

Low prevalence of renal, cardiac, pulmonary, and neurological extra-articular clinical manifestations in spondyloarthritis: analysis of the Brazilian Registry of Spondyloarthritis

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ABSTRACT

Objective: To describe the extra-articular manifestations (cardiac, renal, pulmonary, and neurological), usually not related to spondyloarthritis (SpA), in a large cohort of Brazilian patients. **Materials and methods:** This retrospective study analyzed 1,472 patients diagnosed with SpA and cared for at 29 health care centers distributed in the five major geographic regions in the country, participating in the Brazilian Registry of Spondyloarthritis (BRS). All patients were assessed for the prevalence of major extra-articular manifestations (cardiac, renal, pulmonary, and neurological), classified according to the diagnosis [ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), undifferentiated spondyloarthritis (uSpA), and juvenile SpA], and according to the clinical presentation (axial, peripheral, mixed, and enthesitis). **Results:** Of the patients with SpA assessed, 963 had AS, 271 PsA, 49 ReA, 48 arthritis associated with IBD, 98 uSpA, and 43 juvenile SpA. Cardiac involvement was reported in 44 patients (3.0%), pulmonary involvement in 19 (1.3%), renal involvement in 17 (1.2%), and neurological involvement in 13 patients (0.9%). Most patients with visceral involvement had AS or PsA, and the mixed (axial + peripheral) and/or predominantly axial clinical form. **Conclusion:** Cardiac, renal, pulmonary, and neurological extra-articular manifestations are quite infrequent in SpA, ranging from 0.9% to 3% in this large Brazilian cohort, and affected predominantly patients with AS and PsA.

Palavras-chave: spondylitis, neurology, cardiology, pulmonary medicine, nephrology.

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INTRODUCTION

The spondyloarthritis (SpAs) comprise a set of rheumatic diseases of immune origin and familial pattern, having some characteristics in common, such as inflammatory axial pain, peripheral arthritis, enthesitis, and uveitis associated with

sacroiliitis in genetically predisposed individuals (related to the human histocompatibility antigen HLA-B27).¹ That set of diseases includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), arthritis associated with inflammatory bowel disease (IBD), and undifferentiated spondyloarthritis (uSpA).

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In that broad context, other organic systems can be involved. All conditions and symptoms not directly related to the articular system are considered extra-articular manifestations.² Such manifestations can be divided into two groups as follows: those related to the concept of SpA, such as the involvement of the skin, eye, bowel or urogenital system; and those reflecting a long-term chronic inflammatory process, involving the lungs, heart, kidneys, and nervous system.² The manifestations related to SpA are relatively frequent (20%–60%),³ can occur at any time of disease progression, and sometimes can be related to the axial and peripheral inflammatory process. On the other hand, the renal, cardiac, pulmonary and neurological manifestations are very rare (1%–5%), frequently subclinical, occurring usually in association with long-term disease and not related to the articular manifestations.²

This study aimed at describing the prevalence of the extra-articular manifestations of SpA in Brazilian patients from a national databank, comprising the Brazilian's major tertiary health care centers, focusing on the renal, pulmonary, cardiac and neurological manifestations.

MATERIALS AND METHODS

This is a cross-sectional descriptive study developed at several tertiary health care centers in Brazil participating in the Brazilian Registry of Spondyloarthritis (BRS), representing the five Brazilian geographic macroregions, with patients cared for from January 2006 to December 2009. A common protocol of investigation was applied to 1,472 consecutive patients diagnosed with SpA. The diagnosis of SpA was considered when the patients met the modified New York criteria.⁴ Psoriatic arthritis was considered when the patients met the Moll and Wright criteria.⁵ The diagnosis of ReA was considered when asymmetric inflammatory oligoarthritis of the lower limbs was associated with enthesopathy and/or inflammatory low back pain after enteric and/or urogenital infections.⁶ Arthritis associated with IBD was considered in the presence of inflammatory axial pain and/or peripheral articular involvement associated with IBD (Crohn disease or ulcerative colitis).⁷ Juvenile SpA was considered when the SpA symptoms began before the age of 16 years.⁷

The patients were assessed for the following: prevalence of the major extra-articular manifestations (cardiac, pulmonary, renal, and neurological), which are shown in Table 1; clinical diagnoses (AS, PsA, ReA, arthritis associated with IBD, uSpA, and juvenile SpA); and the clinical forms (axial, peripheral, enthesitic, and mixed).

Table 1

Extra-articular manifestations in spondyloarthritis

Extra-articular manifestations	Clinical manifestations
Cardiac	Aortitis; aortic insufficiency; conduction disorders; bundle-branch and atrioventricular blocks
Renal	Secondary amyloidosis; IgA nephropathy
Pulmonary	Fibrosis of the upper lobe and pleural thickening
Neurological	Cauda equina syndrome

RESULTS

Cardiac involvement

Of 1,472 patients diagnosed with SpA, 44 (3%) had cardiac involvement, mainly conduction disorders and bundle-branch blocks. Regarding the clinical diagnosis, cardiac involvement was more frequent in AS and PsA and no patient with arthritis associated with IBD was diagnosed with cardiac involvement (Table 2). Regarding the clinical forms, cardiac involvement was more frequently found in the mixed and axial forms (Table 3).

Pulmonary involvement

Pulmonary involvement was reported by 19 patients (1.3%), who had pulmonary fibrosis (apical and/or unspecific findings) and pleural thickening. Pulmonary changes clearly predominated in patients with AS (Table 2). Regarding the clinical forms, pulmonary involvement was more frequently found in the mixed and axial forms (Table 3).

Renal involvement

Renal involvement was identified in 17 patients (1.2%), some of whom were diagnosed with IgA nephropathy, while the others had chronic hematuria with no diagnostic elucidation. Among the patients with renal involvement, AS and PsA predominated (Table 2). Regarding the clinical forms, renal involvement was more frequently found in the mixed form (Table 3).

Neurological involvement

Thirteen patients (0.9%) had neurological involvement, mainly paresthesia of their lower limbs, which hindered deambulation. Five patients had the diagnosis of cauda equina syndrome confirmed. Among the patients with neurological involvement, AS (Table 2) and the mixed clinical form (Table 3) predominated.

Table 2
Prevalence of the extra-articular manifestations in spondyloarthritis according to the clinical diagnosis

Clinical diagnosis of spondyloarthritis (n = 1,472)	Extra-articular manifestations			
	Cardiac (n = 44)	Renal (n = 17)	Pulmonary (n = 19)	Neurological (n = 13)
Primary AS	29 (2%)	5 (0.3%)	14 (1.0%)	8 (0.5%)
AS + psoriasis	1 (0.1%)	1 (0.1%)	0	0
PsA	11 (0.7%)	6 (0.4%)	1 (0.1%)	3 (0.2%)
ReA	1 (0.1%)	1 (0.1%)	1 (0.1%)	0
uSpA	1 (0.1%)	0	1 (0.1%)	0
AS + IBD	0	0	1 (0.1%)	0
Arthritis + IBD	0	1 (0.1%)	0	1 (0.1%)
Juvenile SpA	1 (0.1%)	3 (0.2%)	1 (0.1%)	1 (0.1%)

AS: ankylosing spondylitis; PsA: psoriatic arthritis; ReA: reactive arthritis; uSpA: undifferentiated spondyloarthritis; IBD: inflammatory bowel disease; juvenile SpA: juvenile spondyloarthritis.

Table 3
Prevalence of the extra-articular manifestations of spondyloarthritis according to the clinical form

Extra-articular manifestations	Clinical form of spondyloarthritis (n = 1,472)			
	Axial	Peripheral	Mixed	Enthesitic
Cardiac (n = 44)	12 (0.8%)	6 (0.4%)	25 (1.7%)	1 (0.1%)
Renal (n = 17)	2 (0.1%)	2 (0.1%)	13 (0.9%)	0
Pulmonary (n = 19)	9 (0.7%)	0	10 (0.7%)	0
Neurological (n = 13)	2 (0.1%)	2 (0.1%)	9 (0.5%)	0

DISCUSSION

This is the first study describing the major extra-articular manifestations (cardiac, renal, neurological, and pulmonary) of SpA in a large number of Brazilian patients, representing all the five major geographic regions of the country. Systemic extra-articular manifestations, although rare, have high morbidity and, thus, should be diagnosed and treated early.

Cardiac symptoms in patients with AS are rarely reported; cardiac diseases occur in 2%–10% of those patients, mainly in those with long-term disease, and are not associated with joint disease activity.² HLA-B27 positive individuals can have a syndrome characterized by aortic insufficiency (with isolated regurgitation and no stenosis) associated with aortic root dilation and fibrosis with retraction of the cusps, which could progress to complete atrioventricular block and endarteritis obliterans of the small arteries.⁸ Third-degree atrioventricular block requiring the use of pacemaker and with no defined cause

in young men seems to be associated with a higher prevalence of HLA-B27,⁹ and can even be considered an uSpA.¹⁰ Currently, the occurrence of aortic insufficiency in SpA is not frequent,^{11,12} in accordance with the clinical findings of the present study. In this Brazilian cohort, cardiac involvement was observed in 3% of the 1,472 patients assessed, predominating in those with AS and PsA, with the mixed clinical form, followed by the axial form.

In recent years, both AS and PsA seem to be associated with an increase in cardiovascular morbidity and mortality.^{13,14} An extensive study assessing 28,208 patients with rheumatoid arthritis (RA), 3,066 patients with PsA, and 1,843 with AS, and comparing them with the healthy North-American population has revealed that both the cardiovascular diseases and their risk factors are more frequent in RA, PsA, and AS as compared with the paired control group.¹⁵ That Brazilian study has not assessed actively the occurrence of metabolic syndrome in patients with SpA, which can be studied in the second phase of the BRS.

Pulmonary involvement in AS is unusual and estimated to occur in less than 1% of the patients, especially in severe long-term disease.¹⁶ We observed 1.3% of pulmonary involvement in patients with SpA, with predominance of unspecific fibrotic changes in the high-resolution computed tomography of patients with AS. Tomographic studies, usually in patients with AS, have also reported unspecific tomographic changes.^{17–19} Usually such changes have no direct relationship with disease progression. Involvement of the costovertebral joints and ankylosis of the thoracic vertebral column will lead to limitation of the thoracic expansion, which can affect the patient's respiratory capacity, but rarely leads to restrictive respiratory disorder, because the diaphragmatic function is preserved.²

The symptomatic renal involvement is usually rare in patients with SpA. IgA nephropathy has been described in spondylitic patients for decades, being characterized by hematuria and proteinuria (usually mild), with mesangial IgA deposits on the renal biopsy, and no poor prognosis.²⁰ The most frequent finding of the renal involvement in SpA is hematuria, usually microscopic; in such cases, in addition to IgA nephropathy, interstitial nephropathy due to non-steroidal anti-inflammatory drugs or renal lithiasis should be considered.^{21–23} In this Brazilian multicenter study, only 1.2% of the patients had renal involvement, mainly chronic hematuria with no specific cause. A recent Brazilian study has reported intermittent microscopic hematuria in 44.7% of 76 spondylitic patients, of whom only 10.5% could have a glomerular etiology.²⁴

Renal amyloidosis, not described in this cohort and very rarely described in Latin-American case series,²⁵ is usually more often reported in European patients with SpA. Renal

amyloidosis was the cause of death in 13% of the spondylitic patients of a Finnish case series followed up for a long time.²⁶ A Spanish study using the method of abdominal fat aspiration has found amyloidosis in 7% of the 107 patients assessed.²⁷

The neurological involvement in SpA is a clinical manifestation found almost exclusively in AS. In our cohort, of the 13 patients with neurological manifestations, eight had AS. The neurological changes more often reported in the literature are atlantoaxial subluxation and cauda equina syndrome.^{28,29} A recent literature review assessing the evolution of the

neurological complications after vertebral column fracture has revealed a 17.7% mortality after three months.³⁰

In conclusion, extra-articular manifestations (cardiac, renal, pulmonary, and neurological) are extremely rare in Brazilian patients with SpA, ranging from 0.9%–3%, being, thus, in accordance with data in the literature.¹ Such manifestations should be considered in patients with refractory long-term disease. Their diagnosis requires strong clinical suspicion, because the symptoms are unspecific and often subclinical. Initial check-up and regular control of such manifestations should, thus, be part of those patients' follow-up.

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