

# Undifferentiated Spondyloarthritis: A Longterm Followup

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**ABSTRACT.** *Objective.* To analyze the longterm followup of a series of Brazilian patients with undifferentiated spondyloarthritis (uSpA).

*Methods.* Prospective study analyzing a group of 111 patients with the diagnosis of uSpA, fulfilling the European Spondylarthropathy Study Group and the Amor criteria, who were followed for 5 to 10 years in a single university referral center. Patients had their outcome analyzed at 5, 7, and 10 years.

*Results.* There was a predominance of men (81.1%), white ethnicity (78.4%), and positive HLA-B27 (61.3%), with a mean age at onset of 27.2 years. Twenty-seven patients presented development to ankylosing spondylitis (AS; 24.3%) and 3 to psoriatic arthritis (PsA; 2.7%), while 25 patients (22.5%) went into remission during the followup. Univariate logistic regression analysis revealed that ethnicity, HLA-B27, buttock pain, inflammatory low back pain, ankle involvement, grade I sacroiliitis at the beginning of the study, and the use of sulfasalazine were statistically associated with progression to AS. Multivariate logistic regression analysis revealed that HLA-B27 ( $p = 0.035$ , OR 6.720, 95% CI 11.45–39.43) and buttock pain ( $p = 0.009$ , OR 6.211, 95% CI 1.591–24.25) were statistically associated with progression to AS.

*Conclusion.* In a longterm followup of 111 Brazilian patients with uSpA, HLA-B27 and buttock pain were significant predictors of progression to a definite disease. (First Release May 1 2010; J Rheumatol 2010;37:1195–9; doi:10.3899/jrheum.090625)

## Key Indexing Terms:

UNDIFFERENTIATED SPONDYLOARTHRTISIS OUTCOME HLA-B27 SACROILIITIS

Undifferentiated spondyloarthritis (uSpA) involves signs and symptoms suggestive of a spondyloarthritis (SpA), but patients with uSpA do not fulfill the diagnostic criteria for any of the currently established diseases in the group<sup>1</sup>. Although often considered a provisional diagnosis, uSpA has in the last 2 decades often been described as an SpA<sup>2–4</sup>. This uSpA is characterized predominantly by inflammatory low back pain (ILBP), peripheral arthritis (frequently affecting large joints in the lower limbs), and enthesitis, with more women and HLA-B27-negative patients than in ankylosing

spondylitis (AS)<sup>5</sup>. The classification criteria for SpA<sup>6,7</sup> encompassed the diagnosis of uSpA. Decision trees were proposed to help physicians make an early diagnosis of axial SpA in patients with ILBP without sacroiliitis<sup>8</sup>. Recently, a new set of criteria for the diagnosis of axial SpA was published<sup>9,10</sup>, and a new set of criteria for the diagnosis of peripheral SpA was proposed<sup>11</sup>.

In 2001, our group described the 2-year followup of 68 patients with symptomatic uSpA who fulfilled the European Spondylarthropathy Study Group (ESSG) criteria<sup>7</sup>; AS (10%) and PsA (2%) were present at the end of followup, with 75% of the patients continuing with uSpA. Logistic regression analysis showed that buttock pain and HLA-B27 (trend) were statistically associated with progression to a definite SpA<sup>12</sup>. Subsequently, we analyzed the importance of HLA-B27 and the B7-CREG alleles in the disease characterization and progression of 80 patients with uSpA (40 positive and 40 negative HLA-B27 patients), and found that the presence of the HLA-B27 alleles was associated with the progression to AS, while the presence of B7-CREG alleles was associated with uSpA in the HLA-B27-negative group<sup>13</sup>. We analyzed the longterm outcome of 111 patients with uSpA, who fulfilled the ESSG and the Amor criteria for SpA, and described the variables associated with a diagnosis of a definite disease at 5, 7, and 10 years.

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## MATERIALS AND METHODS

Our study was designed in January 1994 and intended to investigate the longterm outcome of consecutive adult patients with the diagnosis of uSpA who attended the spondyloarthritis outpatient clinic of the Hospital de Clínicas of the University of Campinas, a tertiary referral university hospital in Brazil. Initially, adult patients not fulfilling the criteria for a definite diagnosis of any of the SpA at the initial visit and who fulfilled the ESSG<sup>7</sup> criteria for SpA were included. Subsequently, it was also necessary to fulfill at least 6 points in the Amor<sup>6</sup> set of criteria to be considered a patient with uSpA.

A total of 156 consecutive adult patients were referred to our institution between January 1994 and December 2002 with the diagnosis of uSpA. Forty-five patients had to be excluded from our study because they fulfilled 4 or 5 points in the Amor set of criteria or had a diagnosis of a definite SpA. So 111 patients with uSpA were included in our study.

Ethnicity was divided into whites and nonwhites; the latter included African Brazilians (black patients of unmixed ancestry and mulattoes, i.e., originating from the mixture of white and black populations) and East Asians (Japanese origin). Most patients came from the metropolitan area of Campinas, with a population of roughly 3 million, located in an industrial region of the state of São Paulo in southeast Brazil, where the white population includes people of predominantly Portuguese, Italian, and/or Spanish ancestry.

Clinical evaluation included a search for initial symptoms and the presence of axial and peripheral joint involvement, and heel enthesopathies. Initial symptoms included ILBP, asymmetric oligoarthritis (predominantly affecting large joints of the lower limbs), and heel enthesopathies (Achilles tendinitis and/or plantar fasciitis). ILBP was considered according to established criteria<sup>14</sup>.

Imaging methods performed at study entry included pelvic and calcaneal radiography. After 2, 5, 7, and 10 years of followup, another pelvic radiography examination was performed. Each sacroiliac joint was scored according to the modified New York criteria<sup>15</sup>; to be enrolled in the study, patients had to present sacroiliitis graded as normal or below grade II bilateral or below grade III unilateral. The radiographs were independently analyzed by 1 rheumatologist and 1 blinded radiologist (who changed 3 times during the 15-year study period). When there were different interpretations of a radiograph, the 2 analysts conferred and agreed on a diagnosis.

After 2, 5, 7, and 10-year followup, patients who fulfilled the modified New York criteria<sup>15</sup> were diagnosed as having AS and patients who presented with characteristic psoriatic skin lesions were diagnosed as having PsA. Disease remission was defined as a complete remission of clinical symptoms for at least 1 year (without symptomatic medication).

HLA-B alleles were typed at low resolution using polymerase chain reaction-amplified DNA hybridized with sequence-specific oligonucleotide primers (Dynal Biotech Ltd., Merseyside, UK).

**Statistical analysis.** The chi-squared and Fisher's exact tests were used to verify the association of the variables of interest; *p* values  $\leq 0.05$  were considered to be significant, and  $0.10 \leq p < 0.05$  were considered to be a statistical trend. To verify the influence of risk factors for progression to AS (compared to the patients who progressed to remission) in the 5, 7, and 10-year outcome of the patients with uSpA, univariate and multivariate logistic regression analyses were used.

## RESULTS

There were 90 men (81.1%) and 21 women (18.9%) patients, with a male:female ratio of 4.3:1. There were 87 whites (78.4%), 22 African Brazilians (19.8%), and 2 East Asians (1.8%) of Japanese origin; the African Brazilian group included only mulattoes, with no patient presenting pure black ancestry. The mean age at onset was 27.2 years (SD  $\pm 9.5$  yrs), and the mean age at diagnosis was 29.9 years

(SD  $\pm 9.6$  yrs); the mean time to diagnosis was 2.7 years. HLA-B27 was positive in 68 (61.3%) patients, with 13 (11.7%) of them having a family history of SpA, predominantly AS.

The most frequent initial symptoms were peripheral arthritis (45.9%), ILBP (28.8%), enthesitis (15.3%), and buttock pain (8.1%). Patients' characteristics at the initial evaluation and the joint manifestations shown during the longterm followup are described in Table 1.

Peripheral involvement was common during the study period, affecting 93 (83.8%) patients. The most frequent peripheral joints involved were ankles (79.3%), knees (58.6%), wrists (11.7%), and elbows (6.3%); involvement of small joints in upper and lower limbs was infrequent. During the followup, 67 (60.4%) patients had enthesopathy; the most frequent entheses involved the Achilles tendon (43.2%) and plantar fascia (35.1%). Sausage fingers were observed in 8 patients (7.2%).

During the study period, 75 patients (67.6%) had ILBP, 59 (53.2%) had buttock pain, and 12 (10.8%) had cervical inflammatory pain in the followup. Involvement of the girdle joints was noted in 37 patients (33.3%), mainly affecting hip (16.2%), shoulder (10.8%), and sternoclavicular joints (9%).

Twenty-four patients (21.6%) presented grade I sacroiliitis at the initial radiograph. Fourteen patients presented unilateral and 10 bilateral grade I sacroiliitis; no patient presented grades II, III, or IV sacroiliitis (unilateral or bilateral) at the initial radiograph.

All the patients took nonsteroidal antiinflammatory drugs (NSAID), and 32 (28.8%) took glucocorticoids, mainly low doses of prednisone. Methotrexate was prescribed for 30.6% and sulfasalazine for 71.2% of the patients during the study

Table 1. Percentage of patients with various symptoms at initial evaluation and longterm followup.

Variable	Baseline, %	Followup, %
ILBP	28.8	67.6
Buttock pain	8.1	53.2
Cervical spine	0	10.8
Peripheral joint	45.9	83.8
Knees	28.8	58.6
Ankles	35.1	79.3
Elbows	0	6.3
Wrists	0	11.7
Girdle joints	10.8	33.3
Hips	10.8	16.2
Shoulders	0	10.8
Sternoclavicular	0	9
Enteseal pain	15.3	60.4
Achilles tendinitis	10.8	43.2
Plantar fasciitis	9	35.1
Sausage finger	0	7.2

ILBP: inflammatory low back pain.

period. In most patients, the followup ended before biologic drugs became regularly available for SpA in Brazil.

All the patients were followed for 2 years, 105 (94.6%) for 5 years, 84 (75.7%) for 7 years, and 42 (37.8%) for 10 years. Two patients died during the followup for reasons not related to SpA. Four patients were considered lost to followup at 5 years, 25 at 7 years, and 67 at 10 years. Twenty-seven patients progressed to AS (24.3%) and 3 to PsA (2.7%), while 25 patients (22.5%) went into remission during the followup. The outcomes at 2, 5, 7, and 10 years are shown in Figure 1. The proportion of patients with progression to AS and to remission was similar at 2, 5, 7, and 10 years. The percentage of patients with the diagnosis of uSpA decreased significantly with progress of the followup, from 82.9% at 2 years to 16.7% at 10 years.

Univariate logistic regression analysis revealed that ethnicity, HLA-B27, buttock pain, inflammatory low back pain, ankle involvement, sacroiliitis grade I at the beginning of the study, and the use of sulfasalazine were statistically associated with progression to AS, compared to the patients who went into remission during the study period (Table 2).

Multivariate logistic regression analysis revealed that HLA-B27 ( $p = 0.035$ , OR 6.720, 95% CI 11.45–39.43) and buttock pain ( $p = 0.009$ , OR 6.211, 95% CI 1.591–24.25) were statistically associated with progression to AS, compared to the patients who went into remission (Table 3).

## DISCUSSION

Our study confirms that uSpA can be considered a provisional diagnosis in a significant number of patients, especially in those with longterm followup, and that AS is the main outcome variable in the SpA group. Also important is the association of the axial and peripheral components in the characterization of the uSpA diagnosis in a heterogeneous population such as that in Brazil. A recent publication of the Brazilian Registry of Spondyloarthritis, analyzing 1036 patients who submitted to a common protocol of investigation in 28 university centers, showed that pure axial disease

Table 2. Univariate logistic regression analysis of patients' characteristics and symptoms at various followup intervals.

Variable	2 Yrs	5 Yrs	7 Yrs	10 Yrs
Sex	0.312	0.638	0.597	0.952
Ethnicity	0.043	0.024	0.047	0.013
Family history	0.331	0.638	0.366	0.939
HLA-B27	0.232	0.01	0.012	0.028
Buttock pain	0.027	0.005	0.003	0.06
ILBP	< 0.001	< 0.001	< 0.001	< 0.001
Hip	0.319	0.087	0.077	0.119
Shoulder	0.331	0.3	0.511	0.512
Sternoclavicular	0.198	0.101	0.065	0.296
Knees	0.125	0.103	0.233	0.06
Ankles	0.016	0.028	0.03	0.003
Elbows	0.274	0.322	0.332	—
Wrists	0.365	0.225	0.166	0.296
Enthesopathy	0.549	0.708	0.351	0.198
Achilles	0.198	0.896	0.464	0.407
Plantar	0.319	0.708	0.992	0.482
Sausage finger	0.331	0.975	0.332	0.296
Glucocorticoids	0.984	0.756	0.533	0.783
Methotrexate	0.54	0.712	0.499	0.428
Sulfasalazine	0.013	< 0.001	< 0.001	0.004
Biologics	—	—	—	0.324
Sacroiliitis grade I	< 0.001	< 0.001	< 0.001	< 0.001

ILBP: inflammatory low back pain.

was found in 36.7% of the patients and that pure peripheral involvement was observed in 10.7%, while the mixed pattern (axial, peripheral, and enthesal) was observed in 47.9% of the patients; uSpA was diagnosed in 6.3% of these patients<sup>16</sup>.

Among the classification criteria for SpA, the ESSG criteria<sup>7</sup> are the most widely used, with a sensitivity of 87% and a specificity of 87%; they are practical and easy to apply. The Amor criteria<sup>6</sup> are less frequently used in daily practice by rheumatologists. Although both sets of criteria are efficient to classify SpA, we demonstrated that fulfilling the 2 sets can be important to better characterize the population under study with uSpA. Collantes, *et al*, analyzing

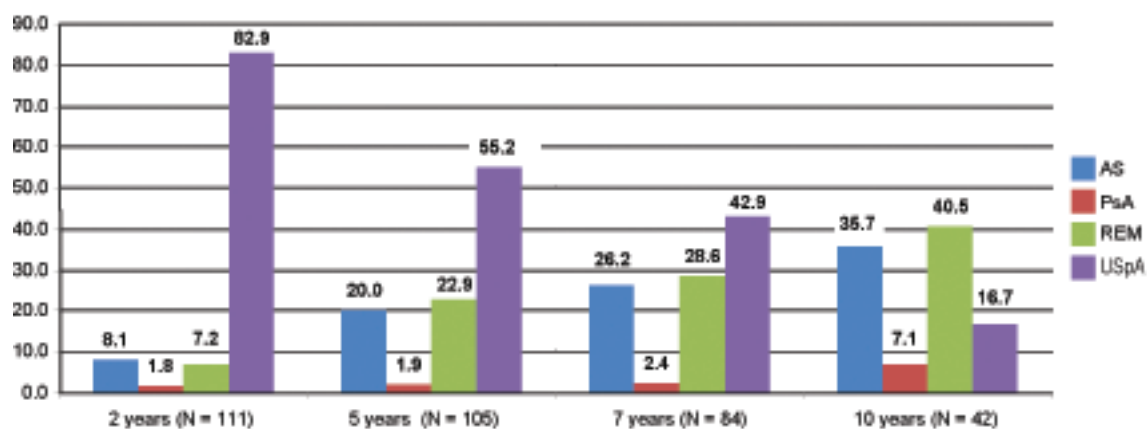


Figure 1. Patient outcomes after 2, 5, 7, and 10 years. N = 111. AS: ankylosing spondylitis; PsA: psoriatic arthritis; REM: remission; USpA: undifferentiated spondyloarthritis.

Table 3. Multivariate logistic regression analysis of characteristics statistically associated with progression to ankylosing spondylitis.

Variable	Coefficient	Standard Error	p	OR	Lower 95% IC	Upper 95% IC
Buttock pain	1.826	0.695	0.009	6.211	1.591	24.252
B27	1.905	0.903	0.035	6.720	1.145	39.434
Constant	-2.641	0.954	0.006			

102 Spanish patients with uSpA in a 5-year followup, found that the Amor and ESSG criteria both allowed early identification of uSpA, but that the Amor criteria performed better<sup>17</sup>.

The selection of patients with ILBP, asymmetric oligoarthritis (affecting predominantly large joints in the lower limbs), and enthesopathies (Achilles tendinitis and/or plantar fasciitis) was intended to include only patients with symptomatic SpA, to establish patterns of disease outcome. Peripheral involvement was the most common initial symptom (45.9%), and was found in 83.8% of the patients during the followup. Enthesitis was found in 15.3% as an initial symptom and in 60.4% during the followup. These data emphasize the importance and the high percentage of peripheral symptoms in Brazilian patients with uSpA, as shown in a recent study of 1036 Brazilian patients with SpA<sup>16</sup>. Although ILBP was found as an initial symptom in 28.8% of patients and buttock pain in 8.1%, during the longterm followup, ILBP was found in 67.6% and buttock pain in 53.2%. In the short-term and longterm followup, no patient progressed to other diseases not included in the SpA group.

The epidemiologic variables of the patients with uSpA in our study were similar to those observed in patients with AS at our institution<sup>18</sup>, with a predominance of white (78.4%) and male (81.1%) patients, with young age at onset (mean 23.7 yrs), and family history of SpA in 11.7%. The HLA-B27 positivity was lower in patients with uSpA (61.3% vs 78.2%), compared to patients with AS. Another Latin American study, from Mexico<sup>19</sup>, following up on 62 patients with uSpA, with a predominance of male (52%) and HLA-B27-positive (63.8%) patients, found younger age at onset (mean 20.4 yrs) and positive family history in 16%. A study by Collantes, *et al*, in Spain<sup>17</sup> observed male predominance (53%), with older age at onset (mean 31.8 yrs) and lower HLA-B27 positivity (20.6%), and with a family history in 8.8%. The study by Mau, *et al*, in Germany<sup>20</sup>, analyzing 88 patients in a longterm followup, also presented male predominance (male:female ratio 1.9:1).

Peripheral involvement was an important point in the characterization of the patients with uSpA in our study. Arthritis predominating in large joints in the lower limbs was the most frequent initial symptom (45.9%), with a significant number of patients presenting knee (58.6%) and ankle (78.3%) involvement and enthesopathy (60.4%) dur-

ing the followup. Analyzing studies involving patients with uSpA, peripheral arthritis was found in 43.1%<sup>17</sup>, 82%<sup>19</sup>, and 60%<sup>20</sup> in various studies.

White ethnicity was statistically associated with progression to AS in the univariate analysis in this study. The Brazilian white population has predominantly European ancestry (from Portugal, Spain, and/or Italy); it is noteworthy that, among the African Brazilians, no pure black patient was diagnosed as having uSpA; mixing among white and black individuals is an important characteristic of the African Brazilian population.

Radiographic grade I sacroiliitis is another variable associated with progression to AS at the univariate analysis. The same results were observed by Huerta-Sil, *et al* in a Mexican series<sup>19</sup> that showed radiographic sacroiliitis grade < II bilateral or grade < III unilateral with an OR = 11.18, and grade I bilateral with an OR = 12.58. These results emphasize the importance of grade I radiographic sacroiliitis in patients with uSpA. This finding could be considered an early recognition of AS.

Magnetic resonance imaging (MRI) is the most sensitive method to detect early inflammatory changes in sacroiliac joints<sup>21</sup>. The new Assessment of Spondyloarthritis International Society criteria for axial SpA include MRI as an important instrument for the diagnosis of early disease<sup>9,10</sup>.

All the patients took NSAID during the followup in our study. Because of the large number of patients with uSpA who had peripheral joint involvement, methotrexate (30.6%) and sulfasalazine (71.2%) were frequently prescribed. Sulfasalazine use presented a statistical association with progression to AS in the univariate analysis.

In a longterm followup, there was a significant and progressive number of patients presenting a diagnosis of AS (24.3%). The Mau series showed that 59% of 54 patients with uSpA in a 10-year followup progressed to AS, while 19% continued with the diagnosis of uSpA<sup>20</sup>. In an Indian study analyzing the 11-year followup of 22 patients with uSpA, 15 (68%) presented AS, 1 PsA, 2 went into natural remission, and 4 continued with uSpA<sup>22</sup>. Although the percentage of patients with uSpA who progressed to AS was significantly lower (24.3%) in our study, compared to the German (59%) and the Indian (68%) series, the percentage of patients continuing with uSpA in the longterm followup was similar in the 3 studies (16.7%, 19%, and 16%). In our

study, HLA-B27 and buttock pain were associated with AS in the multivariate analysis, compared to the patients who went into remission. Buttock pain was an infrequent initial symptom (8.2%) in the patients with uSpA, but was found in 50.3% of them during the followup, and presented an OR = 6.211 at the multivariate analysis. These results were similar to those observed in the 2-year followup of the initial patients with uSpA observed in our service<sup>12</sup>. Progression of uSpA to PsA is rather unusual; in our study, 3 patients progressed to PsA.

Our study had some deficiencies that should be mentioned. First, the percentage of patients lost to followup at 7 years (24.3%) and 10 years (62.2%) does not allow definite conclusions. Second, the fact that the radiographic scoring was not blinded, and the interobserver and intraobserver reliability was not analyzed, places doubt on the accuracy of the diagnoses. Indeed, these are problems of a real-world longterm followup that should be observed in future studies.

Our study showed that AS is the most frequent definite disease diagnosed in the longterm followup of a series of Brazilian patients with uSpA, and that HLA-B27 and buttock pain were the best predictors of progression to AS.

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