Comparison on radiographic progression over 5 years between juvenile onset ankylosing spondylitis and adult onset ankylosing spondylitis: an observational study of the Korean SpondyloArthropathy Registry (OSKAR) data

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Abstract

Objective

To evaluate differences in radiographic progression between adult-onset ankylosing spondylitis (AoAS) and juvenile-onset ankylosing spondylitis (JoAS).

Methods

A total of 533 patients (418 patients with AoAS and 115 patients with JoAS) from the Observation Study of Korean spondyloArthropathy Registry (OSKAR) cohort were enrolled. All baseline OSKAR data were analysed in relation to disease onset and radiographic progression was analysed between the groups over 5 years. The modified Stoke AS Spinal Score (mSASSS) were used by two experienced radiologists. Clinical data were collected to investigate the associations between clinical factors and radiographic progression. Radiographic scores were compared using analysis of covariance model after adjusting for confounding factors.

Results

Inter-reader reliability for baseline mSASSS was very good. Inter-reader reliability for the changes in the mSASSS was also good. A significant difference in baseline mSASSS (mean ± SD) unit was detected between the AoAS and JoAS groups (18.1±17.4 vs. 14.3±13.8, p=0.015). We assessed the change in mSASSS to confirm whether age at onset affected radiographic progression. A simple comparison revealed a significant difference between changes on the mSASSS (mean ± SEM) between the JoAS and AoAS groups (1.75±0.71 vs. 3.77±0.56, p<0.001). After adjusting for multiple comparisons, change on the mSASSS remained lower in patients with JoAS than those with AoAS (0.28±1.33 vs. 4.08±0.62, p=0.016).

Conclusion

Patients with JoAS had slower radiographic spinal damage progression over 5 years than those with AoAS.

Key words

ankylosing spondylitis, juvenile onset ankylosing spondylitis, modified Stoke AS spinal score

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Introduction

Ankylosing spondylitis (AS) is characterised by inflammation of the axial skeleton (1). The most characteristic features of AS are subchondral eburnation and syndesmophytes, which can lead to ankylosis and spinal fusion. Symptoms of AS typically begin in early adulthood, but can occur in childhood. The disease is termed juvenile-onset AS (JoAS) when symptoms begin in patients <16 years of age (2).

Differences in functional outcomes have been reported between adult-onset AS (AoAS) and JoAS; however results vary widely. Some studies have reported worse functional outcomes in patients with JoAS (3, 4), whereas others have shown no difference in outcomes between patients with JoAS and AoAS (5, 6). Although several observational studies have compared JoAS and AoAS cases in terms of epidemiological, clinical, imaging characteristics, and prognosis, few studies have compared spinal bone formation between patients with AoAS and JoAS (7, 8). Considerable interest has been generated in the rate of progression of structural damage in patients with AS, but only limited and inconsistent data are available regarding the effect of age of onset on structural damage. Moreover, prospective study mainly focusing on radiographic progression between patients with AoAS and JoAS has not been conducted.

Therefore the objective of this study was to determine whether age at onset affects the progression of structural damage in patients with AS.

Materials and methods

Patients and study design

The Observation Study of Korean spondyloArthropathy Registry (OSKAR) is an ongoing, longitudinal observational study on the clinical and structural outcome of spondyloarthropathy in Korea (9). A total of 533 patients (418 patients with AoAS and 115 patients with JoAS) from the OSKAR data, who met the modified New York criteria for AS (10), were included in this study. All clinical and radiographic data were stratified in relation to the age at onset for the baseline analysis. Then, available radiographs indicating spinal progression were analysed between the groups over 5 years. This study was approved by the Institutional Review Board of Hanyang University Hospital and Chonnam National University Hospital, and written informed consent was obtained from all participants.

Assessment of radiographic progression

Radiographs were obtained when clinical parameters were assessed. All clinical data were blinded, and radiographs were scored independently by two radiologists (S. Lee and Y. Song). The modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) is the most sensitive scoring method (11). Therefore, the cervical and lumbar spine was scored according to the mSASSS method as follows: 0 = normal; 1 = erosion, sclerosis or squaring; 2 = syndesmophyte; and 3 = bridging syndesmophyte (range: 0–72). For the analysis, the mean mSASSS scores of both readers were used.

Clinical data and definition of each data type

All clinical parameters were examined by rheumatologists in our registry. Clinical data included age, sex, disease duration, non-steroidal anti-inflammatory drug (NSAID) index (12), and use of tumour necrosis factor (TNF) blocker. When symptoms began in individuals <16-years-of-age, the disease was termed JoAS; otherwise, it was classified as AoAS. Laboratory tests included C-reactive protein (CRP) level and human leukocyte antigen (HLA)-B27 status.

Statistical analyses

Intra- and inter-reader reliability was evaluated using the intraclass correlation coefficient (ICC) for each radiograph. Clinical comparisons were performed using *t*-tests for normally distributed continuous variables, and the Mann-Whitney U-test was used for continuous variables that were not normally distributed. The chi-square test was used for categorical variables. Radiographic scores were compared by analysis of covariance model after

adjusting for confounding factors using the Bonferroni correction. A *p*-values ≤0.05 was considered significant. All statistical analyses were performed using SPSS v. 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

Inter-reader agreement

Inter-reader reliability for the baseline mSASSS was very good (ICC, 0.96; 95% confidence interval [CI], 0.95–0.96). Inter-reader reliability for the change in the mSASSS was also good (ICC, 0.74; 95% CI, 0.69–0.78).

Baseline demographic features between patients with AoAS and JoAS

In total, the 533 enrolled patients with AS were comprised of 418 patients with AoAS and 115 patients with JoAS. The baseline characteristics of the patients are summarised in Table I. As expected, those with JoAS were younger, had a younger age at AS onset and longer disease duration. A simple comparison revealed a significant difference in the mSASSS (mean ± standard deviation [SD]) between patients with AoAS and JoAS (18.1±17.4 *vs*. 14.3±13.8, *p*=0.015) (Fig. 1).

Table I. Baseline data for radiographic progression of ankylosing spondylitis according to age at onset.

Clinical features	Onset		*p*-value
	AoAS (n=418)	JoAS (n=115)	
Age (years), mean (SD)	40.8 (9.1)	33.5 (5.9)	0.001
Male, n (%)	372 (89.0)	107 (93.0)	0.227
Disease duration (years), mean (SD)	16.1 (7.1)	20.1 (6.6)	0.001
CRP (mg/dl), mean (SD)	1.9 (2.4)	2.1 (2.4)	0.388
HLA-B27, n (total, %)	394 (96.6)	111 (99.1)	0.211
Use of TNF blocker, n (total, %)	169 (40.4)	66 (57.4)	0.001
Baseline mSASSS (units), mean (SD)	18.1 (17.4)	14.3 (13.8)	0.015

SD: standard deviation; CRP: C reactive protein; HLA: human leukocyte antigen; TNF: tumour necrosis factor; mSASSS: the modified Stoke Ankylosing Spondylitis Spinal Score.

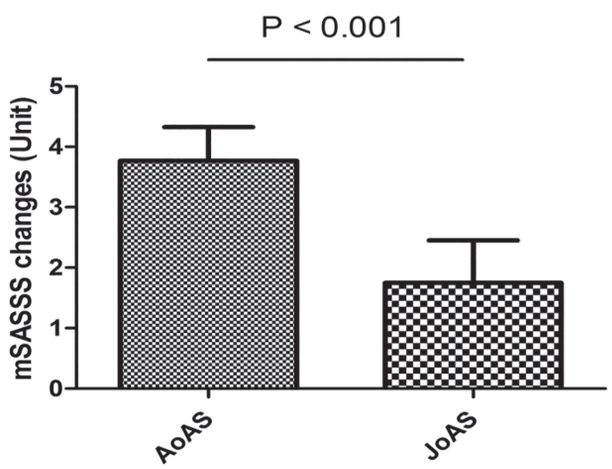

Fig. 1. Comparison of radiographic scores for all patients in the two groups over 5 years. Significant differences between adult-onset ankylosing spondylitis (AoAS) and juvenile-onset ankylosing spondylitis (JoAS) were observed (3.77±0.56 *vs*. 1.75±0.71, *p*<0.001). mSASSS, the modified Stoke Ankylosing Spondylitis Spinal Score.

Analysis of radiographic progression in relation to the age-onset

To confirm whether age at onset affected radiographic progression, we assessed the change in the mSASSS stratified by JoAs or AoAS. Radiographic and clinical information was available for 330 patients (258 patients with AoAS and 72 patients with JoAS). The radiographic follow-up times (mean ± SD, years) from the baseline assessment were comparable (5.0±1.2 *vs*. 5.2±1.3, *p*=0.402). The NSAID index (mean ± SD) during follow-up was 58.09±28.31 for the AoAS and 57.35±26.67 for the JoAS groups (*p*=0.87). A simple comparison showed a significant difference in the change in the mSASSS (mean ± SEM) between patients with AoAS and JoAS (3.77±0.56 *vs*. 1.75±0.71, *p*<0.001) (Fig. 1).

As different clinical factors were observed between the groups, including age, disease duration, percentage use of TNF blocker, and baseline radiographic damage, we re-evaluated the data using the analysis of covariance model adjusting for confounding clinical parameters. After adjusting for multiple comparisons using the Bonferroni correction, the change in mSASSS remained lower in patients with JoAS than those with AoAS (0.28±1.33 *vs*. 4.08±0.62, *p*=0.016) (Table II).

Discussion

Considerable interest has been generated in the rate of progression of structural damage in patients with AS. Several studies have investigated radiographic progression with regard to age of AS onset (6-8, 13, 14) but those studies reported equivocal findings. Cervical spine apophyseal lesions with formation of syndesmophytes occur more frequently in patients with JoAS (15). The Bath Ankylosing Spondylitis Radiology Index (BASRI) hip score and the need for total hip arthroplasty were higher in patients with JoAS (6). Patients with JoAS had spinal syndesmophytes less frequently than those with AoAS, and cervical spine disease was more frequent in patients with AoAS (14). Most analyses of these data were cross-sectional and ignored variations in radiographic assessment time and continuing radiographic progression over time. To overcome these problems, we prospectively evaluated radiographic changes stratified by age at onset. This baseline cross-sectional approach showed that patients with JoAS had lower radiographic damage scores than those with AoAS. Patients with JoAS had consistently slower progression of radiographic spinal damage than those with AoAS, even after adjusting for confounding factors.

Sex was independently associated with new syndesmophyte in patients with AS (16) and was an independent predictor of radiographic progression in our registry (Table III). NSAIDs reportedly retard new bone formation in pa-

Table II. Change in mSASSS between patients with JoAS and AoAS after adjusting for confounding factors.

Dependent variable: change in mSASSS					
Age-Onset	Mean	Std. Error	95% Confidence Interval		*p*-value
			Lower Bound	Upper Bound	
Juvenile onset	0.28*	1.33	-2.35	2.91	0.016
Adult onset	4.08*	0.62	2.85	5.30	

*Bonferroni correction was used to adjust for multiple comparisons (Covariates: age, gender, disease duration, non-steroidal anti-inflammatory drug index, baseline C-reactive protein level, human leukocyte antigen-B27 status, use of tumour necrosis factor blocker, and baseline mSASSS). mSASSS; the modified Stoke Ankylosing Spondylitis Spinal Score.

Table III. Regression coefficients for changes in mSASSS with respect to clinical features.

Dependent variable: change in mSASSS			
Variable	ß	S.E.	*p*-value
Age	0.18	0.09	0.051
Gender	-4.043	1.81	0.026
Disease duration	0.25	0.11	0.028
NSAID index	-.015	0.02	0.460
Baseline CRP	0.05	0.22	0.837
HLA-B27	1.06	2.95	0.719
Baseline mSASSS	-.082	0.04	0.047
TNF blocker use	-1.50	1.32	0.201
AoAS *vs*. JoAS	3.79	1.56	0.016

ß: regression coefficient; S.E.: standard error; mSASSS: the modified Stoke Ankylosing Spondylitis Spinal Score; NSAID: non-steroidal anti-inflammatory drug; CRP: C reactive protein; HLA: human leukocyte antigen; AoAS: adult-onset ankylosing spondylitis; JoAS: juvenile-onset ankylosing spondylitis.

tients with AS (17). However, NSAIDs did not affect our results, as evidenced by comparable NSAID index scores between the groups. CRP level is an independent predictor for radiographic sacroiliitis and spinal progression in patients with AS and axial spondyloarthritis (18, 19). However, no association was observed between baseline CRP level and the change in mSASSS in our data (Table III). In our previous study, we concluded that the carrier state of positive HLA- B27 plays no role in determining the radiographic progression in AS (20). TNF inhibitors appear to reduce radiographic progression in patients with AS (21). Patients with JoAS presented with longer disease duration than those with AoAS but had less radiographic progression. At the same time, patients with JoAS had less structural damage at baseline of the study but used biologics more freqently. Given these findings, patients with less damage at the beginning of the study and who used using biologics more frequently might cause less radiographic progression or TNF blocker may have a better effect if the patient started the treatment at disease onset. However, our registry data showed that TNF blocker failed to affect radiographic progression even after carefully applying propensity modeling and time-varying covariates for propensity (data not shown).

Some limitations of this study should be mentioned. Although the enthesitis assessment in patients with AS can be quantified using a scoring system, it was not performed in this study. Given the association between smoking status and radiographic progression, smoking burden should have been assessed in detail using the pack-year calculation. It has been reported that body mass index affects radiographic progression in patients with AS (22) but was not included in this study. Syndesmophyte and hip joint involvement are also important parameters when assessing radiographic damage (16, 23). Results from long term TNF inhibitor treatment in patients with JoAS showed radiographic progression of sacroiliitis (24). However, we only considered mSASSS (cervical and lumbar spine) to evaluate baseline radiographic damage and progression. However, mSASSS is an accurate measure of radiographic damage in patients with AS and is more sensitive to change over time than the BASRI (11). In general, the mSASSS has been used in most studies of AS radiographic damages rather than the BASRI. The advantage of using the mSASSS is that patients can be grouped into different categories depending on radiographic disease severity. Our mSASSS findings are consistent with radiographic severity data reported previously (6, 8, 13, 14). The strengths of our study include the large, well-stratified sample and examining data focusing on age at onset and radiographic progression.

In conclusion, juvenile onset was a determinant of radiographic spinal damage after adjusting for confounding factors in patients with AS. Patients with JoAS had slower progression of radiographic spinal damage than those with AoAS. Nothing is known about the cause of the relationship between age at onset and radiographic severity in patients with AS. Patients with JoAS patients have more peripheral arthritis than those with AoAS (9) possibly because of peripheral arthritis, which is an independent factor for delayed radiographic progression (25). Further studies are needed to identify the mechanism of this result.

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