# Clinical and Radiographic Features of Adult-onset Ankylosing Spondylitis in Korean Patients: Comparisons between Males and Females

The objective of this study was to investigate clinical and radiographic features and gender differences in Korean patients with adult-onset ankylosing spondylitis. Multi-center cross-sectional studies were conducted in the rheumatology clinics of 13 Korean tertiary referral hospitals. All patients had a confirmed diagnosis of ankylosing spondylitis according to the modified New York criteria. Clinical, laboratory, and radiographic features were evaluated and disease activities were assessed using the Bath ankylosing spondylitis disease activity index. Five hundred and five patients were recruited. The male to female ratio was 6.1:1. Average age at symptom onset was $25.4 \pm 8.9$ yr and average disease duration was $9.6 \pm 6.8$ yr. Males manifested symptoms at a significantly earlier age. HLA-B27 was more frequently positive in males. Hips were more commonly affected in males, and knees in females. When spinal mobility was measured using tragus-to-wall distance and the modified Schober's test, females had significantly better results. Radiographic spinal changes, including bamboo spine and syndesmophytes, were more common in males after adjustment of confounding factors. In conclusion, we observed significant gender differences in radiographic spinal involvement as well as other clinical manifestations among Korea patients with adult-onset ankylosing spondylitis. These findings may influence the timing of the diagnosis and the choice of treatment.

Key Words : *Spondylitis, Ankylosing*

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## INTRODUCTION

Ankylosing spondylitis (AS) is a human leukocyte antigen (HLA)-B27-associated chronic inflammatory disease that predominantly affects the spine and sacroiliac joints. AS occurs worldwide, but its prevalence ranges from 0 to 1.9%, which implies ethnic and geographic differences (1). Historically, AS has been considered to overwhelmingly affect males, but recent studies have shown that a significant number of AS patients are females, with a male to female ratio approaching 2-3:1 (2, 3). Furthermore, the disease pattern also varies by gender, and the spine and pelvis are more commonly affected in males (4). The documented clinical features of AS have been largely derived from studies on Caucasian patients, and studies on Asians are relatively scarce. In particular, gender-based comparisons of clinical manifestations have not been reported in Asia. In the present study, we compared gender differences in the clinical and radiographic features of AS in 505 patients treated at 13 tertiary Korean hospitals.

## MATERIALS AND METHODS

### Patients

Patients were enrolled at the rheumatology clinics of 13 tertiary hospitals between February and December 2006. Patients were included if they met the modified New York criteria for AS (5) and were willing to participate in our registry study of AS. The study hospitals were located in four different Korean provinces. Patients with juvenile onset of AS (an age at onset of <15 yr), and patients with a history of inflammatory bowel disease or psoriasis were excluded. This study was approved by the ethics committees at all participating hospitals and informed consent was obtained from all patients.

### Methods

All participants completed questionnaires, which included questions on demographics, such as age, sex, educational attainment, occupation, exercise, family history of AS, and co-morbidities. Heights (cm) and body weights (kg) were measured to the nearest 0.1 cm and 0.1 kg, respectively, with subjects barefoot and wearing light clothing, to calculate body mass indices (BMI). We also collected clinical data, such as, disease duration, age at disease onset, manifesting symptoms, initial joint symptoms, previous site of joint and enthesis involvement, and history of extra-articular manifestations. Disease activities were evaluated using a validated Korean version of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (6). We performed complete joint and enthesis examinations and physical measurements on all patients at study entry. Lumbar spinal mobility was measured using Macrae's modification of Schober's technique (7). Measure-ments were taken of tragus-to-wall distance and chest expansion at the level of the 4th anterior rib. Joint involvement was defined either if a joint showed swelling, tenderness, or a limited range of motion during physical examination or if the patient reported having arthralgia/arthritis in a joint during clinical data collection. Entheses were examined using direct pressure over standard sites, such as the calcaneal insertions of the Achilles tendon, plantar fascia, tibial tuberosities, costosternal junction, iliac crest, and greater trochanter. Enthesitis was defined as either the presence of entheseal tenderness during physical examination or the history of pain at the above entheseal areas. The laboratory evaluations performed included; complete blood cell count, Westergren erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), HLA-B27, rheumatoid factor (RF), and antinuclear antibody (ANA). The following radiographs were obtained in each case; the pelvis (anteroposterior view), cervical, thoracic, and lumbar spine (anteroposterior and lateral views). Radiographs of the spine were assessed for the formation of syndesmophytes and for bamboo spine. Bamboo spine was defined as ankylosis involving all three spinal levels. Patients with bamboo spine was not included in the counting of spinal syndesmophytes. Radiographs were read by academically based rheumatologists experienced at reading spine radiographs.

### Statistics

All data are presented as means and standard deviation (SD) or as percentages. Unadjusted male-female comparisons were performed using the Student's t-test for normally distributed continuous measures, and using the chi-square test or Fisher's exact test for categorical measures. The odds ratios and 95% confidence interval for bamboo spine was estimated after adjusting age, BMI, duration of disease and HLA-B27 positivity. $P$ value of <0.05 was regarded as significant.

## RESULTS

In total, 434 males and 71 females with AS were studied. Males manifested symptoms at a significantly earlier age, and had longer disease duration at the time of study entry (Table 1). Disease activity as measured using BASDAI, ESR and CRP was not significantly different between genders. HLA-B27 positivity was significantly higher among males (94.8% vs. 87.3%; male vs. females, $P$=0.016). Males experienced joint pain, including back pain, as the first manifestation of AS more often than females (94.7% vs. 85.9%, male vs. females, $P$=0.005), while females more frequently experienced uveitis as the first manifestation compared to males (3.2% vs. 9.9%, male vs. females, $P$=0.009). The most common joint symptom was back pain (63.4% vs. 54.9%, male vs. females). Excluding the spine, the hips and knees were the most commonly affected joints; knee involvement was significantly more

Table 1. Baseline characteristics of AS patients

| Parameters | Total (n=505) | Males (n=434) | Females (n=71) | P value |
|---|---|---|---|---|
| Age (yr) | 35.0±10.0 | 34.9±10.1 | 35.4±9.6 | ns |
| Age at diagnosis (yr) | 30.0±9.7 | 29.8±9.7 | 31.5±9.7 | ns |
| Age at symptom onset (yr) | 25.4±8.9 | 25.0±8.9 | 27.7±8.8 | 0.015 |
| Duration of disease (yr) | 9.6±6.8 | 9.9±7.0 | 7.7±5.4 | 0.004 |
| Education level (%) | | | | |
| ≤6 yr | 7 (1.4) | 7 (1.7) | 0 | |
| 6-12 yr | 171 (35.2) | 148 (35.5) | 23 (33.3) | ns |
| ≥12 yr | 308 (63.4) | 262 (62.8) | 46 (66.7) | ns |
| BMI (kg/m²) | 22.8±3.1 | 23.0±3.0 | 21.5±3.3 | <0.001 |
| Family history of AS (%) | 64 (12.7) | 55 (12.9) | 9 (12.7) | ns |
| HLA-B27-positivity: n (%) | 465 (93.8) | 403 (94.8) | 62 (87.3) | 0.016 |
| BASDAI | 4.4±2.3 | 4.5±2.4 | 4.2±2.0 | ns |

BMI, body mass index; BASDAI, bath ankylosing spondylitis disease activity index; ns, non-significant.

Table 2. Peripheral joint involvements and spinal mobility of male and female AS patients

| Joints | No. of patients (%) | | | P value |
|---|---|---|---|---|
| | Total | Males | Females | |
| Shoulder | 93 (18.4) | 81 (18.7) | 12 (16.9) | ns |
| Elbow | 13 (2.6) | 10 (2.3) | 3 (4.2) | ns |
| Wrist | 16 (3.2) | 14 (3.2) | 2 (2.8) | ns |
| Hand | 20 (4.0) | 16 (3.7) | 4 (5.6) | ns |
| Hip | 220 (43.6) | 196 (45.2) | 24 (33.8) | ns |
| Knee | 166 (33.5) | 128 (30.1) | 38 (54.3) | <0.001 |
| Ankle | 66 (13.1) | 55 (12.7) | 11 (15.5) | ns |
| Foot | 28 (5.5) | 22 (5.1) | 6 (8.5) | ns |
| Mobility* | | | | |
| Occiput-to-wall distance | 3.7±5.2 | 4.0±5.3 | 2.0±4.0 | <0.001 |
| Chest expansion | 3.4±1.8 | 3.4±1.9 | 3.6±1.5 | ns |
| Modified Schober's test | 3.6±2.1 | 3.4±2.0 | 4.3±2.5 | 0.001 |

*cm, mean±SD.

frequent in females (30.1% vs. 54.3%, male vs. females, P< 0.001), and hip involvement tended to be more frequent in males (45.2% vs. 33.8%, male vs. females, P=0.074) (Table 2). When spinal mobility was measured using tragus-to-wall distance and the modified Schober's test, females had significantly better results; however, chest expansion was not significantly different. In our study subjects, Achilles tendinitis was the most common form of enthesitis, followed by plantar fasciitis. Plantar fasciitis was significantly more frequent in females (6.0% vs. 15.5%, males vs. females, P=0.004), as was uveitis (19.4% vs. 32.4%, males vs. females, P=0.013).

The pattern of spinal involvement manifesting as syndesmo-

Table 3. Patterns of radiographic spinal involvement in AS patients

| Radiographic findings | No. of patients (%) | | | P value |
|---|---|---|---|---|
| | Total | Males | Females | |
| Lumbar syndesmophyte | 123 (24.4) | 106 (24.4) | 12 (24.5) | ns |
| Thoracic syndesmophyte | 61 (12.8) | 59 (13.6) | 2 (2.8) | 0.027 |
| Cervical syndesmophyte | 13 (2.6) | 10 (2.3) | 3 (4.2) | ns |
| Bamboo spine | 104 (20.6) | 96 (22.1) | 8 (11.3) | 0.023 |
| Normal | 266 (52.7) | 220 (50.7) | 46 (64.8) | 0.042 |

phytes or bamboo spine is shown in Table 3. Bamboo spine and syndesmophytes in the thoracic spine was significantly more common among male patients. Male patients had significantly increased odds ratio for bamboo spine compared to females after adjustment of age, BMI, duration of disease and HLA-B27 positivity (unadjusted odds ratio [OR] 2.24 [95% confidence interval [CI] 1.34-3.74], adjusted OR 1.90 [95% CI 1.13-3.39]).

## DISCUSSION

In this study, we aimed to investigate the clinical and radiographic features of 505 Korean patients with adult-onset AS and to identify gender differences. It was observed that males manifested symptoms at a significantly earlier age, had a greater HLA-B27 positive rate, and had more extensive radiographic spinal involvement. On the other hand, females had more uveitis.

As compared with previous reports of male-to-female ratios of 1.9:1 to 3:1 (2, 8-9), we found a ratio of 6.1:1 in the present study, which concurs with previous Korean and Chinese reports on patients with AS (10, 11). However, we do not know whether this higher male to female ratio is a specific feature among Asian subjects. The majority of Asian studies have been conducted at single centers, usually referral hospitals, and thus, patients with more severe symptoms may have been selectively recruited. Although most of the study centers involved in the present study were university affiliated tertiary hospitals, the study included hospitals located in 4 different Korean provinces (Seoul, Pusan, Daegu, Kyunggi), and it is one of the largest studies conducted in Asia, and thus, it might be more representative than previous Asian studies. Contrary to a previous report that revealed longer diagnostic delays among female patients (12), no difference in gender-associated diagnostic delays was observed in the present study (4.5 yr vs. 3.8 yr; male vs. female, respectively). Thus, the larger male to female ratio observed in the present study is unlikely to be entirely due to the under-diagnosis of female patients. A larger study involving patients from a community cohort or nationwide patient registry is warranted to determine gender differences in AS prevalence more precisely in Korea.

Although the overall frequency of HLA-B27 positivity of

our subjects was similar to those reported previously, females had significantly lower positivity compared to males in our study patients, which is contradictory to previous reports including that from Korea (10). Whether this discrepancy stems from the limited sample size or true difference among Korean subjects also needs to be investigated in a larger patient registry.

The findings of the present study concur with those of previous studies regarding the common involvements of joints of the lower extremities, particularly the hips, knees and ankles, in AS (10, 13), and although the knee joint was significantly more involved in females and the hip joint in males, peripheral joints including those of the ankle, foot, wrist and elbow were similarly involved in both genders. Furthermore, in line with a previous Korean report, our patients tended to have higher prevalences of shoulder, hip and peripheral joint involvement than Caucasians (1).

Ankylosis is regarded as the end point of the inflammatory process in AS. Sacroiliac joint involvement and spinal ankylosis have been reported to be more frequent among male patients (14). And the present study also shows a higher proportion of males had spinal involvement, which manifested as spinal syndesmophytes and bamboo spine. It is presumed that the better mobility of our female AS patients, despite similar disease activities (as measured by BASDAI) and acute phase reactant levels, were the result of reduced spinal involvement. It would be interesting to determine whether this difference in spinal involvement and mobility is related to better functional outcomes in female patients.

The underlying pathogenetic mechanism that results in gender-associated differences in terms of the manifestations of AS is unknown. Recently, different haplotype combinations in the ankylosis homologue (ANKH) gene were reported in males and females with AS (15). Further genetic studies may identify more genes that contribute to observed ethnic and gender differences and the severity of AS.

The limitations of this study include its cross-sectional design and possible selection bias due to the recruitment of patients from rheumatology clinics in tertiary referral hospitals. In addition, due to limited resources, no standardized reading scheme was used for spinal radiographs, such as the Stoke ankylosing spondylitis spinal scoring system, and only limited analysis of spine involvement extent was performed. The reading was performed by as many as 13 readers, and because of the logistics, we could not obtain inter-reader variability. However, limited inter-reader variability analysis involving 2 readers and 45 subjects showed that the kappa statistics were good for our simple scheme evaluating only the presence or absence of syndesmophytes and bamboo spine. Joint examination findings were recorded at the time of recruitment, and thus, previous involvement may not have been included, which possibly caused peripheral joint involvement to be underestimated.

In conclusion, we have examined the clinical characteristics of a large number of Korean patients with adult-onset AS. We observed significant gender differences in radiographic spinal involvement as well as other clinical manifestations among our subjects. These findings may influence the timing of the diagnosis and the choice of treatment.

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