

## A cross-sectional study of 130 Brazilian patients with Crohn's disease and ulcerative colitis: analysis of articular and ophthalmologic manifestations

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**Abstract** This is a cross-sectional study that analyzed the pattern and frequency of articular and ophthalmologic manifestations in patients with Crohn's disease (CD) and ulcerative colitis (UC), with or without signs of active bowel inflammation. One hundred and thirty consecutive patients with CD ( $n = 71$ ) and UC ( $n = 59$ ) were examined. Simple X-rays of lumbar spine, sacroiliac joints, and calcaneal bone were performed and human leukocyte antigen (HLA)-B27 was typed. Joint manifestations occurred in 41 (31.5%) patients, 27 (38%) with CD and 14 (23.7%) with UC. Peripheral involvement occurred in 22 patients, axial involvement in five, and mixed involvement in 14. The most

frequently involved joints were knees (56.1%), ankles (29.3%), and hips (29.3%), while the predominant pattern was oligoarticular (84.6%) and asymmetrical (65.6%). Enthesitis was identified in seven (5.4%) patients and inflammatory lumbar pain in 13 (10%). Eight of these patients fulfilled the diagnostic criteria for ankylosing spondylitis (6.2%). Radiographic sacroiliitis occurred in 12 patients (9.2%). Ocular abnormalities were present in six patients (6.2%), and HLA-B27 was positive in five (5.8%). In conclusion, the articular manifestations in the present study were predominantly oligoarticular and asymmetric, with a low frequency of ophthalmologic involvement and positive HLA-B27.

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### Introduction

Articular involvement is the most common extraintestinal manifestation in patients with Crohn's disease (CD) and ulcerative colitis (UC) [1–4]. It has been recognized since 1930 [5], but it was only in 1958 that Bywaters and Ansell [6] described the “colitic arthritis” as a specific condition, different from rheumatoid arthritis. It was lately called enteropathic arthritis [7] and classified as one of the diseases of the spondyloarthritis group [8]. The diseases classified as spondyloarthropathies are quite frequent and, recently, their prevalence in the general population of Berlin, Germany was estimated as 1.9% [9], which could

make these diseases, as a group, more prevalent than rheumatoid arthritis.

Historically, two principal patterns of arthritis in inflammatory bowel disease have been recognized: (1) peripheral arthritis, often asymmetric; and (2) axial involvement, including sacroiliitis with or without spondylitis similar to idiopathic ankylosing spondylitis (AS), which course is independent of the intestinal disease and has an association with human leukocyte antigen (HLA)-B27. More recently, in an Oxford study [10], it has been proposed that peripheral arthritis should be divided as: type I, a pauciarticular arthritis, acute and self-limiting, that usually occurs during exacerbations of the inflammatory bowel disease and is not associated with the antigen HLA-B27; and type II, a polyarthritis, which symptoms usually persist for months to years, with an independent course of the intestinal disease. Periarticular manifestations such as enthesitis, tendinitis, and periostitis may occur [11–13].

In the literature, the frequency of articular manifestations in CD and UC ranged from 2.8% to 62%, depending on the methodology of the study, the population assessed, and the duration of the intestinal disease [1–4, 6, 12, 14–26].

The information in the Brazilian population is sparse, as only two studies approached this issue: a retrospective one with 98 UC patients, published by Goldfarb et al. [26] in 1985; and a prevalence study of CD and UC and the extraintestinal manifestations by Souza et al. [2] in 2002. We evaluated the articular complaints in Brazilian patients with CD and UC, as well as the ophthalmologic abnormalities and the frequency of HLA-B27, in order to improve our knowledge of these characteristics.

## Materials and methods

A cross-sectional study was conducted at the Bowel Outpatient Clinic of the Unit of Gastroenterology of the Hospital das Clínicas of Federal University of Minas Gerais, from August 2000 to March 2003, in order to investigate the pattern and frequency of joint manifestations in patients suffering from Crohn's disease and ulcerative colitis, with or without signs of active bowel inflammation. One hundred and forty-four patients were examined, consecutively, by the same rheumatologist, and 130 agreed to participate in the study—71 with CD and 59 with UC. The frequencies of ocular manifestations and of HLA-B27 antigen were also investigated.

The diagnosis of CD and UC was made by a gastroenterologist and was based on clinical, endoscopic, and histological evaluation [27, 28]. The disease activity, assessed by a gastroenterologist, was based on clinical and inflammatory markers and, in some patients, also on

endoscopic and histological evaluation. The extent and localization of intestinal disease were classified according to endoscopic findings: Vienna classification [29] was used for CD patients, and UC patients were classified as described by Farmer [30].

*Patient evaluation* Patients were submitted to a complete clinical examination by a rheumatologist. Actual arthralgia or arthritis, the presence of inflammatory back pain, and the pattern of axial or peripheral joint involvement were defined by the rheumatologist during the clinical examination. They were also asked about the presence of ocular symptoms and skin lesions. Previous articular complaints were not analyzed. Inflammatory back pain was defined as proposed by Calin et al. [31]. Enthesitis was defined as Achilles tendinitis and/or plantar fasciitis and/or pain and/or swelling in tibial tubercle [32]. An ocular examination was performed by the same ophthalmologist, regardless of the presence of any signs or symptoms of ocular abnormalities.

*Radiological evaluation* Anteroposterior view of the sacroiliac joints, in Ferguson incidence, was obtained. Sacroiliitis was classified according to the New York criteria [33]. Patients were also submitted to calcaneal and lumbar spine X-rays. Radiographs were analyzed independently by three investigators: the author, another rheumatologist, and a radiologist that did not know patients' clinical complaints. The end result was defined by a consensus among the investigators.

*HLA tissue typing* Eighty-six patients were typed for HLA-B27 antigen by polymerase chain reaction. HLA-B27 subtypes were not investigated.

*Statistical Analysis* Student's *t* test was used to compare continuous variables and the chi-squared test was used to compare the different groups. Yates' correction was used if necessary. If one cell had an expected count less than one, Fischer's exact test was used. *P* values of <0.05 were regarded as significant.

*Ethics* The study was approved by the Ethics and Research Committee of the Federal University of Minas Gerais.

## Results

One hundred and thirty consecutive patients with the diagnosis of CD ( $n = 71$ ) and UC ( $n = 59$ ) were submitted to a detailed examination by the same rheumatologist. Demographic features are shown in Table 1. Comparative

**Table 1** Patients characteristics in Crohn's disease ( $n=71$ ) and ulcerative colitis ( $n=59$ )

Characteristics	Crohn's disease	Ulcerative colitis	<i>P</i>
Gender [ <i>n</i> (%)]			
Male	29 (40.8)	24 (40.7)	0.873
Female	42 (59.2)	35 (59.3)	
Age (years) <sup>a</sup>	39.4±11.8	40.9±13.8	0.494
Ethnic [ <i>n</i> (%)]			
Caucasians	21 (29.6)	18 (30.5)	0.993
African–Brazilians <sup>b</sup>	50 (70.4)	41 (69.5)	
Disease duration (years) <sup>a</sup>	5.3±5.1	4.5±4.7	0.252

<sup>a</sup> Mean ± SD<sup>b</sup> Black individuals of unmixed ancestry and individuals originating from the mixture of white and black population.

analysis between the two groups showed no statistically significant differences.

Intestinal disease distribution in CD was: 16.9% ileitis, 18.3% colitis, 26.8% proximal small bowel disease, and 35.2% ileocolonic. The disease extent in UC patients was: 20.3% proctitis, 23.7% pancolitis, 25.4% left colon, and 30.5% proctosigmoiditis. Concomitant to the rheumatological evaluation, there was inflammatory activity of the bowel disease in 55.4% of the patients: 47.9% of CD patients and 64.4% of UC patients ( $p = 0.087$ ).

**Locomotor involvement** Joint manifestations were present in 41 (31.5%) patients, 27 (38%) being of the CD group and 14 (23.7%) of the UC group ( $p = 0.119$ ; Table 2). Peripheral involvement—painful joint and/or arthritis and/or enthesitis—occurred in 22/41 (53.7%) patients, 13/27 (48.1%) being with CD and 9/14 (64.2%) with UC ( $p = 0.820$ ). Five of 41 patients (12.2%) presented axial involvement: 4/27 (14.8%) with CD and 1/14 (7.1%) with UC ( $p = 0.376$ ). Mixed involvement, i.e., peripheral and axial, was present in 14 (34.1%) patients: 10/27 (37.0%) with CD and 4/14 (28.6%) with UC ( $p = 0.292$ ).

During the study, arthritis was identified by physical examination in 21 (16.2%) of the 130 patients: 14 (19.7%) of the CD group and seven (11.9%) of the UC group ( $p = 0.331$ ), while inflammatory arthralgia, without swelling, was observed in seven patients with CD and in five patients with UC ( $p = 0.973$ ). The most frequently involved peripheral joints were knees (56.1%), ankles (29.3%), and hips (29.3%), while the predominant pattern of joint involvement was oligoarticular (84.6%) and asymmetrical (65.6%). The median duration of arthritis was 8 weeks in the individuals with CD and 4 weeks in those with UC ( $p = 0.272$ ).

Seven (5.4%) patients presented enthesitis, which was the only articular manifestation in three. The insertion of the Achilles tendon was most frequently involved (six

patients). It predominated in CD (five patients), although there was no statistical significance ( $p = 0.219$ ). One UC patient showed pain and swelling in the insertion of the patella tendon at the right tibial tubercle.

Inflammatory lumbar pain was present in 13 (10%) patients, eight (11.3%) being of the CD group and five (8.5%) of the UC group ( $p = 0.814$ ). Eight of these patients fulfilled the diagnostic criteria for AS, corresponding to 6.2% of all patients studied; they were predominantly men (6/8) and presented CD (8/8).

Peripheral involvement was associated with episodes of activity of the bowel disease, in contrast to the axial involvement ( $p = 0.006$ ). Articular manifestations were predominant in individuals with CD with colonic involvement but with no statistical significance. The bowel disease preceded the articular signs and symptoms in all patients with exclusive peripheral arthritis. In contrast, the articular manifestations preceded CD diagnosis in five of eight patients who fulfilled the diagnostic criteria for AS.

**Radiographic abnormalities** Abnormalities of the sacroiliac joint X-rays were identified in 12/130 patients (9.2%): ten (14.1%) patients of the CD group and two (3.4%) of the UC group ( $p = 0.072$ ), being bilateral in the majority of the cases (91.7%). Other characteristics of the sacroiliitis are shown in Table 3.

The analysis of lumbar spine X-rays showed a normal exam in all UC patients and some abnormalities in four CD patients, which fulfilled the criteria for AS. The abnormalities were sindesmophytes, Romanus sign, and squaring of vertebra. Calcaneal X-rays were normal in all 130 patients.

**Table 2** Characteristics of locomotor involvement in patients with inflammatory bowel disease ( $n=130$ ), with Crohn's disease ( $n=71$ ) and ulcerative colitis ( $n=59$ )

Characteristics	Total, <i>n</i> (%)	Crohn's disease, <i>n</i> (%)	Ulcerative colitis, <i>n</i> (%)	<i>P</i> value
Inflammatory arthralgia	12 (9.2)	7 (9.9)	5 (8.5)	0.973
Arthritis	21 (16.2)	14 (19.7)	7 (11.9)	0.331
Oligoarticular	28 (21.5)	18 (25.3)	10 (16.9)	0.344
Polyarticular	5 (3.8)	3 (4.2)	2 (3.4)	1.000
Asymmetric	22 (16.9)	13 (18.3)	9 (13.6)	0.621
Inflammatory back pain	13 (10)	8 (11.3)	5 (8.5)	0.814
Ankylosing spondylitis <sup>a</sup>	8 (6.2)	8 (11.3)	Z	0.007

Z Null

<sup>a</sup> Fulfilled classification criteria

**Table 3** Radiographic abnormalities of sacroiliac joints in patients with inflammatory bowel disease (total), Crohn's disease, and ulcerative colitis

Radiographic sacroiliitis	Total (n=12)	Crohn's disease (n=10)	Ulcerative colitis (n=2)
M/F	8/4	7/3	1/1
Unilateral	1	0	1
Bilateral			
Grade II	1	1	0
Grade III	8	7	1
Grade IV	2	2	0
Asymptomatic	2	1	1

M Male, F female

**HLA-B27** Eighty-six patients were tested for the HLA-B27 antigen (50 CD and 36 UC), which was positive in five (5.8%). It was tested in 25 from 27 CD patients who had articular symptoms: six had axial symptoms, all of them fulfilled AS criteria, and only one patient had a positive test. Between UC patients, 12 were tested from 14 who had articular symptoms; two of them had axial symptoms, both were negative for HLA-B27. None fulfilled criteria for AS. All patients positive for HLA-B27 had CD ( $p = 0.071$ ). Three female patients had articular manifestations (60%). One had only inflammatory back pain, another had enthesitis of Achilles tendon, and the other had inflammatory back pain, radiographic sacroiliitis, and peripheral arthritis. This last patient fulfilled criteria for AS. HLA-B27 was tested in six of the eight patients with AS and was positive in one (16.7%).

**Ocular manifestations** Eye examination was performed in 96 patients (59 CD and 37 UC) and showed some type of involvement in six (6.2%): four with CD and three females. Anterior uveitis was identified in four (two females), being bilateral in two individuals. One of the two males with anterior uveitis had AS. None had the acute form and one had posterior synechias. A female with CD had unilateral anterior nodular scleritis while a male with CD had unilateral nodular episcleritis, recurrent peripheral arthritis, and psoriasis.

The frequency of eye involvement at the time of examination was similar between patients with CD (6.8%) and UC (5.4%;  $p = 1.000$ ) and between sexes ( $p = 0.678$ ). There was no statistical association with inflammatory activity of bowel disease or with arthritis. It was not possible to analyze the association between the HLA-B27 and ocular abnormalities because only three of the six patients had been tested for HLA-B27; all of them were negative for this antigen.

## Discussion

The precise prevalence of articular manifestations of spondyloarthropathy in patients presenting inflammatory bowel disease has been difficult to determine because of methodological differences in the studies. Most of them were performed before the development of the European Spondyloarthropathy Study Group criteria [8]; some were conducted by gastroenterologists, others by rheumatologists, and some did not use routine radiographic studies to identify asymptomatic sacroiliitis [11, 22, 24]. Table 4 presents the frequency of articular manifestations and HLA-B27 in patients with Crohn's disease and ulcerative colitis, according to different studies.

We studied a population of patients with CD and UC from a tertiary referral center, in a cross-sectional way, for the presence of articular manifestations. The frequency was higher than in previous studies performed in the general population [1, 22, 24, 34] and was similar to those which used a study methodology similar to ours [23]. The inclusion of patients from a tertiary referral center might reflect referral bias, as they might represent more severe and complicated cases.

The prevalence of the different musculoskeletal manifestations was similar in CD and UC patients, in accordance with many other studies [1, 15, 17, 22, 24]. An exception was AS-like involvement, which was observed only among patients with CD. The absence of such a manifestation in UC patients in the literature is uncommon.

The frequency of peripheral synovitis was high and comparable with other recent studies [18, 21]. The oligoarticular pattern was the predominant one, as described in many reports [1, 18, 19, 22, 23]. This pattern may resemble the type I arthropathy reported by Orchard et al. [10]. The type II arthropathy occurred in only one patient in this study. Interestingly, there was a high frequency of monoarticular involvement (36.3%), such as reported by De Vlam et al. [23] (50%). The high frequency of hip involvement is remarkable, which was as frequent as the ankles but less frequent than the knees. Among nine patients that had pain and/or limitation of the hips, five fulfilled the classification criteria for AS.

Enthesitis was found in a frequency similar to other studies [18, 23, 24]. Interestingly, it was the only rheumatological manifestation in three patients, a fact that has also been recognized by De Vlam et al. [23]. One of these patients was positive for HLA-B27. This is a relevant data as enthesitis is a specific manifestation of spondyloarthropathies and may be the sign of presentation of one of the diseases of this group, specially in young people [35, 36].

The frequency of AS-like involvement in this study is in accordance to several other authors that identified frequen-

**Table 4** Frequency of articular manifestations and HLA-B27 in series of patients with Crohn's disease and ulcerative colitis according to several authors

Author (year)	Crohn's disease, <i>n</i>	Ulcerative colitis, <i>n</i>	Arthritis, <i>n</i> (%)	Sacroiliitis, <i>n</i> (%)	Ankylosing spondylitis <sup>a</sup> , <i>n</i> (%)	HLA-B27 (%)
Goldfarb et al. (1985) <sup>b,c</sup>	–	98	14 (4.3)	–	–	–
Scarpa et al. (1992) <sup>d</sup>	–	79	23 (29.1)	34 (43)	20 (25.3)	12.2
Maeda et al. (1994) <sup>d</sup>	203	–	21 (10.3)	–	3 (15)	–
Veloso et al. (1996)	449	343	128 (16.2)	–	23 (2.9)	–
Silva et al. (1998)	35	27	19 (30)	15 (24) <sup>e</sup>	2 (3.7)	24
Orchard et al. (1998) <sup>d</sup>	483	976	108 (7.4)	–	15 (1)	–
Triantafyllidis et al. (2000) <sup>d</sup>	155	–	46 (30)	–	–	–
De Vlam et al. (2000)	78	25	10 (10)	33 (32)	10 (10)	9.2
Salvarani et al. (2001) <sup>d</sup>	59	98	17 (10.6)	5 (3.6)	5 (3.1)	3.6
Palm et al. (2001) <sup>d</sup>	133	273	18 (3.5)	–	–	–
Palm et al. (2002) <sup>d</sup>	133	273	–	8 (2)	15 (3.7)	13
Christodoulou et al. (2002) <sup>c</sup>	37	215	7 (2.8)	15 (6)	–	–
Souza et al. (2002) <sup>b,c</sup>	126	131	37 (14.4)	–	–	–
Al-Shamali et al. (2003) <sup>c</sup>	–	90	8 (8.9)	–	–	–
Lanna et al. (2007) <sup>b</sup>	71	59	33 (25.4)	12 (9.2)	8 (6.2)	5.6

<sup>a</sup> Fulfilled classification criteria<sup>b</sup> Brazilian study<sup>c</sup> Retrospective study<sup>d</sup> Multicentric study<sup>e</sup> Asymptomatic

cies varying from 2.9% to 10% [12, 15, 19, 22–24]. Despite being more common in males, the association between axial AS-like involvement and sex was not statistically significant, probably due to the small number of patients with AS in this study. This issue is controversial in the literature. Some authors detected results similar to ours [22, 37], while others identified a predominance of male sex [24, 38].

It is difficult to compare the frequencies of radiographic sacroiliitis among the studies in the literature due to the differences in the methods used. Some authors analyzed only symptomatic patients, and another evaluated all patients by image. Evaluation of pelvic radiographs for the presence of sacroiliitis is difficult and is liable to interobserver variability. We agree with De Vlam et al. [23], who stated that although other techniques, such as computerized tomographic scans or magnetic resonance imaging, are superior in detecting sacroiliitis, they cannot be used for screening due to the high radiation exposure, high cost, and limited availability.

The extent of gastrointestinal inflammation was similar in patients with or without articular manifestations in both CD and UC groups and coincides with some studies [12, 16]. Previous studies have shown conflicting results; early reports indicated a correlation of the incidence of peripheral

arthritis and the extent of bowel inflammation in UC [14]. A higher prevalence of arthritis with colonic involvement in CD patients was described by some authors [18, 22].

The frequency of HLA-B27 was low if compared to similar studies carried out in other countries [18, 23, 24] and similar to others [15, 16, 22]. They described frequencies between 3.6% and 24%. This might be related to the low frequency of this antigen in Brazilian population: 4% in one study [39] and 3.5% in another [40]. It is known that the strength of disease association with HLA-B27 varies markedly among the various diseases of spondyloarthropathy group as well as among different ethnic populations. In Brazil, there is no other study of HLA-B27 and articular manifestations in patients with inflammatory bowel disease. So, it is not possible to compare our data. The analysis of association between HLA-B27 with the type of articular involvement, with sex, and with ocular manifestations was not possible because of the reduced number of patients positive for this antigen (five patients of 86 tested). Otherwise, it is interesting to notice that the low frequency of HLA-B27 seemed not to influence the frequency of ocular and rheumatological manifestations in the studied gut diseases as the frequency of those manifestations was similar to various studies in the literature, as already reported.

The frequency of ocular abnormalities identified in our patients is in accordance with other authors, who showed a variation of 1.5% to 11.8% [12, 17, 25, 34]. The characteristics of the uveitis in individuals of our study were similar to those described by other investigators [40–44], which are insidious onset, chronic, and bilateral. It is interesting to notice that it is quite different from the uveitis associated to AS and to HLA-B27 [44–46]: anterior, acute, unilateral, and recurrent.

In conclusion, the analysis of this series of Brazilian patients with CD and UC showed us that the frequency of the articular manifestations was high in those patients and similar to other series studied all over the world. The pattern of the articular manifestations was also in accordance to studies carried out in other countries. The low frequency of HLA-B27 might be related to the low frequency of this antigen in our population. This seemed not to influence the frequency of ocular and rheumatological manifestations in the gut diseases studied. Physicians must pay attention to the presence of some rheumatological manifestations related to spondyloarthropathies in order to make a prompt and proper diagnosis and to initiate the specific therapy, which will certainly improve the prognosis.

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