

# Prevalence and Risk Factors of Anterior Atlantoaxial Subluxation in Ankylosing Spondylitis

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**ABSTRACT. Objective.** In ankylosing spondylitis (AS), the cervical spine, like other sections of the spine and sacroiliac joints, is vulnerable during the disease process. Atlantoaxial subluxation (AAS) has been studied in connection with AS, but its risk factors and progression have not been clarified. Therefore, this study assessed the prevalence and risk factors of AAS in patients with AS.

**Methods.** A total of 819 patients with AS who fulfilled the modified New York criteria and were examined with a full-flexion lateral view of the cervical spine by radiograph were enrolled from an outpatient clinic. The medical records of the patients were retrospectively reviewed and the anterior atlantodental interval (AADI) in the lateral flexion view of the cervical spine radiograph was investigated by 2 experienced musculoskeletal radiologists. We defined the AAS as an AADI of > 3 mm, and progression rate > 0.5 mm/year.

**Results.** AAS was found in 14.1% (116/819) of patients. Progression of AADI occurred in 32.1% (26/81) patients with AAS and 5.0% (16/320) patients without AAS ( $p < 0.001$ ). The development of AAS was significantly associated with elevated C-reactive protein [CRP; OR 2.19 (1.36-3.53)], peripheral arthritis [OR 2.05 (1.36-3.07)], use of anti-tumor necrosis factor antagonists because of failure of nonsteroidal antiinflammatory drugs/disease-modifying antirheumatic drugs [NSAID/DMARD; OR 2.28 (1.52-3.42)], and uveitis [OR 1.71 (1.13-2.59)]. These factors were adjusted for age, sex, and disease duration by logistic regression analysis. No clear association was found for HLA-B27, seropositivity, or smoking status with AAS.

**Conclusion.** AAS is a frequent complication, and the progression of AADI was more rapid in cases with AAS. The presence of peripheral arthritis, or high disease activity with elevated CRP level or refractory to conventional NSAID/DMARD, independently increased the risk of AAS, suggesting that clinicians should focus on the detection and monitoring of AAS, especially in cases with associated risk factors. (J Rheumatol First Release Oct 1 2012; doi:10.3899/jrheum.120260)

## Key Indexing Terms:

ANKYLOSING SPONDYLITIS    ATLANTOAXIAL JOINT    PERIPHERAL ARTHRITIS

Ankylosing spondylitis (AS) is a chronic, progressive condition that involves axial and peripheral joints. The cervical spine is also vulnerable. Neck pain, stiffness, and limitation of motion can be present in late periods of disease<sup>1</sup>. The pathologic changes in cervical spine in AS are squaring, syndesmophytes, ankylosis, ossification of the longitudinal ligaments, and atlantoaxial subluxation (AAS)<sup>2</sup>. To date, AAS has mostly been reported in rheumatoid arthritis (RA)<sup>3,4</sup>, with a prevalence of 12%–33% and even up to 86% in some reports<sup>5,6</sup>. The prevalence is 2%–6.7% and up to 21% in AS<sup>2,7,8,9,10,11,12</sup>, other spondy-

loarthropathies<sup>7,13,14</sup>, and rarely, mixed connective tissue disease<sup>15</sup>, systemic lupus erythematosus<sup>16</sup>, and Behçet's disease<sup>17,18</sup>. Although most patients with AAS remain asymptomatic in AS as well as in RA<sup>19</sup>, about 32% show radiologic progression during followup<sup>20</sup>. A clear assessment is important because AAS may lead to spinal cord compression, vascular compression, and other serious complications that may require surgical intervention during the course of AS<sup>9,20,21</sup>. The discrepancy between symptomatic and radiologic findings makes it difficult to coordinate the monitoring with surgical management<sup>19</sup>.

Risk factors for AAS in AS are a longer duration of AS and the presence of peripheral arthritis<sup>2,10,19</sup>, while risk factors reported for rheumatoid AAS include a later onset of RA (age > 45 yrs), active synovitis, rapidly progressive erosive peripheral arthritis, and rheumatoid factor (RF)<sup>22</sup>.

However, the prevalence and risk factors vary depending on study subjects, and have limitations due to small study size. In our retrospective study, we evaluated prevalence and risk factors for development and progression of AAS in Korean patients with AS.

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## MATERIALS AND METHODS

**Subjects.** A total of 819 consecutive patients from an AS cohort at the outpatient AS clinic of Hanyang University Hospital for Rheumatic Disease were enrolled from 1998 and 2010 using an electronic database. They were classified as having either juvenile AS (146 patients) or adult AS (673 patients) according to the modified New York criteria<sup>23</sup> and had been evaluated by cervical spine radiograph more than once after the diagnosis. Our clinic is a tertiary hospital clinic and many patients with AS were transferred from other primary clinics and through the Internet. Patients were excluded if they had a history of reactive arthritis, psoriasis, inflammatory bowel disease, or other concomitant disease of the cervical spine, such as definitive osteoarthritis or trauma. Discrimination of juvenile AS from AS was dependent on age at disease onset (juvenile AS < 16 yrs).

Demographic and clinical data were retrospectively reviewed by 2 rheumatologists from the electronic medical records (EMR), including age, sex, family history of spondyloarthropathy, age at symptom onset, age at AS diagnosis, presence of peripheral arthritis and uveitis, and the use of anti-tumor necrosis factor (TNF) antagonists. The status of smoking was collected by direct or telephone interview and recorded as never, former, and current. The age at symptom onset was defined as the time when the inflammatory back pain and peripheral arthritis that was compatible with AS had occurred. Inflammatory back pain was defined according to the modified New York criteria<sup>23</sup>. Peripheral arthritis was defined as the presence of swelling and/or limitation of motion in at least 1 peripheral joint (excluding the shoulder and hip joints), which was previously confirmed by a physician or confirmed during the study. Cases of severe peripheral arthritis, in which symptoms persisted > 1 year, were analyzed separately again. Uveitis was defined as a history or confirmed by an ophthalmologist. The laboratory data collected included HLA-B27 and its genotype using the microcytotoxic method, rheumatoid factor (RF; positive result > 15 IU/ml), and anticitrullinated protein antibodies (ACPA; positive result > 25 IU/ml). Seropositivity was defined as having a positive RF or ACPA. An elevation in acute-phase reactants (APR) was defined as > 0.3 ml/dl of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) of 20 mm/h during the first visit and persistent elevation after > 3 consecutive repeat tests performed over defined followup periods.

**Radiological assessments.** The cervical spine was examined by lateral spine plain radiograph in full-flexion in all patients and was re-read to assess the progression rate of AADI for  $32.9 \pm 13.5$  months in 401 patients. Two experienced musculoskeletal radiologists prospectively reviewed the plain radiograph of the cervical spine in a concealed and randomly selected order, were blinded for all clinical data, and ignored the other clinician's interpretation. The intrarater reliability of the main reader was assessed in the same way, leaving an interval of 4 weeks between measurements of AADI. The AADI (the distance from the posteroinferior margin of the anterior arch of the atlas to the anterior surface of the odontoid), was measured and analyzed. Anterior AAS was defined as an AADI of > 3 mm in the plain radiograph of the cervical spine<sup>24</sup>. The study population was divided into negative and positive AAS groups based on the absence or presence of AAS. Anterior AAS progression of > 0.5 mm/year was considered significant. Magnification factors could be error-prone problems in assessing radiographs in followup studies. These problems were corrected using the C3 width ratio differences between consecutive radiographs. If the ratio of distance of C3 between 2 radiographs was not equal, the measurements of AAS in consecutive radiographs were proportionally corrected<sup>20,25,26,27</sup>.

Spinal radiographs at the time that AADI was measured were scored using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)<sup>28</sup>. Briefly, the anterior vertebral edges of the cervical and lumbar spine were evaluated using the lateral views only and scored as follows: 0 normal, 1 erosion, sclerosis, or squaring, 2 syndesmophyte, and 3 bridging syndesmophyte. The score range is 0-36 in each cervical and lumbar region, and the total score range is 0-72.

We retrospectively reviewed all images and measured the AADI on a

picture archiving and communication system (PACS) workstation (PathSpeed, GE Healthcare).

**Statistics.** Interrater reliability of diagnosing AAS (more than 3 mm in AADI) was assessed using Cohen's kappa index with 95% CI: 0.00-0.20 slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81-1.00 good agreement<sup>29</sup>. Differences in frequencies and mean values of the measurements investigated between the 2 groups were analyzed using the chi-square test for noncontinuous variables and a paired t-test for continuous variables. For identification of risk factors of AAS and control for confounding, we carried out logistic regression analysis adjusted for age, sex, disease duration, and associated variables. Differences in the median values of mSASSS score between groups were determined using the Mann-Whitney U test. All statistical analyses were performed with PASW Statistics 18 for Windows (IBM SPSS).

## RESULTS

Table 1 shows the demographic and clinical characteristics of the patients. The mean age was  $36.2 \pm 9.7$  years, the male/female ratio was 8.64:1, and the disease duration of AS was  $6.3 \pm 4.4$  years.

**Agreement between readers.** The reliability of diagnosing AAS was good within and between experts. The interrater and intrarater reliabilities were 0.770 and 0.808, respectively, based on Cohen's kappa ( $p = 0.000$ ).

**Prevalence of AAS and progression of AADI.** AAS was present in 14.1% (116/819 patients) as AADI > 3 mm, and 5.1% (42/819 patients) as AADI > 4 mm. Nine patients (1.1%) revealed atlantoaxial ankylosis, and 2 patients with AAS consequently underwent surgery because of cervical spine instability with neurological problems. AADI of all patients was mean  $2.32 \text{ mm} \pm 1.10$  and 14.6 mm maximum (Table 2).

Among the 401 patients for whom comparison of cervical radiographs was possible, progression of the AADI was seen in 42 patients (10.5%) and more frequent in the AAS-positive group (32.1%; 26/81 patients) compared to the AAS-negative group (5.0%; 16/320 patients;  $p < 0.001$ ). The mean progression rate of the AADI was also remarkably higher in the AAS-positive group (0.50 mm/yr) than in the AAS-negative group (0.24 mm/yr;  $p < 0.001$ ; Table 2). Magnification factor was calculated from 0 to 12.0% (average  $1.91 \pm 1.76\%$ ).

**Risk factors for development of AAS.** Classification was based on the presence of AAS, and there were no differences in sex, age, family history of spondyloarthropathy, smoking status, mSASSS score, HLA-B27, or seropositivity (positive RF or ACPA) between the 2 groups (Table 1). AAS was more significantly found in patients with a longer duration of AS (mean 7.9 and 6.0 yrs), longer periods of AS symptoms (mean 15.6 and 13.0 yrs), elevated ESR/CRP, peripheral arthritis (54.3 and 35.7%), uveitis (43.1 and 29.6%), and in those treated with anti-TNF antagonists because of the failure of conventional NSAID/DMARD (56.9 and 35.3%), respectively (Table 1).

After adjusting for age, sex, and disease duration, the development of AAS was significantly associated with

Table 1. Demographic and clinical characteristics according to the presence of AAS in patients with AS. Data are n (%) unless otherwise indicated.

	Total, n = 819	AAS, n = 116	No AAS, n = 703	p
Sex, M:F	8.64:1	11.9:1	8.3:1	0.318
Age, yrs, ± mean	36.2 ± 9.7	36.8 ± 10.8	36.1 ± 9.5	0.468
Disease duration, yrs ± mean*	6.3 ± 4.4	7.9 ± 5.4	6.0 ± 4.2	0.001
Symptom duration, yrs ± mean†	13.3 ± 7.8	15.6 ± 8.8	13.0 ± 7.5	0.003
Family history of spondyloarthropathy	113 (13.8)	15 (12.9)	98 (13.9)	0.770
Diagnosis				
AS	673 (82.2)	88 (75.9)	585 (83.3)	0.055
Juvenile AS	146 (17.8)	28 (24.1)	118 (16.8)	0.055
Delayed diagnosis of AS, ≥ 5 yrs	454 (55.4)	71 (61.2)	383 (54.5)	0.177
Delay between symptom and diagnosis of AS (yrs ± mean)	7.0 ± 6.7	7.7 ± 7.3	6.9 ± 6.6	0.217
Smoking status, n = 484				
Never smoker	177 (36.6)	32 (45.7)	145 (35.0)	
Ever smoker	307 (63.4)	38 (54.3)	269 (65.0)	0.086
Current smoker	174 (49.6)	20 (28.6)	154 (37.2)	0.164
mSASSS, total score ± mean, n = 768	16.5 ± 17.7	19.2 ± 20.3	16.0 ± 17.2	0.167
Cervical spine, n = 819	9.6 ± 9.1	11.6 ± 10.7	9.3 ± 8.8	0.058
Lumbar spine, n = 768	6.9 ± 10.5	7.9 ± 11.5	6.7 ± 10.3	0.412
HLA-B27 positivity, n = 784	754 (96.2)	110 (97.3)	644 (96.0)	0.605
HLA-B27 homozygosity, n = 357				0.278
Heterogenous	211 (59.1)	44 (66.7)	167 (57.4)	
Homogenous	116 (32.5)	19 (28.8)	97 (33.3)	
Seropositivity (RF+ or ACPA+, n = 690)	32 (4.6)	5 (5.3)	27 (4.5)	0.790
RF positivity, n = 641	21 (3.3)	3 (3.4)	18 (3.2)	0.999
ACPA positivity, n = 356	14 (3.9)	3 (7.1)	11 (3.5)	0.221
Elevated APR, n = 812				
ESR at 1st visit, n = 812	585 (72.0)	92 (80.0)	493 (70.7)	0.040
ESR at followup, n = 810	306 (37.8)	65 (56.5)	241 (34.7)	<0.001
CRP at 1st visit, n = 812	513 (63.2)	90 (78.3)	423 (60.7)	<0.001
CRP at followup, n = 810	248 (30.6)	56 (48.7)	192 (27.6)	<0.001
Peripheral arthritis	313 (38.3)	63 (54.3)	250 (35.7)	<0.001
Persistent	70 (8.6)	13 (11.2)	57 (8.1)	
Uveitis	258 (31.5)	50 (43.1)	208 (29.6)	0.004
Use of anti-TNF antagonists	314 (38.3)	66 (56.9)	248 (35.3)	<0.001

\* Based on the time of AS diagnosis. † Including inflammatory back pain and peripheral arthritis. AS: ankylosing spondylitis; AAS: anterior atlantoaxial subluxation; mSASSS: modified Stoke Ankylosing Spondylitis Spine Scoring system; RF: rheumatoid factor; ACPA: anticitrullinated protein antibodies; APR: acute-phase reactants; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TNF: tumor necrosis factor.

elevated CRP [OR 2.19 (1.36-3.53)], peripheral arthritis [OR 2.05 (1.36-3.07)], usage of anti-TNF antagonists because of NSAID/DMARD failure [OR 2.28 (1.52-3.42)], and uveitis [OR 1.71 (1.13-2.59); Table 3]. High disease activity with elevated CRP level [OR 1.73 (1.06-2.84)], peripheral arthritis [OR 1.63 (1.07-2.49)], or being refractory to conventional NSAID/DMARD [OR 1.79 (1.17-2.75)] independently increased the risk of AAS, adjusted for age, sex, disease duration, and the risk variables (Table 4).

We also analyzed the risk factors based on the AS and juvenile AS subgroups. We found that elevated CRP level, uveitis, and being refractory to conventional NSAID/DMARD meant significantly greater associations with AAS in adult-onset AS than in juvenile-onset AS (Table 4).

*Relationship between AAS and ankylosis of cervical and lumbar spines.* The mSASSS was not associated with the

presence of AAS in the cervical (p = 0.058) and lumbar spines (p = 0.412) as well as the total score (p = 0.167; Figure 1, Table 1). Complete atlantoaxial ankylosis was seen in 9 patients (1.1%), and this was not associated with AAS (p = 0.902; data not shown).

## DISCUSSION

To our knowledge, this study is the first to evaluate the risk factors of AAS in a large number of patients with AS. One of our main observations was that the prevalence of AAS in patients with AS was 14.1% by definition (> 3 mm in AADI), while it was 5.1% (420/819 patients) based on another definition of AAS (> 4 mm in AADI). In previous reports, the prevalence of AAS varied according to the characteristics of study subjects<sup>2,7,8,9,10,11,12</sup>, including 18.0% (11/61 patients) with longstanding AS (disease

Table 2. Prevalence of anterior atlantoaxial subluxation (AAS) and progression of anterior atlantodental interval (AADI) in patients with AS.

	Positive/All Patients (%)		
Frequency according to definition of AAS			
AADI > 3 mm <sup>†</sup>	116/819 (14.1%)		
AADI > 4 mm	42/819 (5.1%)		
AADI (total, mm, mean ± SD)	2.32 ± 1.10 (range 0.0 ~ 14.6)		
AADI (with AAS)	4.30 ± 1.55 (range 3.1 ~ 14.6)		
Atlantoaxial ankylosis <sup>‡</sup>	9/819 (1.1%)		
Surgery (fixation)	2/819 (0.24%)		
	With AAS	Without AAS	p*
With followup cervical radiograph, n = 401			
Progression rate, mm/yr	0.50 ± 0.51	0.24 ± 0.31	< 0.001
Progression > 0.5 mm/yr (42/401, 10.5%)	26/81 (32.1%)	16/320 (5.0%)	< 0.001

\* Chi-square analysis. <sup>†</sup> AAS defined as AADI > 3 mm in this study. <sup>‡</sup> Prevalence of AAS was not included in cases in this study because it was impossible to assess the AADI, and the association with AAS was not clear. AS: ankylosing spondylitis.

Table 3. Logistic regression analysis of variables affecting the development of AAS in patients with AS.

Variables	Total AS, n = 819	
	No. AAS+/AAS-, n = 116/703	OR* (95% CI)
Elevated acute-phase reactant	97/514	1.79 (1.04–3.06)
Elevated ESR	92/493	1.59 (0.97–2.60)
Elevated CRP	90/423	2.19 (1.36–3.53)
Peripheral arthritis	63/250	2.05 (1.36–3.07)
Persistent	13/57	2.06 (1.05–4.05)
Uveitis	50/208	1.71 (1.13–2.59)
NSAID/DMARD failure	66/248	2.28 (1.52–3.42)

\* OR adjusted for age, sex, and disease duration. AAS: anterior atlantoaxial subluxation; AS: ankylosing spondylitis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug.

duration > 7 yrs)<sup>10</sup>, 17% with juvenile chronic arthritis<sup>30</sup>, and up to one-third of AS patients with persistent peripheral arthritis<sup>31</sup>. We found AAS in 14.1% of the entire study population taken from the AS cohort, similar to previous reports. These findings, in which the frequency of AAS varied according to the study subjects with some factors, imply the presence of risk factors that influence the develop-

ment of AAS. In some studies, risk factors reported were a longer duration of AS<sup>2,10,19</sup> and the presence of peripheral arthritis<sup>19,31</sup>. Duration of disease has been recognized as a major factor that determines cervical spine involvement, including AAS in AS and spondyloarthropathy. We consider AAS to be proportionally increased because of irreversible changes as a result of the chronic inflammatory process. Peripheral arthritis was also reported as a risk factor for cervical spine diseases in psoriatic spondylitis<sup>19</sup>, and AAS occurred in up to two-thirds of cases that had persistent peripheral arthritis<sup>31</sup>. Our study revealed that a longer duration of AS and the presence of peripheral arthritis were risk factors of AAS, similar to previous studies. Because atlantoaxial instability is mainly supported by transverse ligament, odontoid and arch of the atlas, and synovial lining tissues, it is theoretically possible that AAS is more frequent in patients with peripheral arthritis.

In contrast to other studies, we found associations between AAS and elevated APR, uveitis, or the usage of anti-TNF antagonists. Several previous studies have confirmed that peripheral arthritis is associated with higher ESR, more frequent enthesitis, more uveitis, involvement of the hips, shoulders, and whole spine, though some controversial results remain<sup>32,33,34,35</sup>. Also in our study, uveitis was

Table 4. Multiple logistic regression analysis of variables affecting the development of AAS in patients with AS.

Variable	Total AS, n = 819		AS, n = 673		Juvenile AS, n = 146	
	No. AAS+/AAS-	OR* (95% CI)	No.	OR* (95% CI)	No.	OR* (95% CI)
Elevated CRP	90/423	1.73 (1.06–2.84)	69/343	2.06 (1.17–3.63)	21/80	0.77 (0.26–2.24)
Peripheral arthritis	63/250	1.63 (1.07–2.49)	42/183	1.59 (0.99–2.59)	21/67	2.10 (0.78–5.67)
Uveitis	50/208	1.50 (0.98–2.30)	41/169	1.71 (1.05–2.78)	9/39	0.91 (0.36–2.29)
NSAID/DMARD failure	66/248	1.79 (1.17–2.75)	47/187	1.80 (1.11–2.91)	19/61	1.93 (0.75–4.97)

\* OR adjusted for age, sex, disease duration, and above variables. AAS: atlantoaxial subluxation; AS: ankylosing spondylitis; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug.



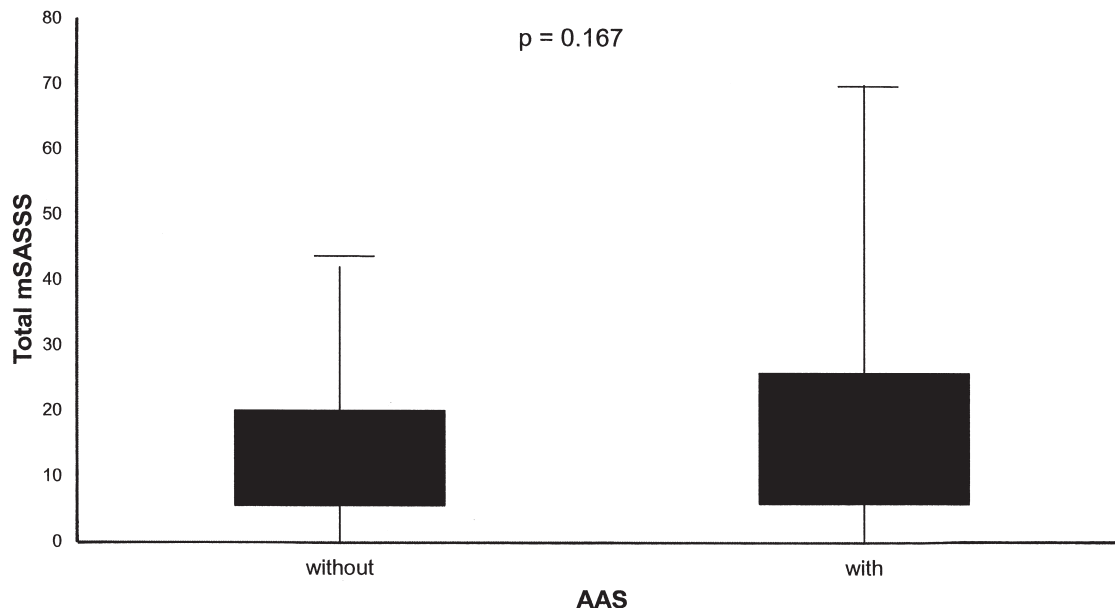


Figure 1. Modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) according to the presence of atlantoaxial subluxation (AAS).

a risk factor for AAS, but its significance disappeared after adjustment for variables [OR 1.50 (0.98-2.30)]. Elevated ESR or CRP level is a common finding in patients with active AS and correlates with clinical disease activity, radiological progression, and frequent peripheral arthritis in AS<sup>36,37</sup>. And patients managed with anti-TNF antagonists represent those with more active disease and a higher Bath Ankylosing Spondylitis Disease Activity Index score (> 4)<sup>38</sup>. Therefore, the associations with AAS and elevated APR or anti-TNF antagonists indicate that patients with high disease activity had more AAS, as an independent risk factor.

Progression is also as important as the development of AAS. The 2-year followup data of anterior and vertical AAS in AS reported by Ramos-Remus, *et al*, showed progression of AAS in 32% (7/16) of patients, among whom 2 operations were performed because of myelopathy and 3 because of progression of AAS without neurological sequelae<sup>20</sup>. In our study, progression of AADI was seen in 32.1% (26/81) of patients with AAS, equal to findings of Ramos-Remus, *et al*<sup>20</sup>. The progression was more frequently seen and was more aggressive in the group with AAS compared to the group without AAS, and associated with elevated APR. Our findings support other studies that identified active disease status as a predictor of anterior AAS in RA<sup>39,40</sup>.

There was no significant relationship between AADI and mSASSS or complete atlantodental ankylosis. A similar pathogenesis may suggest the association between AAS and spinal atlantodental ankylosis, but the small number of complete atlantodental ankylosis cases (9 patients) might have affected the results. A similar pathogenesis of AAS and spinal and atlantodental ankylosis suggests associations between them, such as inflammatory and bone healing

processes taking place in the atlantoaxial region, followed by ossification and new bone formation, and even bony ankylosis<sup>1,41</sup>. However, similar to our results, previous studies have not clarified these relationships<sup>10</sup> and further studies are needed to verify the associations.

There are some limitations in our study. First, our hospital is a special medical center for rheumatic diseases. Patients with more active disease and complications visit from local clinics and other hospitals in Korea. Study subjects from our AS cohort may have more severe and complicated courses of disease. Second, our study was designated for cross-sectional study in an AS cohort. Although we tried to evaluate regularly, there were not enough subsequent films of cervical spine radiographs, and a prospective cohort would have been preferable. Clinical characteristics, including peripheral arthritis, uveitis, and demographics were collected through retrospective review of EMR, and smoking status was by recall telephone interview. Third, because our study was done retrospectively, and anteroposterior and lateral views of the cervical spine were the only ones evaluated, other forms of AAS besides anterior AAS were not examined.

AAS was found to be a frequent complication in 14.1% of patients with AS regardless of cervical symptom. Thus, patients with AS should have regular radiological assessment to detect AAS because it can cause severe complications, especially in patients with longer AS duration, accompanying peripheral arthritis, and high disease activity, or who are refractory to conventional NSAID.

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