

CONCISE REPORT

Relationship between disease activity and infection in patients with spondyloarthropathies

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Objective: To assess the relationship between disease activity and signs and symptoms of infection in Mexican patients with spondyloarthropathies (SpA).

Methods: A cross sectional study of 95 non-selected patients with SpA (62 men; mean age 26.4 years), who were examined for signs and symptoms of infection and their association with disease activity. 52 had ankylosing spondylitis (AS), 32 undifferentiated SpA (uSpA), 6 chronic reactive arthritis (ReA), and 5 psoriatic arthritis (PsA). Categorical data were analysed by χ^2 or Fisher's tests.

Results: 53 (56%) patients had infections: 41 (43%) upper respiratory tract (URT), 34 (36%) enteric, and 20 (21%) genitourinary infections. More infections occurred in HLA-B27 positive patients as a whole (39 v 5; $p=0.003$) and in uSpA (12 v 2; $p=0.005$). In AS and uSpA, infections occurred in ~50%. 30/39 (77%) patients with active disease (group A) and 23/56 (41%) (group B) ($p=0.001$) had infection. There were more enteric infections in group A (47%; $p<0.001$) and more URT infections in group B (52%; $p=NS$). 22/30 (73%) patients attributed disease activity to infection.

Conclusion: Enteric, and less commonly, URT infections in Mexican patients with SpA, particularly those who were HLA-B27 positive, seem to have a role in the active phase of AS and uSpA.

It is recognised that bacterial infections may set off the onset of reactive arthritis (ReA), Reiter's syndrome, and undifferentiated spondyloarthropathy (uSpA), but little is known about their role as triggers of disease activity in longstanding spondyloarthropathies (SpA). Few reports have described the relationship between disease activity in ankylosing spondylitis (AS) and other SpA with infections, including long term urogenital infections¹ and sporadic infections by *Salmonella*,^{2–4} *Yersinia*,^{5–7} and *Campylobacter*.⁸ Controversial associations between disease activity and the faecal carriage of *Klebsiella pneumoniae*⁹ and serum anti-bacterial antibodies^{11–12} of patients with AS, but no clinical evidence of infection have been described.

An interesting report by Bardin *et al* suggested a significant association between relapses of post-venereal Reiter's syndrome and gonococcal and non-gonococcal reinfections in a population highly exposed to venereal infections.¹³ We, therefore, suggest that the high prevalence of bacterial infections in the Mexican population may account for the high incidence of recurrent episodes of disease activity in our patients.

METHODS

This is a cross sectional study of consecutive patients with SpA¹⁴ seen over 10 months by two independent observers:

one observer classified each case disease as active (group A) or inactive (group B) and the other searched for current or past infection asking 22 questions about enteric, genital, urinary, and upper respiratory tract (URT) infections throughout three time periods before the study visit: 0–4 weeks, 5–8 weeks, and 9–12 weeks. The presence of at least two of the following signs: (a) peripheral arthritis; (b) peripheral enthesitis by digital pressure; (c) inflammatory back pain; and (d) uveitis plus raised serum C reactive protein or erythrocyte sedimentation rate defined active disease.

Diagnostic criteria for each of the three types of infection were (a) enteric: fever or chills and diarrhoea (loose stools); (b) URT: common flu, nasal discharge, productive cough, and sore throat; and (c) genital or urinary: urethral discharge or fever or chills plus dysuria, vesical tenesmus, suprapubic pain, urinary urgency, or renal pain. Because some patients had only historical signs of infection, we did not consider any bacteriological test in this study. The relation between disease activity and infection was established at the time of the visit, and in group B at the time of the last episode of disease activity.

Statistical analysis

Comparisons between groups were carried out by χ^2 or Fisher's test analysis.

RESULTS

Ninety five patients (62 men; mean (SD) age 26.4 (8.4) years; HLA-B27 in 61/77 (79%)) were included in the study; 52 had AS¹⁵ (40 men; mean (SD) age 26.7 (9.0) years; disease duration 9.7 (4.1) years), 32 uSpA¹⁴ (17 men; 26.0 (6.3) years; disease duration 4.2 (2.5) years), 6 reactive arthritis¹⁶ (ReA; 3 men; 18.6 (4.3) years; disease duration 3.6 (1.2) years; first episode triggered by gut infection in 4, and vaginal infection in 2), and 5 psoriatic arthritis (PsA; 3 men; 34.6 (8.7) years; disease duration 8.7 (5.3) years). None of the patients had been diagnosed as Crohn's disease or ulcerative colitis. Fifty three (56%) patients had infection, which in rank order affected the URT, gut, and genitourinary system (fig 1). The prevalence and site of infection differed between groups. Infections occurred in ~50% with AS and uSpA and $\geq 80\%$ with ReA and PsA. In contrast with the other diagnostic groups, the prevalence of enteric infections in AS was higher than those of the URT.

More infections occurred in HLA-B27 positive than in HLA-B27 negative SpA as a whole (39 v 5; $p=0.003$) and, particularly, uSpA (12 v 2; $p=0.005$) (fig 2).

Two thirds of all infections occurred 0–4 weeks before the study visit or last episode of disease activity in group B: 22.6% between 5 and 8 weeks, and 11.3% between 9 and 12 weeks

Abbreviations: AS, ankylosing spondylitis; PsA, psoriatic arthritis; ReA, reactive arthritis; SpA, spondyloarthropathies; URT, upper respiratory tract; uSpA, undifferentiated spondyloarthropathy

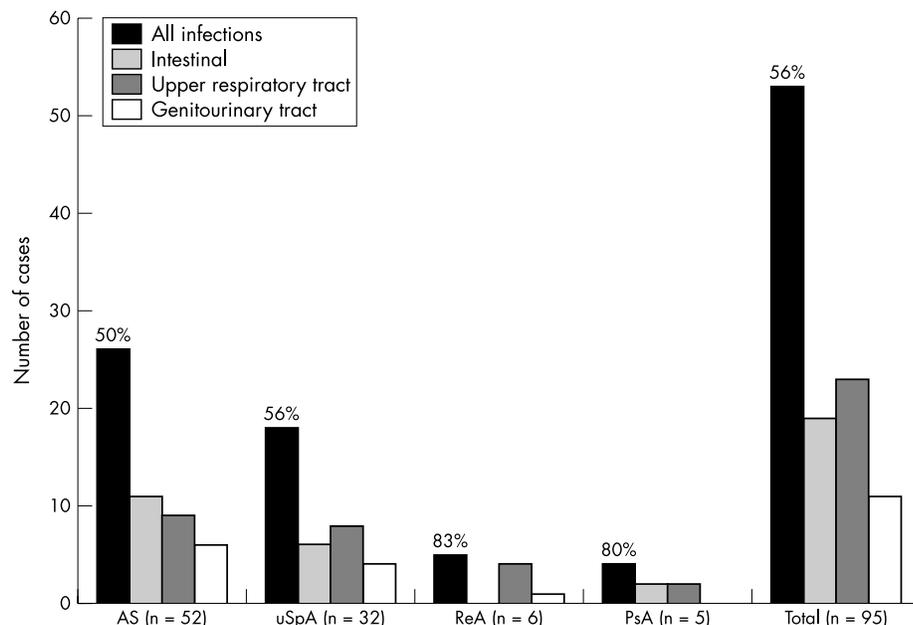


Figure 1 Overall prevalence of infections according to diagnoses and relative prevalence according to the type of infection. Apart from the groups with ReA and PsA (which contained few patients), the overall prevalence of infection in the SpA, particularly AS and uSpA was around 50%. Whereas intestinal infections predominated in AS, those of the URT occurred more commonly in the other groups.

($p < 0.001$). The mean (SD) time between infection and the onset of disease activity was 3.2 (2.5) weeks.

The number of patients receiving prednisone or sulfasalazine was similar in patients with ($n = 8$ and $n = 43$) and without ($n = 7$ and $n = 38$) infection, and no patient received methotrexate or tumour necrosis factor α blockers.

Thirty nine (41%) patients had active disease (group A) and 56 (59%) inactive disease (group B) at the time of the investigation. Thirty patients (77%) in group A and 23 patients (41%) in group B had infection ($p = 0.001$) (fig 3). The overall prevalence of infection and the relative prevalence of enteric infection were significantly higher in group A than in group B ($p < 0.001$). URT infections were most commonly found in group B. Seventeen of 28 (61%) patients from group B had enteric ($n = 8$), URT ($n = 5$), and genitourinary ($n = 4$) infections during their last episode of disease activity.

The prevalence of infection, particularly of the gut and URT in AS, was higher in patients with active disease (table 1). Only the prevalence of intestinal infection in uSpA was

higher in group A. One enteric and one URT occurred in active ReA and three URT in group B; one enteric infection occurred in each of both groups of PsA and two URT infections in group B.

Twenty two (73%) of the 30 patients with infections in group A and 12 (52%) in group B attributed the onset of their last episode of disease activity to infection, and more patients with active disease received antibiotics at the time of infection: 19/30 (63%) in group A and 8/23 (35%) in group B ($p < 0.001$). The effect of this treatment on disease activity was, however, not determined.

DISCUSSION

We found a high prevalence of signs and symptoms of infection significantly associated with disease activity in consecutive patients with SpA. The prevalence of enteric and URT infections in active SpA, particularly AS, was

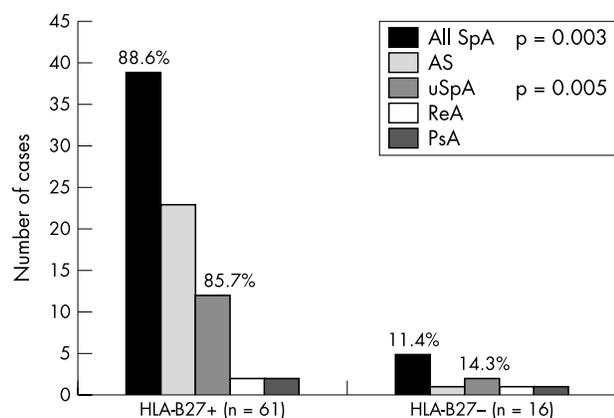


Figure 2 Overall prevalence of infections in 77 HLA-B27 positive (HLA-B27+) or HLA-B27 negative (HLA-B27-) subjects. More infections occurred in HLA-B27+ patients, particularly in the group of SpA as a whole ($p = 0.003$ in comparison with the prevalence of infections in HLA-B27- subjects) and the subgroup of uSpA ($p = 0.005$ v B27- subjects with infection).

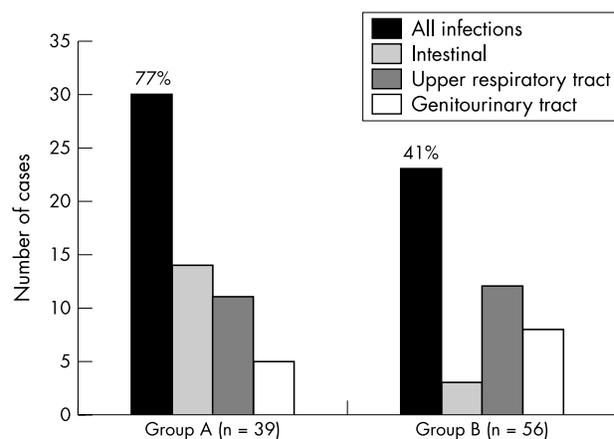


Figure 3 Overall prevalence of infections in active (group A) and inactive (group B) SpA and relative prevalence according to the type of infection. The prevalence of all types of infections and particularly those of the gut were significantly higher in patients with active SpA ($p = 0.001$ and $p < 0.001$, respectively). Although differences between groups did not reach statistical significance, the prevalence of URT and urinary tract infections was higher in patients with inactive disease.

Table 1 Overall prevalence of infections in active and inactive AS and uSpA and relative prevalence according to the type of infection*

	Ankylosing spondylitis (n = 52)			Undifferentiated spondyloarthritis (n = 32)		
	Group A (n = 22)	Group B (n = 30)	p Value	Group A (n = 14)	Group B (n = 18)	p Value
	No (%)	No (%)		No (%)	No (%)	
With infection	18 (82)	8 (27)	<0.001	9 (64)	9 (50)	0.653
<i>Type of infection†</i>						
Intestinal	9 (50)	2 (25)	0.005	5 (56)	1 (11)	0.064
Upper respiratory tract	7 (39)	2 (25)	0.027	3 (33)	5 (56)	1.000
Genitourinary tract	2 (11)	4 (50)	1.000	1 (11)	3 (33)	0.613

*See text for data on ReA and psoriatic arthritis; †relative prevalence.

significantly higher than the prevalence in the group with inactive disease. Interestingly, most patients in both groups attributed their last episode of disease activity to infection. The most common infection in patients with active disease was that of the gut, which accounted for around ~50% in AS and uSpA. Around 35% of patients with active AS and uSpA had URT infection, including common flu, which was the commonest site of infection in patients without disease activity. The prevalence of infection was higher in HLA-B27 positive patients with SpA as a whole and uSpA. Infections in AS occurred in 23 HLA-B27 positive patients and only one HLA-B27 negative subject.

Possibly, the approach we used in this study lacks significant specificity, yet the presence of signs and symptoms of infection may guide the clinician to test for bacterial identification. The post-test probability for a positive diagnostic test in European patients with ReA depends on the presence of signs and symptoms of infection.¹⁷ Recalled biases were reduced by restricting the time frame to 3 months in patients with current active disease and 12 months in patients with no active disease. Interestingly, most infections preceded disease activity by 3 weeks.

There are only sporadic reports on the relationship between symptomatic and asymptomatic infections and disease activity in patients with AS, uSpA, and ReA,¹⁻¹⁰ but there are some data suggesting a significant role of infection in highly exposed populations. For example, reported relapses of Reiter's syndrome in Inuit patients from Greenland treated with penicillin, erythromycin, or tetracycline appeared to be associated with gonococcal and non-gonococcal reinfections.¹³ Additionally, DNA from arthritogenic bacteria were identified in synovial fluid cells of Mexican patients with active long term SpA.¹⁸

In conclusion, our study suggests a relationship between infection and disease activity in SpA, which is apparently facilitated by HLA-B27, in subjects belonging to populations highly exposed to infections.

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