spondyloarthropathies among patients with inflammatory bowel disease: a population study (the IBSEN study). *J Rheumatol* 2002; **29**: 511-515 [PMID: 11908564]
 - 28 **Felekis T**, Katsanos K, Kitsanou M, Trakos N, Theopistos V, Christodoulou D, Asproudis I, Tsianos EV. Spectrum and frequency of ophthalmologic manifestations in patients with inflammatory bowel disease: a prospective single-center study. *Inflamm Bowel Dis* 2009; **15**: 29-34 [PMID: 18626979 DOI: 10.1002/ibd.20584]
 - 29 **Monsén U**, Sorstad J, Hellers G, Johansson C. Extracolonic diagnoses in ulcerative colitis: an epidemiological study. *Am J Gastroenterol* 1990; **85**: 711-716 [PMID: 2353691]
 - 30 **Satsangi J**, Grootcholten C, Holt H, Jewell DP. Clinical patterns of familial inflammatory bowel disease. *Gut* 1996; **38**: 738-741 [PMID: 8707121]
 - 31 **Cosnes J**, Carbonnel F, Carrat F, Beaugerie L, Cattin S, Gendre J. Effects of current and former cigarette smoking on the clinical course of Crohn's disease. *Aliment Pharmacol Ther* 1999; **13**: 1403-1411 [PMID: 10571595]
 - 32 **Louis E**, Michel V, Hugot JP, Reenaers C, Fontaine F, Delforge M, El Yafi F, Colombel JF, Belaiche J. Early development of stricturing or penetrating pattern in Crohn's disease is influenced by disease location, number of flares, and smoking but not by NOD2/CARD15 genotype. *Gut* 2003; **52**: 552-557 [PMID: 12631668]
 - 33 **Picco MF**, Bayless TM. Tobacco consumption and disease duration are associated with fistulizing and stricturing behaviors in the first 8 years of Crohn's disease. *Am J Gastroenterol* 2003; **98**: 363-368 [PMID: 12591056]
 - 34 **Lindberg E**, Järnerot G, Huitfeldt B. Smoking in Crohn's disease: effect on localisation and clinical course. *Gut* 1992; **33**: 779-782 [PMID: 1624159]
 - 35 **Lakatos PL**, Szalay F, Tulassay Z, Molnar T, Kovacs A, Gasztonyi B, Papp J, Lakatos L. Clinical presentation of Crohn's disease. association between familial disease, smoking, disease phenotype, extraintestinal manifestations and need for surgery. *Hepatogastroenterology* 2005; **52**: 817-822 [PMID: 15966211]
 - 36 **Manguso F**, Sanges M, Staiano T, Gargiulo S, Nastro P, Gargano D, Somma P, Mansueto G, Peluso R, Scarpa R, D'Armiento FP, Astarita C, Ayala F, Renda A, Mazzacca G, D'Arienzo A. Cigarette smoking and appendectomy are risk factors for extraintestinal manifestations in ulcerative colitis. *Am J Gastroenterol* 2004; **99**: 327-334 [PMID: 15046225]
 - 37 **Yi F**, Chen M, Huang M, Li J, Zhao J, Li L, Xia B. The trend in newly diagnosed Crohn's disease and extraintestinal manifestations of Crohn's disease in central China: a retrospective study of a single center. *Eur J Gastroenterol Hepatol* 2012; **24**: 1424-1429 [PMID: 22895389 DOI: 10.1097/MEG.0b013e3283583e5c]

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