Clinical, Functional, and Radiographic Differences Among Juvenile-onset, Adult-onset, and Late-onset Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** The aim of our study was to compare the clinical, functional, and radiographic outcomes at different ages of onset in patients with ankylosing spondylitis (AS).

Methods. A total of 546 patients were enrolled consecutively and classified into 3 groups based on their age at symptom onset: (1) juvenile-onset AS (age ≤ 16 years; JoAS); (2) adult-onset AS (> 16 but < 40 years; AoAS); and (3) late-onset AS (≥ 40 years; LoAS). We compared the differences among the 3 groups. OR for disease outcomes were calculated and adjusted for sex, HLA-B27, and disease duration.

Results. There were 67 patients (12.3%) with JoAS, 460 (84.2%) with AoAS, and 19 (3.5%) with LoAS. Male sex and HLA-B27 were associated with a younger age at onset ($p < 0.001$). Compared to patients with AoAS, patients with JoAS were more likely to present with peripheral arthritis, while patients with JoAS and LoAS were less likely to have back pain at the onset of AS ($p < 0.05$). After controlling for multiple covariates, JoAS was found to be associated with a worse functional outcome and global assessment, and a high serum immunoglobulin A level ($p < 0.05$). Patients with JoAS had less lumbar spinal radiographic severity ($p < 0.05$). There were no statistical differences in clinical or functional outcome between the LoAS and AoAS groups. None of the LoAS patients had radiographic hip involvement.

Conclusion. Sex and HLA-B27 are significantly associated with age at onset of AS. Both JoAS and LoAS have their distinctive symptoms/signs at onset and different disease outcomes. (First Release March 15 2012; J Rheumatol 2012;39:1013–18; doi:10.3899/jrheum.111031)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS ONSET AGE OUTCOME

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease that primarily affects the sacroiliac joints and axial spine, causing characteristic inflammatory back pain[1]. The disease can be complicated by peripheral arthritis, enthesitis, and extraarticular manifestations such as uveitis. AS occurs predominantly in young males and has a strong genetic association with HLA-B27. The age of disease onset is usually from the late teens to age 40 years[2]. When symptom onset occurs in patients aged 16 years or less, the disease is termed juvenile-onset AS (JoAS)[3]. Most adult patients experience their first symptoms of AS prior to age 40; however, AS may develop after the age of 40. The initial clinical manifestations may vary among AS patients with different ages at onset[3,4,5]. Chronic inflammation of the skeletal system in AS causes progressive motion restriction and structural damage that can be visible on plain radiography. Differences in functional outcome and radiographic severity have been reported among AS patients with different ages at onset[3,4,5,6]. In addition to the influence on disease expression, the age of symptom onset was significantly different between AS patients with and those without HLA-B27[2], and there was also a sex difference in age at onset of AS[7].

It has been reported that patients with JoAS have a different presentation and clinical course from other patients with AS[3,4,5]. AS patients with late onset (age ≥ 40 years) may also have a distinctive clinical pattern of disease[6,8]. We compared the initial symptoms/signs and the clinical and radiographic outcomes among ethnic Chinese patients with AS with different ages at onset. We divided a large cohort of patients into subgroups depending on the age at symptom onset, and compared these groups. We also examined the association between HLA-B27 and sex and onset age of AS.

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MATERIALS AND METHODS

We consecutively enrolled 546 patients with AS at our outpatient department. All patients met the 1984 modified New York criteria for diagnosis of AS[9]. For each case, we recorded age, sex, age at symptom onset, disease duration, the presence or absence of HLA-B27 antigen, and initial symptoms/signs. No biological agents had been used by these patients. Patients were classified into 3 categories according to the age of onset of musculoskeletal symptoms: (1) JoAS (AS with symptom onset ≤ 16 years of age); (2) adult-onset AS (AS with symptom onset > 16 but < 40 years of age; AoAS); and (3) late-onset AS (AS with symptom onset ≥ 40 years of age; LoAS). The initial symptoms/signs were reviewed retrospectively using self-report questionnaires and/or medical records; symptoms/signs included back pain, sternum pain, peripheral arthritis, enthesitis, and uveitis. To assess disease activity, physical function, and spinal mobility, and make the global assessment, we used the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Functional Index (BASFI), Metrology Index (BASMI), and Patient Global Score (BASG), respectively[10,11,12,13]. These clinical outcomes were evaluated by well-trained nurses and rheumatologists. Laboratory assessments included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and immunoglobulin A (IgA). The severity of radiographic changes in the sacroiliac joints, lumbar spine, cervical spine, and hip joints were each assessed separately using the modified New York criteria, modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), and Bath Ankylosing Spondylitis Radiology Hip Index (BASRI-hip)[9,14,15]. All radiographs were scored twice and blindly. Our study was approved by the local medical research ethics committee and all participants provided written informed consent prior to their inclusion.

Statistical analysis. Comparisons between the 3 groups were performed using the chi-square test or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables, when necessary. For comparison of JoAS and AoAS, we calculated the OR and 95% CI for initial symptoms/signs after adjusting for sex and HLA-B27 in a logistic regression model. The OR of clinical and radiographic outcomes were adjusted for sex, HLA-B27, and disease duration. Comparison of characteristics between LoAS and AoAS was also performed with the same statistical method. If not addressed, p values < 0.05 were considered statistically significant. Data analysis was done using SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Initial symptoms/signs and outcome assessments. Table 1 describes the disease-related characteristics of patients with AS according to age at symptom onset. Of 546 patients, 67 (12.3%) had JoAS, 460 (84.2%) had AoAS, and 19 (3.5%) had LoAS. Patients with JoAS were younger and had longer disease duration. The percentages of male sex and HLA-B27 were highest in the JoAS group. The arthritis pattern of the disease at onset differed significantly between the 3 patient groups: patients with JoAS had more peripheral arthritis; patients with JoAS and LoAS had less back pain than those with AoAS. Sternum pain was a rare

Table 1. Comparison of clinical, laboratory, and radiographic data among patients with ankylosing spondylitis (AS) based on the age of symptom onset. Results are expressed as mean ± SD unless otherwise specified. The sacroiliitis score was assessed using the modified New York criteria.

Characteristic	Juvenile-onset, n = 67	Adult-onset, n = 460	Late-onset, n = 19	p†	p††
Age at onset, yrs	14.5 ± 1.5	24.4 ± 5.8	46.1 ± 6.5	< 0.001*	< 0.001*
Current age, yrs	26.8 ± 7.3	33.9 ± 10.0	52.3 ± 6.4	< 0.001*	< 0.001*
Disease duration, yrs	12.3 ± 7.0	9.5 ± 8.4	6.2 ± 6.1	< 0.001*	0.072
Men, %	89.6	78.5	57.9	0.035*	0.047*
HLA-B27, %	94.0	86.5	89.5	0.083	1.000
Initial symptoms/signs					
Back pain, %	73.1	85.2	63.2	0.012*	0.018*
Peripheral arthritis, %	37.3	21.5	21.1	0.004*	1.000
Enthesitis, %	13.4	10.2	15.8	0.425	0.435
Uveitis, %	10.4	9.6	21.1	0.819	0.112
Peripheral arthritis/ enthesitis only, %	16.4	7.6	5.3	0.017*	1.000
Outcome measures					
BASDAI	4.5 ± 1.9	4.5 ± 2.1	3.9 ± 2.4	0.708	0.303
BASFI	3.7 ± 2.5	2.9 ± 2.5	2.1 ± 2.3	0.005*	0.153
BASMI	2.8 ± 2.6	2.6 ± 2.5	2.1 ± 1.7	0.477	0.772
BASG	6.4 ± 2.6	5.2 ± 2.8	5.0 ± 2.9	0.002*	0.731
CRP, mg/dl	1.6 ± 2.0	1.8 ± 2.0	0.9 ± 0.8	0.973	0.211
ESR, mm/h	26.7 ± 19.7	26.0 ± 21.8	30.1 ± 22.3	0.618	0.607
IgA, mg/dl	404.8 ± 158.0	328.0 ± 129.7	276.8 ± 108.9	< 0.001*	0.203
Sacroiliitis	3.1 ± 1.0	2.9 ± 0.9	2.4 ± 0.8	0.040*	0.034*
BASRI-hip	0.7 ± 1.3	0.3 ± 0.9	0 ± 0	0.020*	0.088
mSASSS cervical spine	8.3 ± 12.5	9.7 ± 12.9	0.8 ± 2.3	0.680	0.014*
mSASSS lumbar spine	4.2 ± 9.8	5.4 ± 9.7	0.6 ± 1.6	0.028*	0.036*

† Juvenile-onset vs. adult-onset groups; †† late-onset vs. adult-onset groups. * Statistical significance. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; BASG: patient global score; BASRI-hip: Bath Ankylosing Spondylitis Radiology Hip Index; mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

initial presentation of AS: only 4 patients with AoAS had this presentation. With regard to outcome evaluation, patients with JoAS had the highest functional index, global assessment score, and serum IgA level. There were no differences in BASDAI, BASMI, ESR, and CRP. The radiographic scores of the sacroiliac and hip joints were worst in the JoAS group, but radiographic changes in the lumbar spine as assessed by mSASSS were worst in the AoAS group. There was no radiographic hip involvement in the LoAS group.

Association between sex and HLA-B27 and age at symptom onset. Men had a younger average age at onset than women (22.8 ± 7.3 vs 28.1 ± 7.4 yrs; $p < 0.001$). Patients with HLA-B27 were also associated with a younger age at onset (23.4 ± 7.4 vs 27.6 ± 8.2 yrs; $p < 0.001$). HLA-B27 positivity was associated with a younger age at onset in male but not in female patients. The association between sex and HLA-B27 and age at symptom onset is shown in Figure 1.

Comparison of initial symptoms/signs and outcomes of JoAS versus AoAS. Significant differences in initial symptoms/signs between the JoAS and AoAS groups were identified (Table 2). After adjusting for sex and HLA-B27, patients with JoAS had more peripheral arthritis and less back pain at symptom onset than those with AoAS. Peripheral involvement (arthritis or enthesitis) without axial involvement was seen more in JoAS than in AoAS. After adjustment for multiple covariates including disease duration, patients with JoAS had significantly higher IgA levels and worse BASFI and BASG values. Adjusted OR showed a 13% increase in the chance of having JoAS rather than AoAS when the BASFI scores increased 1 unit. Similarly, a 17% increase was observed for each unit-increase in the BASG scores. The mSASSS score for the lumbar spine was significantly lower in patients with JoAS. Radiographic evidence of hip disease was seen in 23.9% of the JoAS group and 13.3% of the AoAS group; however, these values were not significantly different between the 2 groups after adjustment.

Comparison of initial symptoms/signs and outcomes of LoAS versus AoAS. The disease pattern at onset was significantly different between the LoAS and AoAS groups (Table 3). Back pain was less common in LoAS than in AoAS. There were no significant differences in clinical outcomes and spinal radiographic changes between LoAS and AoAS.

DISCUSSION

We found an association between sex and HLA-B27 and age at onset of AS. Patients with JoAS were more frequently male and HLA-B27-positive than the patients in the other groups. Age at symptom onset had a great effect on the initial presentations and outcome measures. Although the JoAS and LoAS groups represented a small portion of the total AS population, both of them had their distinctive symptoms/signs at onset and different clinical, functional, and radiographic outcomes.

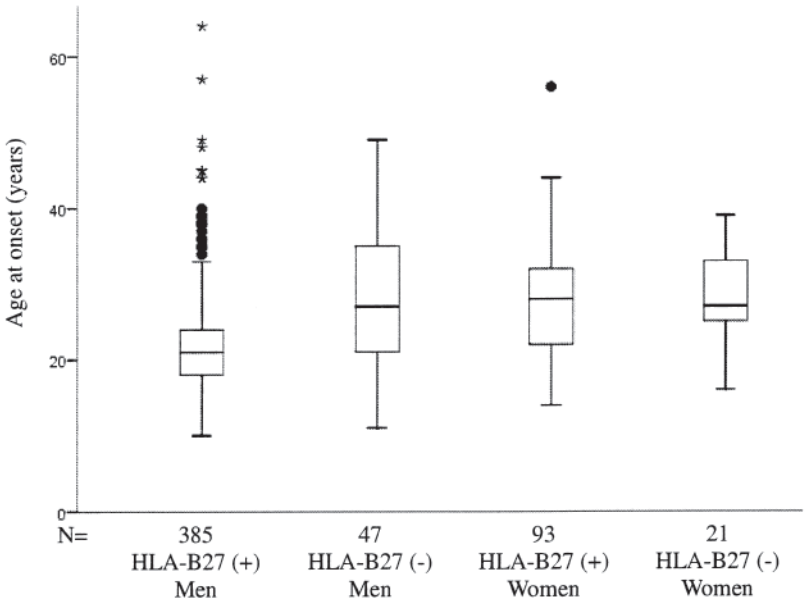

Figure 1. Associations between sex and HLA-B27 and age at symptom onset. Male patients with positive HLA-B27 had younger age at onset than other groups ($p < 0.001$). There were no significant differences between male patients without HLA-B27 and female patients with and without HLA-B27. Boxes indicate lower and upper quartiles; lines show medians. Differences between groups were calculated by Kruskal-Wallis test, followed by multiple comparisons with the Dunn method, if any significance was detected by the former calculation.

Table 2. Association of initial symptoms/signs, and clinical, laboratory, and radiographic features with juvenile versus adult-onset ankylosing spondylitis. The OR corresponds to a unit-increase in the variable if not addressed.

Feature	OR (95% CI)†
Initial symptoms/signs	
Back pain	0.48 (0.26–0.87)*
Peripheral arthritis	2.23 (1.29–3.86)*
Enthesitis	1.41 (0.65–3.05)
Uveitis	1.16 (0.49–2.70)
Peripheral arthritis/enthesitis only	2.35 (1.24–4.45)*
Outcome	OR (95% CI)††
BASDAI	1.01 (0.89–1.14)
BASFI	1.13 (1.02–1.25)*
BASMI	0.93 (0.79–1.10)
BASG	1.17 (1.06–1.30)*
CRP > 0.5 vs ≤ 0.5 mg/dl	2.04 (0.75–5.55)
ESR > 20 vs ≤ 20 mm/h	1.55 (0.77–3.12)
IgA > 453 vs ≤ 453 mg/dl	2.63 (1.38–4.99)*
Sacroiliitis	1.26 (0.91–1.75)
BASRI-hip	1.19 (0.96–1.48)
mSASSS cervical spine	0.97 (0.94–1.00)
mSASSS lumbar spine	0.95 (0.92–0.99)*

† Adjusted for sex and HLA-B27. †† Adjusted for sex, HLA-B27, and disease duration. * Statistical significance. Definitions as in Table 1.

Table 3. Association of clinical, laboratory, and radiographic features with late versus adult-onset ankylosing spondylitis. The OR corresponds to a unit-increase in the variable if not addressed.

Feature	OR (95% CI)†
Initial symptoms/signs	
Inflammatory back pain	0.29 (0.11–0.78)*
Peripheral arthritis	0.96 (0.31–2.97)
Enthesitis	1.46 (0.41–5.27)
Uveitis	2.25 (0.70–7.18)
Peripheral arthritis/enthesitis only	1.57 (0.44–5.63)
Outcome	OR (95% CI)††
BASDAI	0.88 (0.71–1.09)
BASFI	0.89 (0.72–1.11)
BASMI	1.08 (0.78–1.49)
BASG	0.97 (0.82–1.14)
CRP > 0.5 vs ≤ 0.5 mg/dl	0.48 (0.11–2.01)
ESR > 20 vs ≤ 20 mm/h	1.30 (0.29–5.90)
IgA > 453 vs ≤ 453 mg/dl	0.72 (0.09–5.88)
Sacroiliitis	0.87 (0.44–1.73)
mSASSS cervical spine	0.83 (0.63–1.09)
mSASSS lumbar spine	0.85 (0.67–1.08)

† Adjusted for sex and HLA-B27. †† Adjusted for sex, HLA-B27, and disease duration. * Statistical significance. Definitions as in Table 1.

It has been reported that the average age at disease onset is later in HLA-B27-negative AS patients than in HLA-B27-positive patients[2,16,17]. The association between HLA-B27 and age at disease onset is seen not only in AS but also in nonradiographic axial spondyloarthritis (SpA)[16]. In both AS and nonradiographic axial SpA, the highest percentage of HLA-B27 positivity is found in patients with onset ≤ 20 years of age[16]. The association between sex and age at onset is controversial[2,7,16,18]. In a questionnaire study, Feldtkeller, *et al* found that the mean age at onset of AS was somewhat earlier in women than in men, and that the difference appeared only at adult age, not at juvenile age[2]. We found that AS developed earlier in men than in women, consistent with previous reports[7,18]. The age at disease onset was also lower in male patients with nonradiographic axial SpA than in female patients with nonradiographic axial SpA[16]. However, no significant sex difference in the age at onset of AS was observed in that study[16]. The youngest age at symptom onset in our study was in male patients with positive HLA-B27.

We found a lot of differences in the initial presentation and outcome assessment between AS patients with different ages at onset, especially between JoAS and AoAS patients. Compared to patients with AoAS, those with JoAS were more likely to present with peripheral arthritis and had less back pain at onset. Patients with JoAS seemed to have less severe spine disease, as seen radiographically, than those with AoAS, after control for multiple covariates, including disease duration. Many studies have found significant differences between patients with JoAS and those with AoAS[3,4,5,18,19,20]. Patients with JoAS tend to have more peripheral symptoms and fewer axial symptoms at disease onset compared to AoAS[3,18,20,21,22]. Peripheral involvement without axial involvement at onset seems to be a unique feature of JoAS[3,23]. This difference in the axial/peripheral pattern can continue throughout the course of the disease[3]. There is also a tendency for more radiographic hip disease and less radiographic spinal change in JoAS compared to AoAS[4]. We observed that JoAS was associated with a worse functional outcome and global assessment. However, there are conflicting results in the literature[3,19,20]. One older study indicated that functional impairment was more severe in the JoAS group[20], and another study based on a postal survey found that the BASFI scores were worse in JoAS than in AoAS[19]. However, a recent study by O'Shea, *et al* showed that JoAS was associated with a better functional outcome[3]. Some studies also reported that patients with JoAS and AoAS had similar functional outcomes[18,23], even those patients with longstanding disease[4]. The discrepancies may have arisen from different study designs and methodologies. In contrast to Lin's report, we did not find any significant elevation of CRP and ESR in patients with JoAS[5]. But our patients with JoAS had significant elevation of serum IgA levels compared to those with AoAS. Serum IgA levels have been shown to be elevated in AS, and there is an association between IgA levels and disease activity[24,25].

Some differences were also observed between LoAS and AoAS in our study. As noted in the previous report, the onset of AS is uncommon after age 40 years[2]. There is little infor-

mation about the initial presentations and outcome assessments of LoAS. There is also no definition for LoAS. Calin, *et al* have reported that LoAS (35-45 years) was associated with more shoulder pain[8]. In a literature review by Toussirot, the clinical and radiographic features of LoAS patients (onset age ≥ 50 years) were quite different from those of AS patients with younger age at onset[26]. Cervical pain and swelling of the extremities with pitting edema were 2 distinctive clinical presentations of LoAS. The review also showed that only 70% of patients with LoAS were positive for HLA-B27, whereas 90% of patients with a younger age at onset were positive for HLA-B27[26]. In our study, patients with LoAS had less back pain at symptom onset compared to patients with AoAS. The outcome difference between LoAS and AoAS seemed to be less than that between JoAS and AoAS. None of the LoAS patients had radiographic hip involvement, whereas radiographic evidence of hip disease is prominent in patients with JoAS. This finding confirmed that there was a link between age at onset and hip disease[27,28].

Our study enrolled a large, well-characterized population of patients with AS. However, there were some limitations. First, we aimed to examine a hospital population that might not represent the full spectrum of patients with AS. Second, we could not preclude the existence of recall bias when using a retrospective symptom questionnaire. Third, the sample size of patients with LoAS was small. Finally, the study was based on a cross-sectional analysis. Prospective longitudinal cohort studies with large numbers of patients are needed to confirm our results.

HLA-B27 and sex can have a significant association with age at onset of AS. When AS develops at age ≤ 16 years or ≥ 40 years, the disease patterns may be different. Both JoAS and LoAS tend to have their distinctive axial/peripheral symptoms at disease onset. JoAS and LoAS can also have a different disease outcome from AoAS. Therefore, the diagnosis and treatment of AS can vary with different ages at disease onset.

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