

EXTENDED REPORT

Low grade radiographic sacroiliitis as prognostic factor in patients with undifferentiated spondyloarthritis fulfilling diagnostic criteria for ankylosing spondylitis throughout follow up

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Objective: To determine the rate and factors associated with ankylosing spondylitis in a cohort of patients with undifferentiated spondyloarthritis (SpA).

Methods: 62 consecutive patients with undifferentiated SpA seen between 1998 and 1999 underwent clinical and imaging evaluations throughout follow up. The main outcome measure was a diagnosis of ankylosing spondylitis.

Results: 50 patients with peripheral arthritis (n = 35) and inflammatory back pain (n = 24) (26 male; mean (SD) age at onset, 20.4 (8.8) years; disease duration 5.4 (5.7) years) were followed up for 3–5 years. At baseline, >90% of patients had axial and peripheral disease, while 38% had radiographic sacroiliitis below the cut off level for a diagnosis of ankylosing spondylitis (BASDAI 3.9, BASFI 2.9). At the most recent evaluation, 21 patients (42%) had ankylosing spondylitis. Two factors were associated with a diagnosis of ankylosing spondylitis in multivariate analysis: radiographic sacroiliitis grade <2 bilateral, or grade <3 unilateral (odds ratio (OR) = 11.18 (95% confidence interval, 2.59 to 48.16), p = 0.001), particularly grade 1 bilateral (OR = 12.58 (1.33 to 119.09), p = 0.027), and previous uveitis (OR = 19.25 (1.72 to 214.39), p = 0.001). Acute phase reactant levels, juvenile onset, and HLA-B27 showed a trend to linkage with ankylosing spondylitis (NS).

Conclusions: Low grade radiographic sacroiliitis is a prognostic factor for ankylosing spondylitis in patients originally classified as having undifferentiated SpA. Low grade radiographic sacroiliitis should be regarded as indicative of early ankylosing spondylitis in patients with undifferentiated SpA.

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Undifferentiated spondyloarthritis (SpA) constitute a subgroup of SpA in which patients fulfil the European Spondyloarthropathy Study Group (ESSG) classification criteria¹ for SpA, but not specific criteria for ankylosing spondylitis, reactive arthritis, psoriatic arthritis, or inflammatory bowel diseases. The natural course of undifferentiated SpA is variable. In some patients, symptoms disappear after a single or a few episodes of disease activity, while in others the disease progresses to ankylosing spondylitis or other defined spondyloarthropathies after recurrent episodes or persistent inflammation of the entheses and synovial joints.

The proportion of patients with undifferentiated SpA evolving to ankylosing spondylitis, and the duration of the disease at the time when such diagnosis is made, varies across different studies. For example, in the study by Mau *et al*² 59% of 54 patients with undifferentiated SpA fulfilled the diagnostic criteria for ankylosing spondylitis at the 10 year follow up, while in a study by Sampaio-Barros *et al*³ the proportion of patients with ankylosing spondylitis was 10% after two years.

Several factors have been associated with the progression of undifferentiated SpA to ankylosing spondylitis, but differences in the studies reported thus far, particularly in their design, prevent us from drawing accurate conclusions. For example, uveitis, HLA-B27, and peripheral arthritis, but not inflammatory back pain (IBP), appeared to play a role in some studies. The identification of factors involved in the risk of developing ankylosing spondylitis in patients with

undifferentiated SpA, and the identification of ankylosing spondylitis in its earliest form by improved methods, may lead to earlier and more effective treatments (for example, tumour necrosis α blockers), able to halt the progression of the disease.

There is a current focus on the identification of patients with early axial spondyloarthritis among low back pain sufferers in the general population, by following algorithms which include HLA-B27 typing and magnetic resonance (MR) imaging of the sacroiliac joints.⁴ Using such tests, an increase in the sensitivity of diagnostic criteria and the detection of early cases is expected, but their specificity remains to be established.

In this study, our aim was to determine the incidence of ankylosing spondylitis and the factors leading to the diagnosis in a cohort of patients with undifferentiated SpA. We also assessed the role of low grade sacroiliitis in identifying patients who later fulfilled the modified New York diagnostic criteria for ankylosing spondylitis.⁵

METHODS

The study included 62 consecutive patients with undifferentiated SpA from a large cohort of cases assembled in one centre between January 1998 and December 1999, assessed

Abbreviations: BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; ESSG, European Spondyloarthropathy Study Group; IBP, inflammatory back pain; SpA, spondyloarthritis

Table 1 General characteristics of patients (n = 50) completing follow up

Variable	Value
Male	26 (52%)
HLA-B27	30/47 (63.8%)
Family history of SpA	8 (16%)
Age at onset (years)*	20.4 (8.8)
Onset <16 years	18 (36%)
Uveitis	6 (12%)
<i>Clinical data at onset</i>	
Inflammatory back pain	24 (48%)
Peripheral arthritis	35 (70%)
Axial and peripheral, combined	9 (18%)
<i>Clinical data at presentation</i>	
Age (years)*	26.5 (8.8)
Disease duration (years)*	5.4 (5.7)
Inflammatory back pain	46 (92%)
Duration (years)*	5.4 (5.6)
Peripheral arthritis	41 (82%)
Duration (years)*	5.4 (5.8)
Sacroiliac joint pain	16 (32%)
Peripheral enthesitis	34 (68%)
Dactylitis	18 (36%)
Tarsitis	14 (28%)
High ESR or CRP	18/30 (60%)
<i>Sacroiliac joint radiographic findings</i>	
Bilateral grade 0	31 (62%)
Unilateral grade 1	10 (20%)
Unilateral grade 2	1 (2%)
Bilateral grade 1	7 (14%)
Combined, unilateral grades 1 and 2	1 (2%)
BASDAI*	3.9 (2.5)
BASFI*	2.9 (2.3)
Modified Schober's test (cm)*	4.5 (1.2)
Reduced	18 (36%)
Chest expansion (cm)*	4.3 (0.9)
Reduced	6 (12%)
Occiput to wall distance (cm)*	0

Values are n (%) or *mean (SD).
 BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; SpA, spondyloarthritis.

by a group of four investigators (JDL, CP-T, MC, and RB-V). Patients were 18 or more years of age and had SpA¹ but not ankylosing spondylitis.⁵ There was no evidence of infection as a disease trigger, psoriasis, Crohn's disease, or ulcerative colitis at presentation.

At baseline, patients underwent peripheral and axial joint and entheses assessments, metrology evaluations (modified Schober's test, chest expansion, and occiput-to-wall distance), erythrocyte sedimentation rate (ESR) or C reactive protein determinations, HLA tissue typing, and radiographic studies of the pelvis to evaluate the sacroiliac joints (postero-anterior views with 30° caudal angulation). In addition, patients completed the Mexican validated versions⁶ of both the Bath ankylosing spondylitis disease activity index⁷ and the Bath ankylosing spondylitis functional index⁸ (BASDAI and BASFI). Two to three further evaluations, which included the same variables but not HLA tissue typing, were carried out throughout follow up.

The main outcome variable was ankylosing spondylitis according to the modified New York criteria.⁵

As each patient entered the cohort, three investigators (JDL, CP-T, and RB-V) evaluated the clinical data and graded the sacroiliac joint films by consensus. The reading of new films, specifically those obtained beyond the third year of follow up, was carried out in the same way by two new investigators (JC-V and GH-S) and another one who participated in the baseline evaluation (RB-V). Based on clinical and radiographic data, this latter group of investigators also

determined by consensus whether patients had ankylosing spondylitis or otherwise.

The analysis undertaken in this study was based on these radiographic readings and on the diagnosis—undifferentiated SpA or ankylosing spondylitis—reported at the most recent evaluation. No further reading of the films was carried out in order to avoid any post hoc bias in grading our findings.

Statistical analysis

Either the χ^2 or Fisher's exact test, as appropriate, was used to detect differences in descriptor variables and in the frequencies of the different variables between ankylosing spondylitis and undifferentiated SpA at onset and at baseline. Stepwise linear regression analyses were done, entering variables with significant correlations in univariate tests as explanatory variables and ankylosing spondylitis as the outcome variable. Cases with any missing values were excluded from the analysis. All statistical tests were two tailed, and probability (p) values of less than 0.05 were considered significant. Odds ratios (OR) and 95% confidence intervals (CI) were used to quantify the strength of these associations. We used SPSS software, version 10, for the analyses.

RESULTS

There were 62 patients with undifferentiated SpA included in the cohort (36 men, 26 women; mean (SD) age 27.6 (7.5) years). Fifty (80.6%) of these patients were evaluated after a mean of 3.3 (0.6) years (range 3 to 5) (table 1). The male to female ratio was 1.08:1.0, nearly two thirds of the patients had HLA-B27, and there was a family history of SpA in eight. Their mean age at onset was 20.4 (8.8) years and nearly one third had juvenile onset. Initial symptoms were peripheral arthritis in 35 patients (70%), IBP in 24 (48%), and both symptoms in nine (18%). Six patients (12%) had previous episodes of uveitis.

At baseline, the mean duration of symptoms was 5.4 (5.7) years and most patients presented with both axial and peripheral oligoarthritis and enthesitis (table 1). Sixteen patients (36%) had sacroiliac joint pain and 19 (38%) had radiographic sacroiliitis below the cut off level for ankylosing spondylitis (<2 bilateral or <3 unilateral). Dactylitis and tarsitis were found in around one third of the patients. Mean BASDAI was 3.9 and BASFI 2.9. Spinal measurements were essentially within normal values.

At the most recent evaluation, 21 patients fulfilled the modified criteria for ankylosing spondylitis.⁹ Hence, the risk for developing ankylosing spondylitis in this cohort was 42% in the 3.3 year follow up, an incidence of 0.13 cases per year.

In the univariate analysis, the presence of radiographic sacroiliitis grade <2 bilateral or grade <3 unilateral (OR = 6.22 (95% CI, 1.77 to 21.92), p = 0.008) particularly grade 1 bilateral (OR = 11.20 (1.23 to 101.89), p = 0.03) was significantly associated with ankylosing spondylitis. A few additional variables (uveitis history, the presence of high ESR or C reactive protein, juvenile onset, and HLA-B27) showed the same tendency (table 2). On the other hand, the number of disease activity flares (defined as a worsening of the symptoms after a period of clinical stability) during follow up was significantly greater in patients with ankylosing spondylitis (1.52 (1.40) v 0.90 (0.83); p = 0.03).

In the multivariate analysis, sacroiliitis grade <2 bilateral or grade <3 unilateral (OR = 11.18 (95% CI, 2.59 to 48.16), p = 0.001), grade 1 bilateral radiographic sacroiliitis (OR = 12.58 (1.33 to 119.09), p = 0.027), and previous uveitis (OR = 19.25 (1.72 to 214.39), p = 0.001) were significantly associated with a diagnosis of ankylosing spondylitis.

The analysis of several combinations of two or more significant variables in the same individual resulted in no

Table 2 Variables of interest in the univariate analysis

	AS (n=21) (n (%))	USpA (n=29) (n (%))	OR (95% CI)	p Value
Onset <16 years	10 (47.6)	8 (27.6)	2.39 (0.73 to 7.78)	0.14
HLA-B27	15/19 (78.9)	15/28 (53.6)	3.25 (0.86 to 12.28)	0.14
Uveitis	5 (23.8)	1 (3.4)	8.75 (0.94 to 81.64)	0.08
<i>Clinical data at onset*</i>				
Inflammatory back pain	7 (29.2)	17 (70.8)	0.33 (0.06 to 1.79)	0.14
Peripheral arthritis	16 (45.7)	19 (54.3)	1.68 (0.48 to 5.95)	0.62
<i>Clinical data at presentation</i>				
Inflammatory back pain	20 (95.2)	26 (89.6)	2.31 (0.22 to 23.88)	0.63
Sacroiliac joint tenderness	6 (37.6)	10 (62.5)	0.76 (0.22 to 2.57)	0.66
Peripheral arthritis	17 (42)	24 (58)	0.88 (0.21 to 3.80)	1.0
Peripheral enthesitis	15 (71.4)	19 (65.5)	1.32 (0.39 to 4.45)	0.71
Dactylitis	8 (38.1)	10 (34.5)	1.17 (0.36 to 3.76)	0.79
Tarsitis	6 (28.6)	8 (27.6)	1.05 (0.30 to 3.66)	0.93
High ESR or CRP	11/14 (78.5)	7/16 (43.7)	4.71 (0.94 to 23.68)	0.11
<i>Sacroiliac joint radiographic findings</i>				
Any low grade radiographic sacroiliitis	13 (69.9)	6 (20.7)	6.23 (1.77 to 21.92)	0.008
Bilateral grade 1	6 (28.6)	1 (3.4)	11.20 (1.23 to 101.89)	0.03

*Mean age at onset was 20.9 (8.4) years in ankylosing spondylitis and 19.8 (9.3) years in undifferentiated spondyloarthritis (p=0.39).

†Mean age at presentation was 27.3 (8.2) years in ankylosing spondylitis and 26.0 (9.3) years in undifferentiated spondyloarthritis (p=0.61).

AS, ankylosing spondylitis; CI, confidence interval; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; USpA, undifferentiated spondyloarthritis.

further significant associations with ankylosing spondylitis (data not shown).

Comparisons of baseline and final visit disease activity and functioning assessments in both groups yielded significant improvements in some variables in the two groups, particularly those with undifferentiated SpA (table 3).

DISCUSSION

We have determined the rate and factors associated with the progression of undifferentiated SpA to ankylosing spondylitis in an inception cohort of Mexican patients followed up for three to five years. The group consisted of young adults whose most common symptom at onset was peripheral arthritis. Disease duration at baseline was short and most patients presented with both axial and peripheral symptoms. Such features differed from the populations of Mau *et al*,² Schattenkirchner and Krüger,¹⁰ Collantes *et al*,¹¹ and Sampaio-Barros *et al*,⁶ but somewhat resembled that of Sany *et al*,¹² which was essentially constituted of patients with short lasting peripheral arthritis.

In our study the risk of patients with undifferentiated SpA fulfilling criteria for ankylosing spondylitis was 42% after 3.3 years, an incidence rate of 0.13 cases per year. In comparison with previous studies,^{3 10 12} this percentage was greater and the time shorter. The proportion of patients fulfilling ankylosing

spondylitis criteria was 25% and 36% at a five year follow up in two reports,^{2 11} and 25% within two to six years in another.¹⁰ Two shorter follow up studies reported 10% at 24 months³ and 36% at 28 months,¹² while the value in a 10 year follow up by Mau *et al*² was 66%. These studies differed in several aspects: four were carried out in Europe and two, including ours, in Latin America; the diagnosis varied from "HLA-B27 associated oligoarthritis"¹⁰ to "possible ankylosing spondylitis",² "possible SpA",¹¹ and "undifferentiated SpA";³ disease duration at baseline and duration of follow up differed widely; and finally, the design of the studies and the assessments carried out in each of them were different.

In this study, we only included incident cases seen by the same investigators over a period of two years. At entry, the whole group of these patients fulfilled the ESSG classification criteria¹; individually, none of them fulfilled ankylosing spondylitis criteria.⁵ All patients were evaluated in the same way throughout follow up. Ultimately, the sacroiliac joint radiographic grading and the decisions about who met the modified New York ankylosing spondylitis criteria³ or otherwise were made by consensus rather than by independent observers.

Although the number of patients included in this cohort may have weakened the value of some potential prognostic factors, we identified two variables significantly associated

Table 3 Baseline versus final values of major clinical measures

	Patients fulfilling AS criteria (n=21)				USpA (n=29)			
	Baseline	Final	Difference	p Value	Baseline	Final	Difference	p Value
Joints involved (n)†	3.7 (3.4)	1.2 (2.3)	-2.5	0.006	3.5 (2.7)	2.0 (3.2)	-1.5	0.038
Entheses involved (n)†	2.5 (2.1)	2.7 (3.1)	0.1	0.82	2.7 (3.0)	2.5 (3.6)	-0.2	0.77
BASDAI*	3.9 (2.9)	4.5 (4.4)	0.6	0.54	3.8 (2.3)	3.4 (2.2)	-0.3	0.58
BASFI*	3.3 (2.6)	3.3 (2.7)	0.0	0.85	2.8 (2.1)	2.6 (1.8)	-0.9	0.08
Modified Schober's test (cm)*	4.3 (1.0)	5.5 (1.6)	1.2	0.007	4.7 (1.3)	5.5 (1.7)	0.9	0.008
Chest expansion (cm)*	4.1 (1.0)	4.1 (1.5)	0.0	0.89	3.9 (0.9)	3.7 (1.1)	-0.3	0.58
Occiput to wall distance (cm)††	0	0.9 (0.3)	0.9	0.162	0	0.3 (0.7)	0.3	0.058

*Student's *t* test.

†p=0.006, ankylosing spondylitis v undifferentiated spondyloarthritis at final evaluation.

††p=0.028, ankylosing spondylitis v undifferentiated spondyloarthritis at final evaluation.

AS, ankylosing spondylitis; BASDAI, Bath ankylosing spondylitis disease activity index; BASFI, Bath ankylosing spondylitis functional index; USpA, undifferentiated spondyloarthritis.

with the diagnosis of ankylosing spondylitis in multivariate analysis: radiographic sacroiliitis below the cut off level for the diagnosis of ankylosing spondylitis at presentation (see below), and—as in two other studies²¹—a past history of uveitis. Additionally, patients with ankylosing spondylitis had more flares of disease activity throughout the follow up, resembling previous reports of high ESR or C reactive protein associated with ankylosing spondylitis. Neither in this study nor in some of those previously reported did IBP pose a significant risk for ankylosing spondylitis in patients with SpA. Nevertheless, Mau *et al*² and Sampaio-Barros *et al*³ reported an association between decreased mobility of the spine or lumbalgia with ankylosing spondylitis.

The most important finding in our study refers to the role of low grade radiographic sacroiliitis—particularly grade 1 bilateral sacroiliitis—as a prognostic factor at the presentation of undifferentiated SpA. Grade 1 sacroiliitis consists of non-specific abnormalities of the sacroiliac joints below the cut off level (grades 2, bilateral or 3 unilateral) for the radiographic diagnosis of ankylosing spondylitis. Examples of these are non-specific sclerosis or decreased focal thickness of the articular space. In terms of the diagnosis of ankylosing spondylitis, the value of grade 1 sacroiliitis, along with any other low grade sacroiliitis including grade 2 unilateral, is unfortunately set at the level of grade 0, which is regarded as normal (that is, well defined articular margins and a uniformly regular rim)—in other words, the level at which no radiographic abnormalities are found.

Overall, the notion that radiographic sacroiliitis represents structural rather than inflammatory joint changes is based mostly on studies of grade ≥ 2 bilateral or grade ≥ 3 unilateral disease. In contrast, we lack information on the stage of the disease represented by low grade sacroiliitis. Sacroiliitis grading, on the other hand, seems to rely more on the precision of changes such as sclerosis, erosions, joint space narrowing, and ankylosis than on the staging of the whole process. Interestingly, in a follow up study by Oostveen *et al*,¹³ several patients with normal or low grade radiographic sacroiliitis and MR abnormalities suggestive of sacroiliac joint inflammation developed definite radiographic changes within three years. These data suggest therefore that low grade sacroiliitis may be consistent with inflammatory changes of the sacroiliac joints.

In comparison with computed tomography (CT) and MR, radiographic study of the sacroiliac joints—which mainly refers only to definite changes—is much less sensitive.^{14–21} While CT allows the recognition of small erosions in patients with normal radiographic films, MR findings suggest the presence of inflammatory changes in either the joint space or subchondral bone, including the bone marrow, or both, which may significantly correlate with the histopathological aspect of the joint.²² Undoubtedly, the use of such sensitive methods, particularly MR, as a diagnostic tool will allow the identification of patients with early ankylosing spondylitis. In this sense, we postulate that increasing the sensitivity of the radiographic study of the sacroiliac joints by giving low grade radiographic sacroiliitis a role in the early recognition of ankylosing spondylitis will be a move in the same direction as the other imaging methods.

As with CT and MR, the specificity and diagnostic value of low grade radiographic sacroiliitis should be investigated. We certainly should not assume without any substantial proof that low grade radiographic sacroiliitis lacks specificity and therefore has no diagnostic role in the early ankylosing spondylitis, as there is evidence to the contrary, as follows. First, intraobserver and interobserver variations in the radiographic interpretation of the sacroiliac joints mostly concern the changes seen in grades 1 and 2 sacroiliitis,^{23–26} and less often the decision as to whether or not the joints are abnormal.

Second, training radiologists and rheumatologists does not significantly improve such intraobserver and interobserver variation.²⁶ Third, in contrast, the concordance between observers increases to 80% when grading is based on the presence or absence of radiographic abnormalities.²⁷ Finally, the specificity of low grade radiographic sacroiliitis alone has not been tested against the specificity of CT and MR. It is clear that the radiographic study of the sacroiliac joints is much more accessible worldwide than the new methods.²⁸

In addition to providing information on the factors associated with ankylosing spondylitis in patients initially classified as having undifferentiated SpA, the results of our study provide information on the potential role of low grade radiographic sacroiliitis in the recognition of early ankylosing spondylitis. The diagnostic value of such variables needs to be established in further studies.

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