Primary Ankylosing Spondylitis: Patterns of Disease in a Brazilian Population of 147 Patients

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ABSTRACT. ***Objective.*** To analyze patterns of disease in a population of Brazilian patients with primary ankylosing spondylitis (AS).

Methods. Retrospective study (1988–98) analyzing 147 patients with a diagnosis of primary AS according to the modified New York criteria. Selected patients had complete clinical (initial symptom, axial and peripheral involvement, heel enthesitis, extraarticular manifestations) and radiological (sacroiliac, lumbar, thoracic, and cervical spine) investigations, and these data were compared with sex, race, age at onset, and HLA-B27.

Results. There was a predominance of men (84.4%), Caucasian race (75.5%), adult onset (> 16 years, 85%), and positive HLA-B27 (78.2%). Family history of AS was noted in 14.3% of the patients. Pure axial AS was observed in 37 patients (25.2%). The predominant initial symptoms were inflammatory low back pain (61.9%) and peripheral arthritis (22.4%). Thoracic and cervical spine involvement was noted in 70.1% of the patients; radiological findings included syndesmophytes in 46.9% and "bamboo spine" in 20.4% of patients. The extraaxial joints most frequently involved were: ankles (39.5%), hips (36.1%), knees (29.3%), shoulders (19%), and sternoclaviculars (14.3%); heel enthesitis was present in 22.4%. Acute anterior uveitis was noted in 14.3% of patients. Male sex was associated with involvement of thoracic spine ($p = 0.002$), cervical spine ($p = 0.002$), and hips ($p = 0.042$), whereas female sex was associated with sternoclavicular ($p = 0.024$) involvement. Caucasian race presented higher frequency of positive family history ($p = 0.023$); there was no statistical significance of clinical and radiological variables compared with African-Brazilians. Juvenile onset AS presented higher frequency of ankle ($p = 0.012$) and knee ($p = 0.001$) involvement, heel enthesitis ($p = 0.001$), and total hip replacement ($p = 0.038$), whereas adult onset was associated with thoracic ($p = 0.026$) and cervical spine ($p = 0.026$) involvement and positive family history ($p = 0.044$). Positive HLA-B27 was associated with ankle involvement ($p = 0.007$) and heel enthesitis ($p = 0.013$).

Conclusion. In this population women showed a milder axial involvement, Caucasian race presented axial and peripheral involvement similar to African-Brazilians, juvenile onset AS was associated with articular involvement of the lower limbs, and positive HLA-B27 was associated with ankle involvement. (J Rheumatol 2001;28:560–5)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS SEX RACE AGE AT ONSET HLA-B27

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily affects the axial skeleton. Sacroiliac joint involvement is considered the hallmark of the disease, and the spine involvement can lead to progressive ankylosis, although many patients never get to a stage of complete fusion of the spine[1]. The clinical pattern of the disease is influenced by many factors, including sex, race, age at onset, and HLA-B27. Primary AS is more common in males, with a sex ratio ranging from 2 to 5:1; it is not yet fully understood whether the natural course of the disease in women is similar to that in men[2]. Juvenile AS (disease onset before the age of 16 yrs) frequently presents as oligoarthritis and enthesitis, predominantly affecting the lower limbs, with the axial symptoms occurring late in the course of disease[3].

The prevalence of primary AS can vary from country to country, according to genetic and environmental factors[4,5]. Epidemiologic data suggest that 0.1 to 1.0% of Caucasian adults in the general population have AS; the variance in prevalence data is partly due to differences in study design[6]. This predominance is strongly associated with the histo-

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compatibility antigen HLA-B27, positive in 90–95% of Caucasian patients with AS[7]. In black populations of unmixed ancestry, where primary AS is uncommon and HLA-B27 is frequently negative, disease course is usually milder and later in onset, significantly less complicated by acute anterior uveitis, and showing less frequent familial aggregation[8].

The prevalence and clinical picture of primary AS vary considerably in the different populations of the Americas. In the white North American population, longitudinal data suggest that there is a constancy in the epidemiologic features of AS[9] and that the patterns of disease outcome emerge in the first 10 years of the disease[10]. The highest prevalences of both AS and HLA-B27 have been observed in Indians living in Canada and in the United States, whereas AS presents a low prevalence in Central American Indians and is extremely rare in South American Indians[11]. HLA-B27 presents a high prevalence (25–40%) in Eskimos from Alaska and Greenland, where undifferentiated and definite spondyloarthropathies are quite common[12,13]. Mexican mestizos have a predominance of juvenile onset AS, with higher frequencies of peripheral arthropathy and enthesitis[14].

We examined the patterns of disease, according to sex, race, age at onset, and HLA-B27, in a population of 147 patients with primary AS in Brazil.

MATERIALS AND METHODS

We performed a retrospective analysis of 190 patients with the diagnosis of primary AS, according to the modified New York criteria[15], attending the outpatient clinic of the Hospital de Clínicas of the State University of Campinas between 1988 and 1998. Selected patients presented complete clinical and radiological investigations in the 2 years prior to the study. As 43 patients were excluded due to incomplete data, the final group comprised 147 patients. Patients with the diagnosis of psoriatic arthritis, Reiter's syndrome, or inflammatory bowel disease were excluded.

Clinical evaluation included the search for initial symptoms, axial involvement, extraaxial involvement, heel enthesitis and extraarticular manifestations. Axial involvement was considered when inflammatory pain in lumbar, thoracic, and cervical spine was diagnosed[16]. Extraaxial involvement included the presence of arthritis in peripheral and/or girdle joints. Enthesitis included the presence of inflammatory pain in Achilles tendon and/or plantar fascia. Extraarticular manifestations included the presence (reported by the patients and described in their charts) of acute anterior uveitis, cardiovascular, pulmonary, renal, and/or neurological involvement related to AS[17]. Familial occurrence of primary AS was established based on patient information at inital evaluation.

Radiological evaluation included the search for sacroiliitis and inflammatory involvement of the spine. Interpretation of pelvic radiographs was according to the recommendations of the New York Conference for Population Studies[18]. Evaluation of spinal radiographs included the search for isolated syndesmophytes and characteristic "bamboo spine"[19].

HLA-B27 determination was by a complement mediated microlymphocytotoxicity assay on peripheral blood mononuclear cells using purified T cells to detect class I antigens[20], using anti-HLA sera screened in our laboratory.

Clinical and radiological data were compared with those for sex, race, age at onset, and HLA-B27 to establish patterns of disease. Race was divided into Caucasian and African-Brazilian (the latter including black patients of unmixed ancestry and *mulatos*, from mixed white and black populations). Most patients came from an area of 2.5 million inhabitants surrounding the city of Campinas, 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 origin. Juvenile AS was considered when disease onset was before 16 years, and adult AS when disease onset occurred after 16 years.

Statistical analysis. The chi-square test and the Fisher's exact test were used to verify the association of the variables of interest; p values ≤ 0.05 were considered significant.

RESULTS

There were 124 men (84.4%) and 23 women (15.6%) in the group; the sex ratio was 5:1. There were 111 Caucasians (75.5%) and 36 African-Brazilians (24.5%, including 30 *mulatos* and 6 black patients of unmixed ancestry). Adult onset AS comprised 125 patients (85%) and juvenile onset AS 22 patients (15%). Mean age at onset was 24.7 years (range 6–45). Mean age at study entry was 39.5 years (range 18–76), whereas mean disease duration was 14.8 years (range 2–53). HLA-B27 was positive in 115 patients (78.2%). Family history of AS was reported by 21 patients (14.3%).

Regarding the initial symptoms, there was a predominance of inflammatory low back pain (61.9%), followed by peripheral arthritis (22.4%), heel enthesitis (6.1%), buttock pain (6.1%), inflammatory cervical spine pain (2%), and acute anterior uveitis (1.4%). Pure axial AS was observed in 37 patients (25.2%). All patients presented sacroiliac and lumbar involvement, whereas 104 patients (70.1%) presented thoracic and cervical spine involvement. Extraaxial involvement was reported by 110 patients (74.8%); peripheral joint involvement was present in 70 patients (47.6%). Among the peripheral joints, there was involvement of ankles in 58 (39.5%), knees 43 (29.3%), wrists 16 (10.9%), and elbows 7 (4.8%). Heel enthesitis was present in 33 patients (22.4%), 30 in plantar fascia and 24 in Achilles tendon. Regarding girdle joints, there was involvement of hips in 53 (36.1%), shoulders 28 (19%), sternoclaviculars 21 (14.3%), and pubic symphisis 10 (6.8%). Fourteen patients (9.5%) had total hip replacement, 11 bilateral, and 3 unilateral.

Extent of radiographic sacroiliitis was grade 3 in 68 cases (46.3%), grade 4 in 67 (45.5%), and grade 2 in 12 (8.2%). Spinal radiologic evaluation showed syndesmophytes in 69 patients (46.9%) and "bamboo spine" in 30 patients (20.4%). All 33 patients with a clinical complaint of heel enthesitis had radiologic entheseal involvement.

Acute anterior uveitis was reported by 21 patients (14.3%), most of them with recurrent unilateral attacks without permanent sequelae. Renal symptoms were reported by 14 patients (9.5%). Eleven patients presented microscopic hematuria; in 4 cases it was associated with renal calculosis and in another 4 it resolved completely after discontinuing nonsteroidal antiinflammatory drugs. Three

patients presented proteinuria associated with progressive increase in serum creatine levels; 2 patients developed chronic renal failure and one died; however, kidney biopsies did not show amyloidosis. Symptomatic cardiac, pulmonary, or neurological disease considered related to AS was not reported by any patient. Five patients presented posttraumatic spinal fractures. Three patients died during the followup, due to disseminated tuberculosis, chronic renal failure, and acute myeloid leukemia.

Male sex was associated with involvement of thoracic spine, cervical spine, and hips, whereas female sex was associated with sternoclavicular involvement (Table 1). Caucasian race presented higher frequency of positive family history; there was no statistical significance regarding clinical and radiological variables compared with African-Brazilians (Table 2). Regarding age at onset, juvenile onset AS presented higher frequency of ankle and knee involvement, heel enthesitis, and total hip replacement, whereas adult onset AS was associated with thoracic and cervical spine involvement and a positive family history (Table 3). Positive HLA-B27 was associated with ankle involvement and heel enthesitis (Table 4).

DISCUSSION

The patterns of disease in patients with primary AS in this study reflect those of the population of the southeast of Brazil. An epidemiologic investigation of AS in Brazil should take into account the complex heterogeneity of the ethnic groups living in the country.

In our study, there was a male predominance (84.4%), with a sex ratio of 5:1. Although a large UK study involving predominantly Caucasian patients revealed a progressive decrease in the sex ratio in the spondyloarthropathies[21], smaller studies in African blacks[22] and Mexican *mestizos*[14] showed a significantly higher sex ratio. Regarding the predominance in men, the importance of sex hormones in

Table 1. Patterns of disease, according to sex.

	Male (n = 124)		Female (n = 23)		
	No	%	No.	%	p
Race					
Caucasian	91	73.4	20	87.0	NS
African-Brazilian	33	26.6	3	13.0	
Age at onset					
Adult	104	83.9	21	91.3	NS
Juvenile	20	16.1	2	8.7	
HLA-B27	97	78.2	18	78.2	NS
Thoracic/cervical	93	75.0	10	43.5	0.002
Hip	49	39.5	4	17.4	0.042
THR	11	8.9	3	13.0	NS
Knee	36	29.0	7	30.4	NS
Ankle	48	38.7	10	43.5	NS
Heel enthesitis	27	21.8	6	26.1	NS
Shoulder	24	19.4	4	17.4	NS
Elbow	5	4.0	2	8.7	NS
Wrist	11	8.9	5	21.7	NS
Sternoclavicular	14	11.3	7	30.4	0.024
Uveitis	19	15.3	2	8.7	NS
Family history of AS	19	15.3	2	8.7	NS

THR: total hip replacement; AS: ankylosing spondylitis; NS: nonsignificant.

Table 2. Patterns of disease, according to race.

	Caucasian (n = 111)		African-Brazilian (n = 36)		
	No	%	No.	%	p
Sex					
Male	91	82.0	33	87.0	NS
Female	20	18.0	3	13.0	
Age at onset					
Adult	96	86.5	29	80.6	NS
Juvenile	15	13.5	7	19.4	
HLA-B27	90	81.1	25	69.4	NS
Thoracic/cervical	82	73.9	21	58.3	NS
Hip	38	34.2	15	41.7	NS
THR	12	10.8	2	5.6	NS
Knee	31	27.9	12	33.3	NS
Ankle	41	36.9	17	47.2	NS
Heel enthesitis	24	21.6	9	25.0	NS
Shoulder	21	18.9	7	19.4	NS
Elbow	6	5.4	1	2.8	NS
Wrist	13	11.7	3	8.3	NS
Sternoclavicular	17	15.3	4	11.1	NS
Uveitis	15	13.5	6	16.7	NS
Family history of AS	20	18.0	1	2.8	0.023

THR: total hip replacement; AS: ankylosing spondylitis; NS: nonsignificant.

Table 3. Patterns of disease, according to age at onset.

	Adult (n = 125)		Juvenile (n = 22)		
	No.	%	No.	%	p
Sex					
Male	104	83.9	20	90.1	NS
Female	21	16,1	2	9.9	
Race					
Caucasian	96	76.8	15	68.2	NS
African-Brazilian	29	23.2	5	31.8	
HLA-B27	97	77.6	18	81.8	NS
Thoracic/cervical	92	73.6	11	50.0	0.026
Hip	43	34.4	10	45.5	NS
THR	9	7.2	5	22.7	0.038
Knee	30	24.0	13	59.1	0.001
Ankle	44	35.2	14	63.6	0.012
Heel enthesitis	22	17.6	11	50.0	0.001
Shoulder	23	18.4	5	22.7	NS
Elbow	5	4.0	2	9.1	NS
Wrist	11	8.8	5	22.7	NS
Sternoclavicular	19	15.2	2	9.1	NS
Uveitis	15	12.0	6	27.3	NS
Family history of AS	21	16.8	0	0.0	0.044

THR: total hip replacement; AS: ankylosing spondylitis; NS: nonsignificant.

Table 4. Patterns of disease, according to HLA-B27.

	Positive (n = 115)		Negative (n = 32)		
	No.	%	No.	%	p
Sex					
Male	97	84.3	27	84.4	NS
Female	18	15.7	5	15.6	
Race					
Caucasian	90	81.1	21	65.6	NS
African-Brazilian	25	18.9	11	34.4	
Age at onset					
Adult	97	84.3	28	87.5	NS
Juvenile	18	15.7	4	12.5	
Thoracic/cervical	81	70.4	22	68.8	NS
Hip	42	36.5	11	34.4	NS
THR	12	10.4	2	6.3	NS
Knee	34	29.6	9	28.1	NS
Ankle	52	45.2	6	18.8	0.007
Heel enthesitis	31	27.0	2	6.3	0.013
Shoulder	21	18.3	7	21.9	NS
Elbow	5	4.4	2	6.3	NS
Wrist	14	12.2	2	6.3	NS
Sternoclavicular	16	13.9	5	15.6	NS
Uveitis	18	15.7	3	9.4	NS
Family history of AS	19	16.5	2	6.3	NS

THR: total hip replacement; AS: ankylosing spondylitis; NS: nonsignificant.

the pathogenesis of AS is still not completely defined[23,24]. In our study, male patients presented a more extensive spinal involvement, with more frequent hip involvement, whereas female patients had a more frequent sternoclavicular involvement. Patterns of disease in females are still conflicting[2]. Although peripheral involvement tends to be similar in both sexes, milder axial involvement in females can be observed in some studies[25-28]. A recent UK study revealed that the influence of female sex is greater than that of male sex in determining increased susceptibility to AS in children[29]. A large collaborative international study involving 939 female patients showed that AS did not adversely affect fertility, pregnancy outcome, or the neonate, with active disease at conception being a predictor of a postpartum flare[30]. In this study, 2 patients with AS were pregnant during followup, with good pregnancy outcome.

Caucasian-Brazilian AS patients presented a higher frequency of positive family history, although the clinical and radiological variables were similar to the African-Brazilians. A possible reason for such a similar involvement was that the African-Brazilian group was constituted predominantly by *mulatos*, originated from the mixture of white and black populations. The clinical picture of primary AS in white populations of unmixed ancestry is characterized by a more severe spinal and peripheral involvement associated with a higher frequency of extraarticular manifestations and positive HLA-B27[7], compared to predominantly black populations[8,22,31,32]. The clinical picture of the African-Brazilian AS patients of mixed ancestry was more similar to the AS in Caucasians than to the AS in blacks. In the same way, no major differences in patterns of disease were observed in white and *colored* patients in South Africa[33].

This study revealed that patients with juvenile onset AS presented a higher frequency of peripheral involvement (ankle, knee, and heel enthesitis) and total hip replacement, similar to that observed in the literature[3]. A large UK cohort of AS patients showed that juvenile AS is associated with a higher frequency of total hip replacement[34] and a lesser sex ratio[35]. Some patients who started AS in childhood and adolescence had SEA syndrome (seronegative enthesopathy and arthropathy)[36], characterized as an undifferentiated spondyloarthropathy, whereas others started the disease similarly to the adult onset AS, characterizing genuine AS in children[37].

The prevalence of HLA-B27 in the patients studied was 78.2%, associated with ankle and entheseal involvement, whereas spinal involvement was statistically similar to HLA-B27 negative patients. Although AS shows a very strong association with HLA-B27, the strength of this association varies considerably among racial and ethnic groups[5,11]. The prevalence of HLA-B27 in Caucasian European populations varies between 2 and 18%, whereas it is extremely infrequent in African populations of unmixed origin[38]. Family history was reported by 14.3% of the patients, similar to that observed in a previous study[39]. In this study AS patients with a positive family history did not present a different disease outcome compared with those without a family history.

Peripheral involvement was frequent in our study (47.6%). The large joints of the lower limbs were most frequently affected, with heel enthesitis in 22.4% of the patients, predominantly related to juvenile onset AS and positive HLA-B27. AS with peripheral involvement frequently presents a better response to second-line drugs, like sulfasalazine[40,41] and methotrexate[42,43].

Acute anterior uveitis was the most frequent extraarticular manifestation of AS in this study (14.3%), with a predominantly good outcome, similar to that observed in the literature[44,45]; although present preferentially in HLA-B27 positive patients (18 of the 21 affected patients), there was no statistical significance. Kidney involvement was reported by 9.5% of the patients, but its relation to active AS was not confirmed; the kidney biopsies did not show renal amyloidosis or IgA nephropathy, as observed in Caucasian populations[46]. No patients presented symptomatic cardiac, pulmonary, or neurological disease considered related to AS, and only 3 patients died during followup. A Finnish study analyzing mortality and causes of death in a group of 398 AS patients found a mortality of 38.2% after a mean followup of 25 years, superior to that expected in the general population[47].

Analysis of the patterns of disease in this population of 147 Brazilian patients with primary AS revealed that female sex was associated with a milder axial involvement; Caucasian race presented axial and peripheral involvement similar to the African-Brazilians; juvenile onset AS was associated with articular involvement of the lower limbs and total hip replacement; and HLA-B27 was associated with ankle involvement.

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