Relationship between clinical features of Crohn's disease and the risk of developing extraintestinal manifestations

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Objectives **Crohn's disease is frequently associated with extraintestinal manifestations. The aim of this study was to evaluate the degree of association between the development of extraintestinal manifestations, the clinical forms of Crohn's disease according to the Vienna Classification and to the presence of several potential risk factors of the disease.**

Methods **One hundred and seventy-three consecutive Crohn's disease patients were studied. Sex, smoking habits, previous Crohn's disease-related surgery, family history of Crohn's disease, steroid dependency, steroid resistance and the presence of at least one mutant allele in any of the three considered variants of CARD15 gene were considered as potential risk factors. The Vienna Classification was applied, and the presence of extraintestinal manifestations was evaluated.**

Results **A total of 61 (35.3%) patients developed extraintestinal manifestations. They were more frequently seen in women than in men (41.1 vs. 26.7%), (odds ratio 1.92, 95% confidence interval: 0.99–3.70; $P=0.05$) and in steroid-dependent patients than in steroid responders (61.1 vs. 28.5%), (odds ratio 3.94, 95% confidence interval: 1.83–8.49; $P<0.01$). No relationship was found in general between the extraintestinal manifestations of Crohn's disease and smoking habits, previous Crohn's disease-related surgery, a family history of Crohn's disease, steroid resistance and CARD15 mutations. Such relationships were, however, detected for some individual extraintestinal manifestations as between both smoking habits (odds ratio 9.09, 95% confidence interval: 1.15–71.66; $P<0.05$) and the G908R CARD15 mutation (odds ratio 4.76, 95% confidence interval: 1.11–20.43; $P<0.05$), respectively, and erythema nodosum. Patients with any colonic involvement of Crohn's disease (L2 + L3) suffered from extraintestinal manifestations of the disease more frequently than patients without colonic involvement (42.7 vs. 25.9%, respectively; odds ratio 2.12, 95% confidence interval: 1.10–4.07; $P<0.05$).**

Conclusions **Female gender, steroid-dependency and colonic involvement are associated with the risk of developing extraintestinal manifestations of Crohn's disease.** ***Eur J Gastroenterol Hepatol*** **19:73–78 © 2007 Lippincott Williams & Wilkins.**

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Introduction

Crohn's disease (CD), a multifactorial polygenic chronic inflammatory disorder that may affect any part of the gastrointestinal tract, is frequently associated with other chronic inflammatory conditions involving different organs and systems. These conditions are so common in Crohn's patients that they are considered as extraintestinal manifestations (EIMs) of the disease [1]. Some form of EIMs is probably present at some time or other in well over 25% of patients with CD. Among these, the most frequent EIMs are those involving the joints, such as peripheral arthritis (present in about 15–20% of CD patients), ankylosing spondylitis (3–5%), sacroiliitis (10–15%), and skin manifestations, such as erythema nodosum (5–10%) and pyoderma gangrenosum (1%). There are other common EIMs, such as ocular manifestations, mainly episcleritis and uveitis (present in about 10% of patients), thromboembolism (1–2%) or primary sclerosing cholangitis (1–3%, more frequent in ulcerative colitis) [2]. EIMs markedly affect the quality of life of patients with CD, and represent a potential source for morbidity and mortality. Thus, EIMs are highly relevant in the management of CD. Despite that, EIMs of CD are not included in the current Vienna Classification of the disease [3].

Previous reports on EIMs tend to include patients with CD together with the patients with ulcerative colitis.

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Thus, data on EIMs of CD are scarce. Actually, it is not known whether the development of EIMs could be related to the clinical features of the disease according to the Vienna Classification, or to the known risk factors for CD.

The present study aimed at analysing the degree of association between the development of EIMs of CD and the clinical forms of the disease according to the Vienna Classification (age at diagnosis, location and behaviour). The relationship between EIMs and the presence of known potential risk factors for CD, such as smoking habits, previous surgery related to CD, sex, family history of CD and the presence of at least one mutant allele in any of the three known variants of NOD2/CARD15 gene (R702W, G908R and 1007fsinsC), was also evaluated. Finally, special conditions of CD, such as steroid dependency and steroid resistance, were also studied in relation to EIMs on the basis of their possible relevance as indicators of severity of the disease. The study of all these associations may provide new insights into the knowledge of CD that may have important clinical implications.

Methods

A total of 173 consecutive CD patients who were evaluated over the last 12 months in our Inflammatory Bowel Disease Unit have been included in the study. All patients were Caucasian and from Galicia (North-West of Spain). Diagnosis of CD was based on the clinical picture, physical examination, ileocolonoscopy with biopsies for histological confirmation and barium radiology, and enteroclysis for extension study. To avoid different criteria for CD diagnosis, all patients were interviewed, and findings from endoscopic and radiological examinations were reviewed by the same gastroenterologist.

Among the 173 patients with CD included in the present study, 102 were women (59%) and 71 were men (41%). Mean age was 36 years, ranging from 17 to 76 years. Mean follow-up was 7.5 ± 0.5 years (ranging from 1 to 33 years). All patients were classified according to the Vienna Classification on the basis of their age at diagnosis [below 40 years (A1), equal to or above 40 years (A2)], location [terminal ileum (L1), colon (L2), ileocolon (L3), upper gastrointestinal tract (L4)] and behaviour [nonstricturing nonpenetrating (B1), stricturing (B2), penetrating (B3)] (Table 1). Patients who presented both stricturing and fistulizing disease according to the Vienna Classification were included in the B3 group (fistulizing disease).

A complete review of the clinical history of patients was carried out. During the interview, a complete questionnaire was filled in including age, sex, smoking habits, previous surgery related to CD, family history of CD, steroid dependency, steroid resistance, and the presence of EIMs at any time of evolution of the disease. Steroid dependency was defined as a relapse within 30 days after the end of steroid treatment or after at least two attempts of tapering the steroid dose within the last 12 months. Steroid-resistant patients were defined as those who did not respond to steroid therapy (minimum 50 mg of prednisolone) for more than 7 days [4]. A positive family history of CD was defined as the presence of at least one first-degree relative suffering from the disease. A retrospective study of patients regarding previous CD-related surgery was also performed. This analysis was stratified according to the two more frequent procedures in these patients, namely, ileal resection and the treatment of fistulae (mainly perianal). Appendectomy was also evaluated, but it was not considered as a surgery related to CD.

Table 1 Distribution of patients according to the Vienna Classification

	Number (%) of patients
Age at presentation (years)	
A1 (< 40)	143 (82.7)
A2 (>40)	30 (17.3)
Behaviour	
B1 (inflammatory)	70 (40.5)
B2 (stricturing)	36 (20.8)
B3 (penetrating)	67 (38.7)
Location	
L1 (ileum)	75 (43.4)
L2 (colon)	30 (17.3)
L3 (ileocolon)	66 (38.1)
L4 (upper gastrointestinal tract)	2 (1.2)

Patients were genotyped for the three main variants of CARD15 associated with CD (R702W, G908R and 1007fsinsC). These variants have been respectively labelled as SNP8, 12 and 13 by Hugot *et al.* [5]. Blood samples were taken by venipuncture in ethylenediaminetetraacetic acid tubes, once the correspondent's written informed consent was obtained. Genomic DNA was isolated from blood samples using a Roche DNA isolation kit (Roche Molecular Biochemicals, Mannheim, Germany). The genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism [6].

Patients were examined for the main reactive and nonreactive EIMs of CD. Reactive conditions are those related to acute gut inflammation, among them are dermatologic lesions (erythema nodosum and pyoderma gangrenosum), major eye complications (episcleritis and uveitis), oral manifestations and peripheral arthritis. Arthritis was defined as the presence of joint swelling or effusion; patients without an evidence of swelling were classified as arthralgia, which was not included as EIM of CD. Associated nonreactive conditions are those unrelated to gut inflammation, like ankylosing spondylitis, sacroiliitis, thromboembolisms and liver diseases (sclerosing cholangitis and symptomatic gallstones requiring surgery) [2,7]. Sacroiliitis was also confirmed by radio-

graphy in patients who presented characteristic symptoms as inflammatory low back pain or buttock pain. Dermatologic, rheumatologic and ophthalmologic manifestations were confirmed by the corresponding specialist.

EIMs that appear as a consequence of long-standing inflammatory bowel disease, such as anaemia, hypoalbuminaemia and reactive amyloidosis were excluded, as were drug-related manifestations such as pancreatitis and neutropenia [8].

Sixty-one patients (35.3%) developed at least one EIM of CD, 17 of them (9.8% of total) having developed two or more different EIMs over the course of the disease. Peripheral arthritis was the single most common manifestation observed (17.9% of patients), and it was the only EIM in 19 patients (10.9%) (Table 2).

Results are expressed as percentages and odds ratio (OR) with 95% confidence interval (CI). Univariate analysis was performed by the χ^2 test and Fisher's exact test as appropriate. Multivariate analysis was based on unconditional logistic regression, in which the presence or absence of EIMs was considered as the dependent variable, and every recorded clinical data was considered as an independent variable. *P* values less than 0.05 were considered as statistically significant.

Results

Relationship between extraintestinal manifestations and clinical features

The relationship between the presence of EIMs and the different groups of the Vienna Classification is shown in Table 3. EIMs developed more frequently in patients with colonic CD than in those with ileal or ileocolonic CD (Table 3). Patients with any colonic involvement of CD (L2 + L3) suffered from any EIMs of the disease more frequently than patients without colonic involvement (42.7%, 95% CI: 33.3–52.7 vs. 25.9%, 95% CI: 17.5–36.7%, respectively), (OR 2.12, 95% CI: 1.10–4.07; $P < 0.05$). No association was found between the age of presentation and the behaviour of CD and the development of EIMs of the disease as a whole (Table 3).

Table 2 Frequency (%) of the different extraintestinal manifestations of Crohn's disease

Extraintestinal manifestations	Number	Percentage of patients
Peripheral arthritis	31	17.9
Erythema nodosum	13	7.5
Sacroiliitis	12	6.9
Symptomatic biliary lithiasis	10	5.7
Ocular manifestations[a]	6	3.4
Ankylosing spondylitis	4	2.3
Recidivant stomatitis	4	2.3
Primary sclerosing cholangitis	1	0.5
Thromboembolism	0	0

[a]Uveitis, iridocyclitis, episcleritis.

Table 3 Relationship between the clinical presentation of Crohn's disease according to the Vienna Classification and the presence of EIM

Vienna Classification	Number of patients with EIM	Percentage EIM (95% CI)	*P* value
Behaviour	B1 (inflammatory) ($n=22$)	31.4 (21.8–43.0)	NS
	B2 (stricturing) ($n=12$)	33.3 (20.4–49.7)	
	B3 (penetrating) ($n=27$)	40.2 (29.4–52.3)	
Location	L1 (ileum) ($n=20$)	26.6 (18.0–37.6)	$P<0.05$
	L2 (colon) ($n=15$)	50 (33.1–66.8)	
	L3 (ileocolon) ($n=26$)	39.3 (28.5–51.4)	
Age of presentation	A1 (< 40 years) ($n=48$)	33.5 (25.8–41.3)	NS
	A2 (>40 years) ($n=13$)	43.3 (27.4–60.8)	

CI, confidence interval; EIM, extraintestinal manifestation; NS, not significant.

When analysed individually, the presence of erythema nodosum tended to be more frequent in patients with penetrating disease than in those with inflammatory or stricturing disease (OR 4.50, 95% CI: 1.32–15.4; $P < 0.05$). Similarly, sacroiliitis was more commonly seen in colonic CD (OR 4.36, 95% CI: 1.03–20.53; $P < 0.05$) and in patients older than 40 years at onset (OR 3.88, 95% CI: 1.14–13.21; $P < 0.05$). Other EIMs were not significantly related to any clinical feature of CD.

Relationship between extraintestinal manifestations and risk factors for Crohn's disease

Considering EIMs as a whole, they were more frequently seen in women than in men (41.2%, 95% CI: 32.6–51.7 vs. 26.7%, 95% CI: 16.8–38%), (OR 1.92, 95% CI: 0.99–3.70; $P = 0.05$) and in steroid-dependent patients than in steroid-responders (61.1%, 95% CI: 44.9–75.2 vs. 28.5%, 95% CI: 20.9–36%), (OR 3.94, 95% CI: 1.83–8.49; $P < 0.01$). No relationship was found between EIMs of CD and smoking habits, previous CD-related surgery, family history of CD and the presence of steroid resistance.

When analysed individually, peripheral arthritis (OR 5.40, 95% CI: 2.32–12.55; $P < 0.01$) and sacroiliitis (OR 4.36, 95% CI: 1.31–14.48; $P < 0.05$) are significantly associated to the presence of steroid dependency. In addition, smokers developed erythema nodosum more frequently than nonsmokers (OR 9.09, 95% CI: 1.15–71.66; $P < 0.05$). No other significant association was found between individual EIM and risk factors for CD.

Relationship between extraintestinal manifestations and CARD15 mutations

Patients with at least one of the main CARD15 mutations developed any EIMs of the disease in 30.4% (95% CI: 19.1–44.8%) of the cases, compared with 31.6% (95% CI: 23.9–39.4%) of those with no mutation (OR 0.74, 95% CI: 0.36–1.55; NS). The isolated presence of peripheral

Table 4 Frequency (%) and OR 95% CI (%) of EIM as a whole, and of peripheral arthritis, sacroiliitis and erythema nodosum in relation with the three main CARD15 mutations (R702W, G908R and 1007fs)

	EIM	Peripheral arthritis	Sacroiliitis	Erythema nodosum
R702W				
Yes, $n=22$	27.3 (13.1–48.1)	4.5 (0.8–21.8)	4.5 (0.8–21.8)	9.1 (2.5–27.8)
	OR 0.65 (0.24–1.78) (NS)	OR 0.19 (0.02–1.15) (NS)	OR 0.57 (0.07–4.65) (NS)	OR 1.33 (0.27–6.51) (NS)
No, $n=143$	36.4 (28.5–44.2)	19.6 (13.1–26.1)	7.7 (3.3–12.1)	7.0 (2.8–11.2)
G908R				
Yes, $n=13$	46.2	23.1	15.4	23.1
	OR 1.64 (0.52–5.15) (NS)	OR 1.45 (0.37–5.65) (NS)	OR 2.58 (0.50–13.27) (NS)	OR 4.76 (1.11–20.43) ($P<0.05$)
No, $n=152$	34.2 (26.7–41.7)	17.1 (11.1–23.1)	6.6 (2.6–10.5)	5.9 (2.2–9.7)
1007fs				
Yes, $n=14$	21.4	14.3	14.3	0
	OR 0.47 (0.12–1.78) (NS)	OR 0.76 (0.16–3.61) (NS)	OR 2.35 (0.46–11.97) (NS)	–
No, $n=151$	36.4 (28.7–44.1)	17.9 (11.8–24.0)	6.5 (2.3–10.6)	7.9 (3.6–12.3)

CI, confidence interval; EIM, extraintestinal manifestations; NS, not significant; OR, odds ratio.

Table 5 Variables independently associated with extraintestinal manifestations (EIM) of Crohn's disease according to the multivariate analysis

Dependent variable	Independent variables	OR	95% CI	*P*
EIM	Steroid dependency	4.14	1.87–9.19	<0.01
	Women	2.43	1.18–4.98	<0.05
	Colonic involvement	2.30	1.14–4.63	<0.05
Erythema nodosum	Smoking	8.31	1.05–66.12	<0.05
	Penetrating disease	3.58	1.04–12.38	<0.05
Sacroiliitis	Steroid dependency	5.84	1.60–21.29	<0.01
	Age at onset >40 years	5.42	1.43–20.55	<0.05

CI, confidence interval; OR, odds ratio.

arthritis, erythema nodosum or sacroiliitis is also not related to CARD15 mutations as a whole. Patients with the G908R mutation developed erythema nodosum more frequently than those without this mutation, but no other single mutation was associated with the development of any EIMs of CD (Table 4).

Multivariate analysis

Those variables that appeared to be significantly associated to the EIMs of CD in the univariate analysis were included in a multivariate logistic model. Steroid dependency, women and colonic involvement were independently associated with the presence of EIM of the disease (Table 5). Smoking habits and a penetrating disease are independently associated with erythema nodosum, whereas steroid dependency and age at onset older than 40 years are independently associated with the development of sacroiliitis (Table 5).

Discussion

Reports on EIM of CD are scarce. Moreover, most of them include patients with CD as well as patients with ulcerative colitis. The present study represents a complete evaluation of EIMs in patients suffering from CD, paying special attention to their relationship with the clinical features of the disease according to the Vienna Classification.

We observed a high prevalence of EIM in patients with CD (35.3%), higher than that reported by the National Cooperative Crohn's Disease Study (24% of EIM) [9] and the recent Canadian population-based study (6% prevalence of EIM) [10], but similar to that reported by other authors all over the world [11–15], including studies coming from populations ethnically and geographically related to our population [16,17]. Different patient populations (population-based vs. referral centre-based studies) and different EIM definitions may partly explain these discrepancies. In fact, peripheral arthritis was not included as an EIM of CD in the Canadian study [10]. Sample size may also play a role. The number of patients included in our study is, to some extent, lower than in others [9,11,15,17], which may limit the impact of our results. Nevertheless, it must be taken into account that, contrary to our study, most of the previously reported studies on EIMs included both CD and ulcerative colitis patients [12,13,17].

Racial differences should also be considered. Patients of our study were Caucasians from Galicia, a region located in the north-west of Spain, which is characterized by a low immigration rate. For this reason, this population represents a homogeneous group, and results obtained in the present study may not be applicable to other different or more heterogeneous populations. In fact, a higher frequency of EIM in patients with inflammatory bowel disease has been described in African-Americans compared with whites [18,19]. This may allude to common pathways in immune dysregulation being shared by different chronic granulomatous disorders [20–22], for which African-Americans have increased predisposition [23].

A high proportion of patients (9.8%) developed more than one EIM of CD. Most of the studies had previously reported smaller frequencies of multiple EIM [9,10]. These results could be the consequence of the high number of EIMs described in our group of patients, especially if we consider that it is a relatively young cohort, with a mean follow-up from diagnosis of about 7 years.

It is noteworthy that the prevalence of EIM was higher in women. Thus, if only female patients are considered, the rate of EIM increases up to 41%, probably related to the known higher risk of autoimmune conditions in women than in men. This sex difference was also recently observed in Dutch and Hungarian populations [24–26], but not in other previous works [10,11].

Except for erythema nodosum, we have not found a different prevalence of EIM between smokers and nonsmokers. These results differ from Lakatos *et al.* [26], who described a higher prevalence of EIM in smokers. As a higher frequency of EIMs had been previously described in ulcerative colitis smokers than nonsmokers [27], our data again support the different effect of smoking habits in ulcerative colitis and CD patients. Similar differences with ulcerative colitis patients were observed with regard to the role of previous surgery (including appendectomy) in the development of EIMs. In fact, appendectomy has been previously described as a risk factor for EIM in ulcerative colitis [27], which has not been observed in CD patients in the present study.

No previous study analysed the influence of steroid resistance and steroid dependency in the development of EIMs. We observed a higher frequency of EIMs, mainly peripheral arthritis and sacroiliitis, in steroid-dependent patients that, as a hypothesis, could be related to a more sustained and intense inflammatory reaction in these patients.

The present study is one of the first reports correlating the presence of EIMs with the Vienna Classification of CD. Age at diagnosis (< 40 or ≥ 40 years) and the different forms of presentation of CD (inflammatory, stenosing or fistulizing disease) do not seem to have a major influence in the development of EIMs. Nevertheless, we found a more frequent presence of sacroiliitis in patients diagnosed with CD at age above 40 years, as well as a significant association between erythema nodosum and penetrating CD. These findings, reported here for the first time in a relatively low number of patients, deserve further confirmation in studies with a larger sample size.

CD patients with colonic involvement develop EIMs (42.7%), mainly sacroiliitis, more frequently than patients with only small bowel involvement (25.9%). A similar result was observed by Greenstein *et al.* [11], who showed a 42% prevalence of EIM in patients with CD involving the colon. Recently, another two independent studies confirmed a lower prevalence of EIM in ileal CD compared with colonic CD [25,26,28]. Differences in the immune tolerance mechanisms and bacterial flora in colon and ileum could be involved in the origin of this finding.

Three major mutations of NOD2/CARD15 gene (Arg702Trp, Gly908Arg and Leu1007fsinsC) have been identified in relation to CD. We previously reported in our population that, despite CARD15 mutations being present in 27.9% of CD patients compared with 15.2% of controls, only 3.6% of patients were compound heterozygotes or homozygotes [6]. Although these mutations appear to increase the risk of CD, we could not find any relevant relationship between them and the development of EIM of the disease. These results confirm previously reported data to this regard [29,30], but not others supporting a significant association between CARD15 mutations and peripheral arthritis [31] or sacroiliitis [32]. As the influence of CARD15 mutations in our population is rather limited [6], this could also explain their limited contribution to the development of EIM found in the present study.

In conclusion, EIMs of CD are very common in our patient population, and close to 10% of patients developed more than one EIM of the disease. Women and steroid dependency, but not tobacco, a family history of CD, CARD15 mutations and previous CD-related surgery, are clear risk factors for EIM. In relation to the Vienna Classification, colonic involvement, but not the age at diagnosis and the different behaviours of CD (nonstricturing nonpenetrating, stricturing and penetrating behaviour), is associated with the development of EIM.

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