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Clinical and genetic factors associated with sacroiliitis in Crohn's disease

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ABSTRACT

Background and Aim: Radiographic sacroiliitis (SI), often asymptomatic, is considered the most frequent extra-intestinal manifestation (EIM) of Crohn's disease (CD). Data on the association of SI with other clinical features of CD are limited. Association of SI with *CARD15* polymorphisms has recently been suggested. In a multicenter study, we investigated the association of SI in CD patients with clinical phenotypes, other EIM and *CARD15* polymorphisms.

Methods: Radiographs of the sacroiliac joints were taken in 251 CD patients from three Belgian university hospitals and scored by two blinded rheumatologists. Clinical features were obtained from medical records. Forty-three percent of patients carried at least one *CARD15* polymorphism.

Results: Sacroiliitis, defined as the presence of at least grade 2 unilateral changes, was diagnosed in 65 of the 244 scorable radiographs (27%). Only 16 of these patients were previously diagnosed with ankylosing spondylitis (AS). HLA-B27 positivity was observed in 53% of patients with AS and 7% of patients with radiographic SI. In univariate and multivariate analysis, associations between the presence of SI and peripheral arthritis (P = 0.005) and between AS and uveitis (P = 0.005) were found. No associations with other recorded clinical features or with *CARD 15* polymorphisms were observed.

Conclusion: We confirm the high prevalence of radiographic sacroiliitis in a multicenter CD cohort. Uveitis is only associated with AS whereas all patients with SI are more prone to develop peripheral arthritis during their disease course, suggesting similar pathogenetic mechanisms in the development of these EIM. The previously reported association between SI and *CARD15* polymorphisms was not confirmed.

Keywords: association ; *CARD15* ; Crohn's disease ; extra-intestinal manifestation ; sacroiliitis.

INTRODUCTION

Extra-intestinal manifestations (EIM) are quite common in inflammatory bowel disease (IBD) and prevalence rates vary between 21% and 36%.[1] Rheumatic (peripheral and/or axial) articular involvement and cutaneous lesions (erythema nodosum and pyoderma gangrenosum) are commonly seen, but ocular and hepatobiliary complications can also occur.[2]

According to the European Spondyloarthropathy Study Group (ESSG) criteria, the presence of peripheral arthritis and/or axial inflammatory complaints in IBD patients is classified as spondyloarthropathy.[3] Peripheral arthritis is usually pauciarticular and asymmetrical and occurs in 5-20% of IBD patients[4,5]. It is mostly transient, migratory and non-deforming and often coincides with intestinal activity. Associations have been described with colonic involvement, uveitis and erythema nodosum.[5-10]

Axial involvement consists of inflammatory low back pain, spondylitis and sacroiliitis (SI).[6] The criteria for ankylosing spondylitis (AS) are fulfilled in 1.1-11% of IBD patients.[6,11-14] The clinical symptoms, including morning stiffness, inflammatory low back pain or alternating buttock pain, are often unrelated to the bowel disease activity. Usually, a chronic and progressive disease course is observed. Radiographic SI, often asymptomatic, has been described in 10-32% of patients and can be considered the most frequent EIM of IBD.[11,13,14] Unilateral involvement of the sacroiliac joints is not uncommon.[11,13] The prevalence rate of radiographic SI is probably underestimated as reflected by higher prevalence rates found in studies using more sensitive imaging techniques than plain radiographs, such as quantitative SI scintigraphy, computed tomography (CT) and magnetic resonance imaging (MRI).[15-19] These newer techniques are not useful for screening purposes and plain radiographs remain the first line of imaging investigation. Despite the high prevalence of SI in IBD,

data on the association with different clinical phenotypes are scarce.

Although IBD-associated AS is clinically and radiologically indistinguishable from idiopathic AS, there are differences in the prevalence of HLA-B27. Whereas more than 90% of patients with idiopathic AS carry HLA-B27, it decreases to 25-75% in IBD-associated AS and to normal prevalence rates in asymptomatic SI in IBD patients.[11,18,20,21] An association between radiographic SI in Crohn's disease (CD) and polymorphisms in *CARD15*, a well-known susceptibility gene for CD, was observed by our group in a first cohort of patients.[22]

The aim of the present study was to further investigate in a Belgian multicenter cohort of Crohn's disease patients the association of SI with different articular and nonarticular clinical phenotypes of the disease and the *CARD15* genotype.

METHODS

Study population

A total of 251 Caucasian CD patients from three Belgian university hospitals (Gent, $n = 100$; Leuven, $n = 97$; and Liège, $n = 54$)), visiting the IBD outpatient clinic, were included in this cross-sectional study, independent of the presence or history of articular symptoms.

Clinical features were obtained from medical records including sex, age, age at onset of CD, disease duration, family history of CD (first- or second-degree relative), maximal location of the disease (ileal, ileocolonic or colonic), upper gastrointestinal (GI) involvement, history of ileal resections, fistulas (abdominal or perianal), peripheral arthritis, AS, uveitis, erythema nodosum, pyoderma gangrenosum, primary sclerosing cholangitis (PSC) and smoking habit. In five patients, smoking history was unknown. Peripheral arthritis needed to be observed by a physician and was distinguished from arthralgias (articular pain without evidence of joint swelling or effusion). The diagnosis of AS was based on diagnosis by a rheumatologist. Standardized forms, in order to obtain the clinical data used in the present study, were composed before the study. These forms were easy to complete by the gastroenterologist at the time the patient consulted the physician in the outpatient clinic.

Two hundred 33 patients were genotyped (by restriction fragment length polymorphism-polymerase chain reaction [RFLP-PCR]) for the presence of the three common CD-associated *CARD15* polymorphisms (R702W, G908R and 1007fs). There were 136 wild-type patients, 77 heterozygotes (38 R702W, 15 G908R, 24 1007fs), 12 compound heterozygotes (four R702W/ G908R, eight R702W/1007fs) and eight homozygotes (four R702W, two G908R, two 1007fs). DNA was not available from the remaining 18 patients.

Table 1 shows the patient characteristics from the study population. The median disease durations in Leuven (9 years) and Liège (8 years) were longer compared with Gent (5 years, $P = 0.001$ and $P < 0.05$, respectively) and the cohort from Liège had more (ex-)smokers (69%) compared with the other two cohorts (Gent 46%, $P < 0.01$; Leuven 48%, $P < 0.05$). There was also a higher prevalence of uveitis in Leuven (13%) compared with Liège (2%, $P < 0.05$). No other significant differences in clinical phenotypes or *CARD15* genotype were observed between the three different centers.

The local ethical committees approved the collection of all clinical data and the genotyping for *CARD 15* polymorphisms and all patients gave their informed consent.

Diagnosis of sacroiliitis

Radiographs of the sacroiliac joints were taken in all 251 patients and blindly and independently scored by two senior rheumatologists from two different centers using the New York grading system: 0, normal; 1, suspicious changes (no specific abnormalities); 2, localized sclerosis, minimal erosions and joint narrowing; 3, diffuse, definite sclerosis on both sides of the joint, blurring and indistinct margins and erosive changes with loss of joint space; 4, complete fusion or ankylosis.[23] Radiographic SI was diagnosed by the presence of at least unilateral SI grade 2 and only when agreed on by both radiological assessors.[11,13] For discordant scores, a consensus score was obtained after rereading the radiographs. HLA-B27 typing was performed by PCR using Dynal AllSet SSP HLA-B27 (Dynal Biotech, Invitrogen, Merelbeke, Belgium) in patients with pathological sacroiliac joints.

Statistical analysis

For univariate analysis, χ^2 test, Fisher's exact test (when at least one cell had an expected count less than 5) and Mann-Whitney *U*-test (for continuous variables) was used where needed. Multivariate analysis was performed using logistic regression with SI, non-AS SI and AS as dependent variables (compared with non-SI patients). Clinical phenotypes and *CARD15* genotype were included as covariates. A *P*-value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was performed using spss software (SPPS, Chicago, IL, USA).

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Based on the previous study on the association between sacroiliitis in CD and the presence of *CARD15* polymorphisms, a sample size calculation was performed. The number of patients needed to obtain a power of 95% was calculated as 228.

Table 1 *Patient characteristics (n = 251)**

Clinical characteristic	
Age	35 (16-80)
Age at onset of CD	24 (9-76)
Disease duration	8 (CMH)
Male	40
Familial CD	16
Location	
Ileal	25
Ileocolonic	58
Colonic	18
Upper GI involvement	7
Fistulas	
Abdomina	14
Periana	42
Ileal resection	39
EIM	
Peripheral arthritis	29
AS	6
Uveitis	8
Erythema nodosum	9
Pyoderma gangrenosum	1
PSC	1
Smoking history	52

*Data are shown as median in years (range), or % AS, ankylosing spondylitis; CD, Crohn's disease; EIM, extra-intestinal manifestations; GI, gastrointestinal; *n*, total number; PSC, primary sclerosing cholangitis

Table 2 *Prevalence of different clinical phenotypes according to the presence of sacroiliitis*

	No sacroiliitis ***n* = 179** ***n* (%)**	**Sacroiliitis** ***n* = 65** ***n* (%)**	**Non-AS sacroiliitis** ***n* = 49** ***n* (%)**	**AS** ***n* = 16** ***n* (%)**
Disease duration = 5 years	115 (64)	42 (65)	31 (63)	11 (69)
Familial CD	30 (17)	9 (14)	6 (12)	3 (19)
leal involvement	146 (82)	55 (85)	41 (84)	14 (88)
Colonic involvement	134 (75)	49 (75)	39 (80)	10 (63)
Upper GI involvement	15 (8)	2 (3)	2 (4)	0 (0)
leal resection	73 (41)	24 (37)	17 (35)	7 (44)
Fistulas	94 (53)	29 (45)	22 (45)	7 (44)
Abdominal fistulas	24 (13)	9 (14)	7 (14)	2 (13)
Perianal fistulas	81 (45)	24 (37)	18 (37)	6 (38)
Peripheral arthritis	44 (25)	28 (43)*	20 (42)**	8 (50)**
Uveitis	11 (6)	10 (15)**	5 (10)	5 (31)*
Erythema nodosum	14 (8)	9 (14)	7 (14)	2 (13)
	No sacroiliitis *n* = 166 *n* (%)	Sacroiliitis *n* = 60 *n* (%)	non-AS Sacroiliitis *n* = 46 *n* (%)	AS *n* = 14 *n* (%)
CARD15 polymorphism	73 (44)	22 (37)	17 (37)	5 (36)

**P* = 0.005 versus No sacroiliitis; ***P* < 0.05 versus No sacroiliitis AS, ankylosing spondylitis; CD; Crohn's disease; GI, gastrointestinal

RESULTS

Prevalence of radiographic sacroiliitis

The sacroiliac joints of seven patients were not scorable due to insufficient quality of the plain radiographs. Sixty-five (27%) of the remaining 244 patients had radiographic SI. The radiographs of all 16 patients, previously classified as having concomitant ankylosing spondylitis, were recognized as being pathological. Twenty-five of the 65 patients (42%) with positive sacroiliac radiographs had unilateral SI grade 2, whereas 40 patients (58%) had a score more than unilateral grade 2 or bilateral sacroiliitis.

Association of sacroiliitis with clinical phenotypes and *CARD15* genotype

Age, age at onset of CD, sex and smoking history were not associated with the presence of sacroiliitis (data not shown).

Furthermore, no associations were found with disease duration, familial CD, ileal or colonic involvement, upper-GI involvement, history of ileal resection, history of fistulas and *CARD15* genotype (Table 2).

In relation to other EIM, there was a significantly higher prevalence of peripheral arthritis and uveitis in patients with SI. No significant difference was found for erythema nodosum. One of the two patients with a history of pyoderma gangrenosum had radiographic SI, whereas the two patients with PSC had normal sacroiliac joints.

In both subgroups of patients with non-AS SI and AS, the association with peripheral arthritis was confirmed, whereas uveitis only seemed to be related to AS.

Association of ankylosing spondylitis, uveitis and peripheral arthritis with HLA-B27

Conclusive results on the HLA-B27 phenotype could be obtained in 60 of 65 patients with SI. Eight of 15 patients (53%) with AS, of whom DNA was available, were positive for HLA-B27, whereas this was only the case in three of 45 patients (7%) with pure radiographic SI ($P < 0.001$, OR 16, 95% CI 3.4-75.3).

Within the group of patients with SI, no relationship with HLA-B27 could be found for uveitis ($P = 0.37$, OR 2.3, 95% CI 0.5-10.6) or peripheral arthritis ($P = 0.75$, OR 0.8, 95% CI 0.2-2.9; data not shown).

Multivariate analysis

Logistic regression was performed to investigate whether peripheral arthritis and uveitis could be identified as independent predictors for SI or AS. Three models were fit, using three different dependent variables: the presence of radiographic SI ($n = 65$), non-AS SI ($n = 49$) and AS ($n = 16$; Table 3). As covariates we included sex, disease duration (more or less than 10 years), familial CD, ileal involvement, history of ileal resection, fistulas, peripheral arthritis, uveitis, smoking (ever *vs* never) and *CARD 15* genotype (wild-type *vs* polymorphism carrier).

The multivariate analyses confirmed that the presence of radiographic SI is associated with the occurrence of peripheral arthritis (independent of the presence of AS). Furthermore, CD patients with AS also have a higher risk of developing uveitis.

Table 3 *Logistic regression with the presence of SI, non-AS SI and AS as dependent variable*

Covariate	SI versus non-SI			non-AS SI versus non-SI			AS versus non-SI		
	P	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**
Sex	0.69	1.1	0.6-2.3	0.78	1.1	0.5-2.3	0.49	1.6	0.4-5.9
Disease duration	0.54	0.8	0.4-1.7	0.82	0.9	0.4-2.1	0.40	0.5	0.1-2.3
Familial CD	0.33	0.6	0.2-1.6	0.26	0.5	0.2-1.6	0.78	0.8	0.2-4.1
leal involvement	0.10	2.2	0.9-5.9	0.19	2.0	0.7-5.7	0.26	3.1	0.4-21.3
leal resection	0.57	0.8	0.4-1.7	0.42	0.7	0.3-1.6	0.98	1.0	0.2-4.0
Fistulas	0.42	0.8	0.4-1.5	0.36	0.7	0.3-1.5	0.89	1.1	0.3-4.2
Smoking	0.31	1.4	0.7-2.8	0.56	1.3	0.6-2.7	0.40	1.8	0.5-6.8
Peripheral arthritis	0.007	2.7	1.3-5.6	0.048	2.3	1.0-5.0	0.017	5.1	1.3-19.4
Uveitis	0.11	2.3	0.8-6.7	0.56	1.5	0.4-5.2	0.008	9.8	1.8-53.5
CARD15 genotype	0.19	0.6	0.3-1.3	0.37	0.7	0.3-1.5	0.19	0.4	0.1-1.6

AS, ankylosing spondylitis; CD, Crohn's disease; CI, confidence interval; OR, odds ratio; SI, sacroiliitis.

DISCUSSION

The present study confirms the high prevalence of radiographic SI in CD.[6,11,13,14,22] Overall, we found

radiographic signs of SI in 27% of patients. The prevalence of AS in our population was 6%, which is consistent with previously reported prevalence rates.[11-14]

In our study, patients with CD-associated AS have a higher risk of developing peripheral arthritis and uveitis compared with CD patients without axial involvement, confirming previous findings.[5,6,12,18,24] Peripheral arthritis and uveitis are also known to be mutually associated;[5-7,25] however, multivariate analysis confirmed that both EIM were independently associated with AS. This finding might point to similar pathogenetic mechanisms in the development of AS, peripheral arthritis and uveitis. The circulation of inflammatory cells or bacterial components towards these different organs distance from the gut remains an interesting hypothesis.[26] Studies on the expression of specific adhesion molecules (homing receptors and endothelial ligands) provide increasing evidence for the homing of lymphocytes, derived from inflamed gut, to extra-intestinal sites.[27-31] Furthermore, both degradation products and DNA from gut-derived bacteria (such as *Salmonella*, *Shigella* or *Campylobacter sp.)* have been detected in the synovial fluid of spondyloarthropathy (SpA) patients.[32,33]

In our study, patients with non-AS SI also had a higher prevalence of peripheral arthritis in their medical history. Previous data on this association, limited to two studies performed in smaller populations, were not fully consistent.[11,13] As in the study of Queiro *et al.* we found no association between non-AS SI and the incidence of uveitis (as opposed to AS).[13]

Similar to a study by McEniff *et al.*[34] we found no association between SI and disease duration. This is in contrast to the study by de Vlam *et al.* (where the mean disease duration was slightly longer, 10.6 years *vs* 8 years in our study).[11] We found no associations with other clinical characteristics such as age, sex, disease location or behavior.

An association with *CARD15* polymorphisms, as suggested in a recent paper from one of the centers in this study, could not be confirmed in this larger, multicenter cohort.[22] This may reflect again issues of poor reproducibility in genetic association studies of complex multigenic diseases.[35-38] In the numerous genotype-phenotype studies concerning *CARD 15* polymorphisms, several conflicting data have been reported considering associations with fibrostenosing and fistulizing disease, familial occurrence of CD and early onset of disease, even in ethnically similar populations.[39,40]

Although SI is generally seen as the hallmark of ankylosing spondylitis, isolated radiographic SI and AS are considered separate entities in IBD. HLA-B27 positivity has been described in 25-75% of IBD patients with AS.[11,18,20] Conversely, isolated radiographic SI is not related to HLA-B27, as confirmed again in the present study.

The clinical evolution and importance of radiographic SI is still unclear. To our knowledge, only one follow-up study has been performed addressing this question.[13] Sixty-two IBD patients were followed up for 4 years and no significant change in radiological score was observed. In the present study there was no association between disease duration and the presence of AS or SI. To determine whether radiographic SI is clinically insignificant or whether it represents a fruste form of AS or a partially resolved SI in response to treatment, larger and longer follow-up studies are necessary.

Recognition of SI on radiographs of the sacroiliac joints is difficult and requires experience. Many studies have addressed the inter- and intra-observer variability of this technique and CT and MRI scans have proven to be more sensitive and specific.[3,15-17,41] Nevertheless, due to the limited availability, high radiation exposure and/or relative high cost of these techniques, plain sacroiliac radiographs remain the initial diagnostic tool.[11,18] Moreover, no validated classification criteria for SI based on these newer techniques are available.[13] Computed tomography or MRI scans may be particularly helpful in patients with a high probability of SI in whom conventional radiographs are negative or inconclusive.

In conclusion, we confirm the high prevalence of radiographic SI as an EIM of CD. Furthermore, the presence of (both non-AS and AS) SI is associated with a higher incidence of peripheral arthritis, suggesting common pathogenetic factors in the occurrence of arthritic manifestations of CD. Uveitis is associated with AS but not with isolated radiographic SI. The clinical importance of radiographic SI is still uncertain and future studies are needed to identify those patients at risk for development of AS.

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