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Higher Prevalence of Peripheral Arthritis Among Ankylosing Spondylitis Patients

This study was performed to define the clinical spectrum and disease manifestations of ankylosing spondylitis (AS) in a referral hospital setting. We identified the differences in clinical manifestations according to the sex, the age at onset, the presence of peripheral arthritis and the presence of HLA B27. A total 412 patients (357 males, 55 females) were recruited. Eighty-seven percent were men and 155 out of 412 patients (35%) were juvenile-onset. HLA B27 was detected in 385 patients (93%). Peripheral joint involvement was noted in 287 of total AS cases (juvenile-onset ankylosing spondylitis (JOAS), 82%; adult-onset ankylosing spondylitis (AOAS), 61%), and was more common than those reported in other studies. A greater portion of patients with JOAS had peripheral arthritis and peripheral enthesitis than the patients with AOAS. The patients with peripheral arthritis showed a younger age at onset and an increased tendency of having enthesitis and trauma history. The natural history of Korean AS appears largely similar to those seen in Europe and North America, except a few differences. JOAS was quite common and AS was about nine times more common in men than in women. In addition, the HLA B27 antigen frequency was 93%, which is higher than those reported in other studies.

Key Words : *Spondylitis, Ankylosing; Peripheral Arthritis*

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INTRODUCTION

Ankylosing spondylitis (AS) is found worldwide and more often in Caucasians than in other races (1). It is recognized that race, sex, and HLA B27 status are factors that may influence both the clinical presentation and course of the disease (1). The precise role of racial and ethnic patterns in the clinical feature is unknown. However, the association has been explained by the different prevalence of HLA B27 (1). The prevalence of HLA B27 among Koreans was reported to be between 2.3 and 3% (1, 2). As there are marked differences in the prevalence of AS among many racial and ethnic groups, comparative studies involving different populations are necessary to clarify the role of racial and ethnic patterns.

There have been studies on clinical features of AS depending upon the race and areas (3-5), but no study has been published so far on the clinical spectrum of AS in Korea. The aim of this study was to determine the symptom profile of AS. Also, we analyzed the differences in the clinical manifestations according to the sex, the age of onset, the presence of peripheral arthritis and the of HLA B27 status.

MATERIALS AND METHODS

Patients

A total of 412 AS patients attending The Hospital for Rheumatic Diseases, Hanyang University from 1985 to 1999 were studied retrospectively. The diagnosis of AS was given to those who fulfilled the criteria of the modified New York criteria (1). We excluded the patients with reactive arthritis, psoriasis, arthritis associated with inflammatory bowel disease and undifferentiated spondyloarthropathy. Data were collected retrospectively from the patients' medical records, and we collected the information or findings that might have been present but were not recorded in the medical charts during follow-up. We excluded those patients in whom sufficient information was lacking.

Demographic data

Data on age, sex, age at symptom onset, symptom duration, and onset and duration of inflammatory back pain were recorded. Age at symptom onset was defined as time when the first symptom, whether it was axial symptom, peripheral

arthritis, or enthesitis, had developed. Symptom duration was calculated by subtracting the year of symptom onset from 1999.

Clinical data

Patients were asked about family history (first-and second-degree relatives) of spondyloarthropathies (SpA). All data were recorded about the details of inflammatory back pain, peripheral arthritis, enthesitis, trauma, uveitis, dactylitis, oral ulcer, and renal involvement. The determination of current or previous inflammatory back pain was made based on symptoms persisting at least 3 months, improving with exercise and worsening with rest. Peripheral arthritis was defined as the presence of swelling and/or restricted range of motion in at least one peripheral joint, and/or history of previous swelling in at least one peripheral joint confirmed at that time by a rheumatologist (not including hip or shoulder joints) (1). Enthesitis was defined as inflammation and/or pain of peripheral entheses such as in calcaneal insertions of the Achilles tendon, plantar fascia, tibial tuberosities, costosternal junction, iliac crest, and greater trochanter (1). Oral ulcer was defined as ulcer on mucous membrane involvement of nose or mouth. As emotional trauma is difficult to assess in a quantitative manner, we only included the direct physical trauma that had occurred before the joint involvement. Dactylitis was defined as diffuse digit swelling extending beyond the margin of the joint capsule (1). Renal abnormality was considered when proteinuria, hematuria, impairment of renal function, and other abnormalities on light microscopy were seen. We identified the differences in clinical manifestations according to the sex and the presence of peripheral arthritis. Also, data from the juvenile-onset ankylosing spondylitis (JOAS) (onset before the age of 16 yr) and adult-onset ankylosing spondylitis (AOAS) (onset after the age of 16 yr) groups were compared.

Table 1. Clinical features of ankylosing spondylitis patients

Feature	Cases (%)
Sex, M/F	357 (55), 87 (13)
Age at onset, years	19.2±7.1
Duration of disease	11.0±6.7
AOAS/JOAS	267/145
Peripheral arthritis	287 (70)
Knee	262 (64)
Ankle	170 (41)
Small joint of feet	71 (17)
Elbow	63 (15)
Small joints of hand	53 (13)
Wrist	41 (10)
Hip	248 (60)
Shoulder	121 (29)
Enthesitis	217 (53)
Achilles tendon	191 (88)
Plantar fascitis	128 (31)
Tibial tubercle	119 (29)
Costosternal junction	118 (28)
Iliac crest	95 (23)
Greater trochanter	81 (20)
Family history of spondyloarthropathy	58 (16)
Trauma history	44 (11)
Uveitis	91 (22)
Renal involvement	24/395 (6)
Oral ulcers	40/356 (11)
Dactylitis	4/406 (1)
HLA B27	385 (93)
Rheumatoid factor	50 (12)

Laboratory data

Routine diagnostic laboratory tests (complete blood counts, erythrocyte sedimentation rate, serum creatinine, urinalysis) and rheumatoid factor (RF) by nephelometry (normal: <20 IU/mL) were done on every individuals and HLA-B27 status was determined by microcytotoxicity method. Radiographs including pelvis, lumbar spine, certain painful joints, and chest were obtained. We compared the differences in clinical manifestations according to the positivity of HLA B27.

Statistical analyses

Statistical analyses was performed using the SPSS statistical package. Chi-square tests and t-tests for independent values were used. p-value of <0.05 was regarded as significant.

RESULTS

Overall outcome

During the study period, 412 were diagnosed with AS. The clinical characteristics are shown in Table 1. The male-to-female ratio in AS was about 9:1. One hundred and forty five out of 412 patients had a juvenile onset. Two hundred and eighty seven patients (70%) were found to have peripheral joint involvement. The most commonly affected joints were knee (91%) and ankle (59%). The most common enthesitis was Achilles tendinitis (n=191, 88%). Hematuria or proteinuria was found in 24 patients of 395 (6%), and biopsy was done in 6 patients, all of whom were diagnosed with IgA nephropathy. Two patients were found to have other concomitant connective tissue diseases, which were mixed connective tissue disease and lupus, respectively (6). One patient who suffered from severe diarrhea was diagnosed with intestinal amyloidosis. No patient showed pulmonary fibrosis of lung.

Distribution of initially-affected joints

The sites initially involved were the axial joints including hip and shoulder (53%), peripheral joints (36%), and enthe-

Table 2. The number of sites affected initially

Site	Number (%)
Sacroiliac joints	147 (36)
Knee	112 (27)
Hip	62 (15)
Ankle	29 (7)
Heel	29 (7)
Tarsal	9 (2)
Shoulder	8 (2)
Plantar	4 (1)
Others	14 (3)

Table 3. Clinical presentations according to sex

	Men (n=357, %)	Women (n=55, %)	*p* value
Age at onset, years	18.8±6.9	22.2±8.0	0.001
Duration of disease (yr)	11.0±6.5	11.3±8.0	
AOAS/JOAS	229/127	36/18	
Peripheral arthritis	247 (69)	40 (73)	
Knee	227 (64)	35 (64)	
Ankle	141 (39)	29 (53)	0.065
Hand	35 (14)	18 (33)	0.00
Wrist	33 (13)	8 (16)	
Elbow	51 (21)	12 (22)	
Enthesitis	183 (51)	34 (62)	
Family history of SpA	48 (13)	9 (16)	
HLA B27	332 (93)	53 (96)	

ses (11%), in decreasing order (Table 2). The axial joints that were most commonly involved initially were the sacroiliac joints (37%). The peripheral joint that was most commonly affected initially was the knee (27%).

Serologic findings

HLA B27 status was determined in all patients, and 385 (93%) were positive for HLA B27. All were serologically tested for RF on one or more occasions with positive result in 50 cases (12%), but the titers were low.

Comparisons between male and female AS

The mean age at disease onset was 18.8±6.9 yr in men, and 22.2±8.0 yr in women (Table 3). Considering only AOAS patients, mean age was significantly younger in men than in women (22.0±5.9 vs 26.0±6.8, p=0.001). The pattern of joint involvement was significantly different between the two groups: the involvement of hand joints was more common in women. No significant difference in extra-articular manifestation was found between men and women. There was no significant difference in the laboratory findings between the two sexes.

Comparisons between JOAS and AOAS

Nearly 85% of patients with JOAS had peripheral joint disease, which contrasts with a figure of 61% found in AOAS (p=0.00). Sixty percent of JOAS and 49% of AOAS patients had peripheral enthesitis (p=0.028) (Table 4) .

Table 4. Clinical presentations according to age at onset

	JOAS (n=145, %)	AOAS (n=267, %)	*p* value
Sex, M/F	127/18	230/37	
Duration of disease (yr)	11.2±6.4	11.0±6.9	
Enthesitis	87 (60)	130 (49)	0.028
Peripheral arthritis	123 (85)	164 (61)	0.00
Knee	112 (77)	150 (56)	0.00
Ankle	78 (54)	92 (34)	0.00
Elbow	33 (23)	30 (11)	0.001
Wrist	17 (12)	24 (9)	
Hand	21 (14)	31 (12)	
Shoulder	44	77	0.34
Hip	95	153	0.261
HLA B27	132 (91)	253 (95)	

Comparisons between the patients with and without peripheral arthritis

The age at onset in the patients with peripheral arthritis was significantly younger than that in the patients without peripheral arthritis. Patients with peripheral arthritis had a higher frequency of enthesitis and trauma history. There was no significant difference in the laboratory findings between the two groups.

Comparisons according to the presence of HLA B27

The relevant findings (data not shown) show similar sex ratios, age at disease onset, duration of disease, and the pattern of peripheral arthritis. The positivity of RF had not influenced the peripheral arthritis and onset age.

DISCUSSION

The present study was designed to describe the entire spectrum and to determine the frequencies of various articular and extra-articular manifestations of AS. A total of 412 cases of AS who satisfied the modified New York criteria (1) were studied.

Despite the large number of patients, this study is essentially limited by some features of its design; first, data was collected retrospectively, second, the study was based on cases referred to rheumatologic institutions, and third, it was focused on extraspinal symptoms including peripheral arthritis due to limited data regarding spinal symptoms. These factors should be taken into consideration when interpreting the results.

Demographic data of our patients showed similarities with those of European patients. Khan found the mean age at onset

to be 25 yr in AS, and reported that the onset after the age of 45 was very uncommon (1). Another study reported the mean age at onset to be the early twenties (7). The mean age at onset in our patients was younger than Khan's report by almost 6 yr. One of the possible explanation might be the relatively large number of JOAS included in our study. We also noticed that AS is nine times more common in men than in women, in contrast to the Khan's report, which showed that AS was three times more common in men. Although the earlier estimated male-to-female ratio was 10-20:1, 5:1 has been accepted as a more likely ratio (8). Although racial characteristics might have influenced the male predominance, the male-to-female ratio in this study could be explained by the followings. 1) Referral pattern may account for the scarceness of women in our study, 2) the disease course of AS is more benign in women and the radiologic progression is slower in women than in men (5), 3) the young female patients in their child-bearing ages were reluctant to have their reproductive organs exposed to radiation, 4) had a high threshold for seeking medical advice because they tend to regard back pain or stiffness as somewhat insignificant physical signs in their daily lives. Also, 5) a higher frequency of peripheral arthritis among women could mislead to a diagnosis of rheumatoid arthritis.

We analyzed the differences in clinical manifestations between men and women. The average age at onset in women was reported to be between 22 and 38 yr (4, 9, 10). Two reports comparing men and women concluded that AS started 2 or 4 yr later in women (9, 10). Our data show that AS developed earlier in men than in women. Also, it is widely accepted that women with AS more often exhibit arthritis in the peripheral joints. Studies limited to female AS have demonstrated a prevalence of peripheral arthritis ranging between 23% and 75% (9-11). A few clinical studies have reported a significantly higher incidence of peripheral arthritis in women (12-14). However, our study did not show any difference with respect to the incidence of peripheral joint disease. Instead, it showed a higher frequency of peripheral arthritis in men as well as in women. However, we noticed that the patterns of joint involvement were different: the hand joint involvement was more common in women. Regarding the tests for immune complexes, some investigators have detected circulating immune complexes, while others have not. Khan reported that the sex showed no association with either RF or antinuclear antibody (1). In our study, RF was positive in 13% of men and 9% of women, and however, the difference was not statistically significant. Moreover, even if the RF was positive, the titer was low.

Patients in our study had a higher frequency of peripheral joint involvement. Seventy percent of the patients experienced signs and symptoms of peripheral joint involvement at some time in their disease courses, often followed by the axial signs. When only AOAS is taken into consideration, 61% of the cases showed peripheral arthritis, which was more common than Khan's report. We found that there were some differences in the clinical characteristics depending upon the presence or absence of peripheral arthritis. Patients with peripheral arthritis were younger and the age at the onset of disease was younger than the patients without peripheral arthritis. They also had higher frequencies of enthesitis and trauma history prior to the onset of AS.

To assess the influence of the age at onset, the clinical features and other variables of JOAS patients were compared with those of AOAS. This form of AS accounts for 10 to 21% of Caucasian groups (1, 15, 16) but a significant proportion of JOAS has been found in non-Caucasian groups from Africa, Mexico, and India (15). We found JOAS is quite common. A few previous studies have pointed out the influence at age of onset on the clinical patterns of AS and have reported that patients with a juvenile-onset usually have peripheral arthritis, enthesitis, and systemic symptoms at onset, whereas patients with an adult-onset usually complain of back symptoms and show objective signs of spinal and sacroiliac involvement (1, 15, 16). Peripheral arthritis was a common finding in our group, particularly among patients with a juvenile-onset.

Another common feature of SpA is the familial aggregation, and it has been well documented that HLA B27 is closely associated with the development of SpA (17-28). The prevalence of AS and related SpA seems to correlate directly with that of HLA B27 in general population. When the entire population of SpA was considered, HLA B27 was found to be present in 50-90% of the patients (17-27). According to another study that divided the study group into AS and non-AS SpA, HLA B27 was present in 70.5% and 44.9%, respectively (20). The HLA B27 antigen was positive in 93% of our patients group. HLA B27 (+) patients were shown to have an earlier onset of disease, a more severe clinical course, increased frequencies of acute anterior uveitis and peripheral arthritis (21-23). In our analysis, no difference was found in the age at onset or the prevalences of peripheral joint involvement and extra-articular manifestations between the HLA B27 (+) and HLA B27 (-) groups.

Acute anterior uveitis, the most common extra-articular involvement in patients with AS, is reported to occur in 1.5-30% of patients, and is more common in HLA B27 (+) than in HLA B27 (-) (1, 28-32). Also, there are several reports that have shown the uveitis mostly affects male patients and the classic features of AS are usually not present in the patients with uveitis (28, 30). Uveitis was found in 22% and was closely related with the male sex and HLA B27, however, neither finding showed a statistical significance (data not shown).

The clinical features of our AS appears largely similar to those in other studies, except a few noticeable differences: 1) AS in our study was about nine times more common in men than in women, as compared with Khan's report, in which AS was three times more common in men; 2) peripheral joint involvement was more common in our study than in others;

3) the pattern of joint involvement was significantly different between men and women; the hand joint involvement was more common in women; 4) JOAS was common in our study; 5) the HLA B27 antigen frequency was 93% in our study, which is higher than in others.

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