Cervical spine involvement in longstanding ankylosing spondylitis

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Abstract

Objective

To investigate the degree of ossification and the frequency of ankylosis between the atlas and the dens of the axis in patients with longstanding ankylosing spondylitis (AS), to assess radiological involvement of the cervical spine, and to determine their correlations with structural severity and clinical variables, including neurological abnormalities.

Methods

In 61 AS patients with disease duration over 7 years, the findings of conventional radiographs were graded by the Bath Ankylosing Spondylitis Radiology Index (BASRI), and the ossification levels between the atlas and the dens and the severity of zygapophyseal (ZA) joint lesions were scored using multislice CT. Neurological examinations and somatosensory evoked potentials (SSEP) were performed by neurologists.

Results

According to the BASRI, 50 patients (82.0%) had radiological changes of the cervical spine ≥ score 1. Thirty-seven patients (60.6%) revealed a certain extent of the atlantodental ossification, and the presence of partial or complete atlantodental ankylosis was seen over 30% of the patients. The BASRI-cervical spine score and the atlantodental ossification levels correlated with disease duration. ZA involvement was observed in 49 patients (80.3%), including 23 with ZA fusion (37.7%). Although 4 of 11 patients with atlantoaxial subluxation showed abnormal SSEP, none had significant neurological complications. This might be attributed in part to atlantodental ankylosis and ZA fusion. Finally, ossifications of the anterior and posterior longitudinal ligaments were found 26.2 and 29.5%, respectively.

Conclusion

Cervical spine involvement and atlantodental ossification or ankylosis appear to be common in patients with longstanding AS, and to be particularly more severe in patients with a longer disease duration.

Key words

Ankylosing spondylitis, cervical spine involvement, atlantodental ankylosis, multi-slice spiral computed tomography, neurological complication.

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory and progressive disorder that principally affects the axial skeleton. Structural damage, which leads to characteristic radiological change, is considered essential for a diagnosis and outcome prediction in AS. The primary histopathologic change of this disease is an initial inflammatory and erosive process affecting the enthesis, which is followed by a healing process during which new bone is formed to eventually result in ankylosis (1-3).

In typical disease, ankylosis starts at the lower back and progresses upwards, such that cervical spine involvement usually occurs at a later disease stage (3). Indeed, it has been noted that cervical spine involvement in AS is relatively common and that it correlates well with disease duration (4-7).

The atlantoaxial region has a unique anatomy and function, and contains synovial tissue and several ligaments closely arranged within a small, critical space (8). Involvement of this area in AS can lead to destruction of ligaments, cartilage, and bone, which in some cases results in atlantoaxial instability and neurological complications, rarely being fatal (9). On the other hand, although patients with AS accompanied by partial or complete ankylosis between the atlas and the dens of the axis have infrequently been described (8, 10, 11), little is known about its prevalence or neurological impact on AS. In patients with longstanding AS by means of conventional radiographs and multislice computed tomography (MSCT), therefore, this study was to investigate the degree of ossification and the frequency of ankylosis between the atlas and the dens of the axis, and to assess radiological involvement of the cervical spine, and to determine their correlations with structural severity and clinical variables, including neurological abnormalities.

Patients and methods

Subjects

This study was prospectively undertaken on 61 consecutive Korean patients with longstanding AS with a disease duration of over 7 years who attended the outpatient rheumatology clinics of two tertiary medical centers during a 1-year period. They fulfilled the modified New York criteria (12). Patients with a history of reactive arthritis, psoriasis, inflammatory bowel disease, or cervical trauma were excluded. All patients underwent a thorough physical examination (including history) by rheumatologists and the data were recorded on a standardized form for this study.

Peripheral arthritis was defined as the presence of swelling and/or a limitation of motion in at least one peripheral joint confirmed by the physicians in the present or past, not including the shoulder or hip joints. In addition, inflammatory back pain was defined according to the modified New York criteria (12), and peripheral enthesopathy was determined by a history of spontaneous pain or tenderness at peripheral entheses. Posterior neck pain and/or stiffness were regarded as cervical symptoms, and uveitis was defined as history of the presence of uveitis confirmed by an ophthalmologist. HLA-B27 typing was done by a microcytotoxicity method. The study protocol was approved by the Hospital Ethics Committee and informed consent was obtained from each subject.

Radiological assessments

All of the patients underwent cervical spine radiography with anteroposterior (AP) open-mouth and full flexion lateral views, lumber spine radiography with AP and lateral views, as well as pelvis AP radiography. MSCT was also performed on all of the patients by multidetector-row computed tomography (MDR CT; Lightspeed QX/i; GE medical systems, Milwaukee, Wisconsin, USA) for the cervical spine. Raw data were acquired at a section thickness of 1.25 mm, beam collimation 1.25 mm, table speed 3.75 mm per rotation, and reconstruction interval 0.63 mm. Axial, coronal and sagittal multiplanar reformations were obtained.

Films were evaluated by one radiologist who was unaware of the patients' clinical status. Radiological anterior atlantoaxial subluxation (AAS) was defined as present when the distance between the posterior margin of the ante-

rior arch of the atlas and the anterior aspect of the dens was ≥ 4 mm in the lateral full flexion view. Lateral AAS was considered when the lateral masses of the atlas lay 2 mm or more laterally than the lateral masses of the axis in the coronal view of the cervical spine. Vertical AAS was defined according to the Sakaguchi-Kauppi method, in which it is categorized into four grades (I to IV) exhibiting increased severity (13).

The findings of conventional radiographs of the cervical and lumbar spine, and the hip joints were graded using the Bath Ankylosing Spondylitis Radiology Index (BASRI) (14,15). A BASRI-cervical spine score ≥ 2 was accepted as definite BASRI-cervical spine involvement. The involvement of the sacroiliac joints was graded using the modified New York criteria (12).

In addition, the ossification levels between the atlas and the dens of the axis were originally scored on the MSCT as follows: 0 = no ossified lesions, 1 = maximal diameter of ossified lesions < 2 mm, 2= maximal diameter of ossified lesions ≥ 2 mm and no complete bony fusion or bony bridging between the atlas and the dens (partial atlantodental ankylosis), and 3 = complete bony fusion or bony bridging between the atlas and the dens (complete atlantodental ankylosis) (Fig.1).

In the case of zygapophyseal (ZA) joint involvement of the cervical spine, we applied the plane radiography scoring system proposed by de Vlam *et al.* (16) to MSCT analysis as follows: 0 = normal, 1= joint space narrowing or erosion, 2 = partial blurring or ankylosis, and 3 = complete blurring or ankylosis. This was evaluated at the most severely involved ZAjoint.

The presence of ossifications of the anterior longitudinal ligament (OALL) and the posterior longitudinal ligament (OPLL) was determined by the MSCT. Finally, radiological involvement of the cervical spine was defined as the presence of at least one of the following lesions: definite BASRI-cervical spine involvement, the presence of AAS, or a ZA joint score ≥ 1.

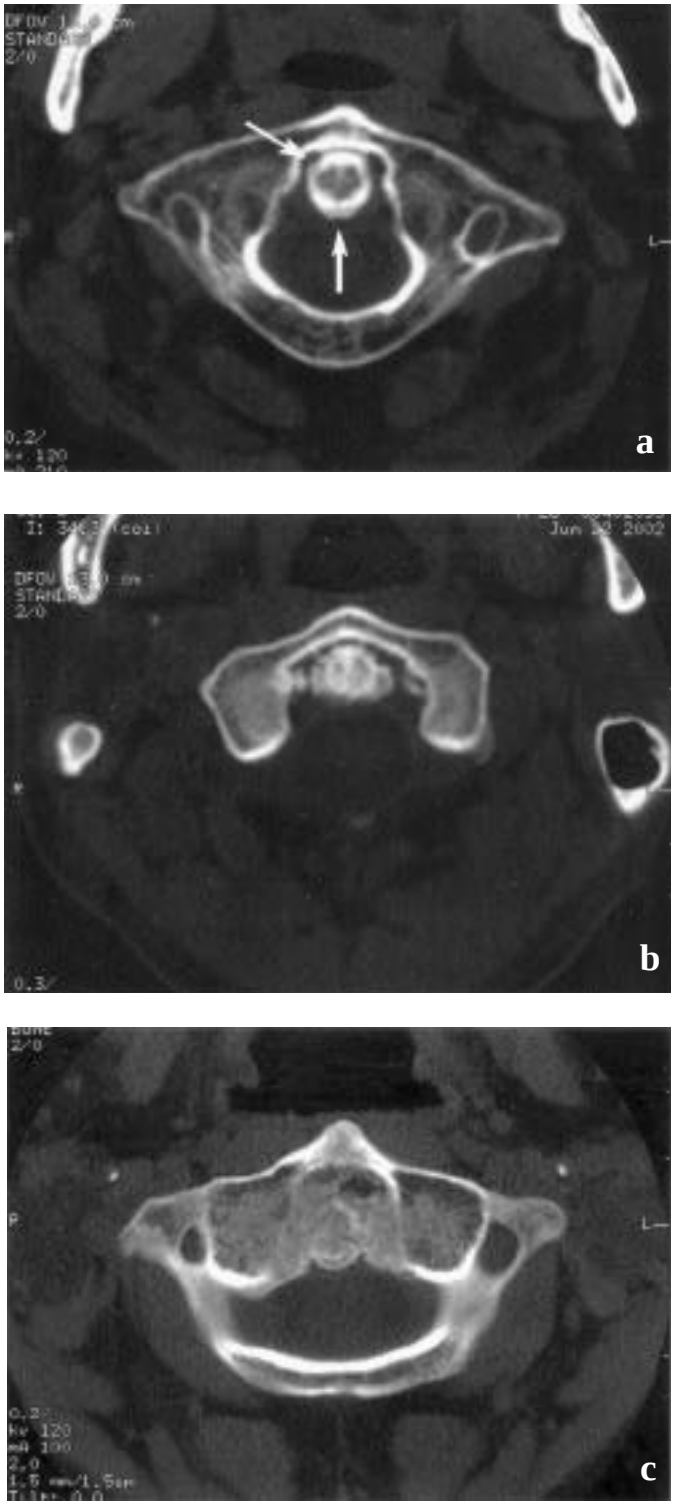

Fig. 1. Axial reformatted images at the level of atlantodental joint show the presence of ossifications between the anterior arch of the atlas and the dens of the axis. (**a**) score 1: small linear ossified lesions less than 2mm in maximal diameter are noted around the dens (arrows); (**b**) score 2: multiple nodular ossified lesions over diameter 2mm are noted between the atlas and the dens, but there is no complete bony fusion or bony bridging; (**c**) score 3: complete bony fusion between the atlas and the dens (complete atlantodental ankylosis) is shown.

Neurological assessments

Two neurologists, who were unaware of the patients' clinical status, assessed the 42 patients with definite BASRI-cervical spine involvement and/or AAS regarding the presence of neurological signs and symptoms of cervical spine involvement, including vertebrobasilar insufficiency and cervical myelopathy. In these patients, somatosensory evoked potentials (SSEP) were carried out on the median nerve by another neurologist, as described previously (17). They were examined with the aid of a CadWell Excel, which recorded four channels simultaneously. SSEP latency values were considered abnormal if they exceeded mean reference values by > 2 SD. Interside amplitude ratio differences were assessed abnormal

when they exceeded normal values by > 50%.

Statistical analyses

Data were analyzed using the SPSS software package version 11.5 for Windows (SPSS Inc, Chicago, IL, USA). Spearman correlation coefficients were calculated to estimate the relationship between the BASRI-cervical spine or atlantodental ossification scores and the radiological or clinical variables. Non-parametric variables were compared using the chi-square test, and the results obtained were re-evaluated by multiple logistic regression analysis. In addition, the mean values between two continuous variables were compared using the Student's *t*-test. P values less than 0.05 were considered to be statistically significant.

Results

Basic demographic findings and radiological features are summarized in Tables I and II, respectively. According to the BASRI, 50 patients (82.0%) showed radiological changes of the cervical spine ≥ score 1 and 38 patients (62.3%) had definite BASRI-cervical spine involvement ≥ score 2 (Table II). The BASRI-cervical spine score positively correlated with current age, disease duration, the atlantodental ossification score, the ZA joint score, the BASRI scores for the lumber spine and the hip joints, and the severity of radiological sacroiliitis (Table III). In addition, 2 x 2 contingency table analyses using the chi-square showed that definite BASRI-cervical involvement was positively associated with OALLof the cervical spine ($p < 0.001$), OPLL of the cervical spine ($p = 0.028$), and cervical symptoms ($p = 0.019$), and negatively associated with the presence of peripheral enthesopathy ($p = 0.033$). But definite BASRI-cervical involvement was not associated with sex, AAS, peripheral arthritis, inflammatory back pain, uveitis, or abnormal SSEP results (all $p > 0.05$). However, when multiple logistic regression analysis using the Enter method was done to evaluate the effect of the patients' characteristics, including age, sex, disease duration, and other clinical and radiological variables, on definite BASRI-cervical involvement, only the presence of peripheral enthesopathy remained statistically significant ($p = 0.039$), showing a negative association (data not shown).

With regard to the ossification levels between the atlas and the dens, 37 patients (60.6%) revealed a certain extent of ossification, and the frequencies of partial and complete atlantodental ankylosis (scores 2 and 3) were 16.4% and 16.4%, respectively (Table II). The atlantodental ossification levels was found to positively correlate with current age, disease duration, the ZA joint score, the severity of radiological sacroiliitis, and the BASRI scores for the cervical and lumbar spines, and the hip joints (Table IV). In addition, the presence of partial or complete atlantodental ankylosis was significantly associated with OALL of the cervical spine ($p < 0.001$), OPLL of the cervical spine ($p = 0.014$), AAS ($p = 0.016$), and cervical symptoms ($p = 0.020$), but was not associated with sex, peripheral arthritis, inflammatory back pain, peripheral enthesopathy, uveitis, or abnormal SSEP results (all $p > 0.05$). After performing multiple logistic regression analysis, however, only the presence of OALL of the cervical spine remained statistically significant ($p = 0.027$) (data not shown).

ZA involvement was found in 49 patients (80.3%), including 23 with ZA joint fusion (37.7%) (Table II). Because AAS, one of the severe cervical complications in AS, is not included in the BASRI, and also because fine assessment of ZAinvolvement may not be feasible by conventional radiographs, in the current study, radiological involvement of the cervical spine was defined as the presence of at least one of the following lesions, as mentioned previously: definite BASRI-cervical spine involvement, the presence of AAS, or a ZA joint score ≥ 1. This was observed in 52 patients (85.2%).

Of 42 patients with definite BASRI-cervical involvement and/or AAS, none

Table I. Basic demographic data of 61 patients with longstanding ankylosing spondylitis.

Age, mean ± SD (yrs)	36.5± 10.3
Male, no (%)	55 (90.2)
Disease duration, mean ± SD (yrs)	13.9 ± 7.4
Inflammatory back pain, n (%)	55 (90.2)
Peripheral arthritis, n (%)	26 (42.6)
Cervical symptoms, n (%)	47 (77.0)
Peripheral enthesopathy, n (%)	24 (39.3)
Uveitis, n (%)	13 (21.3)
HLA-B27 positivity, n (%)	58 (95.1)

Table II. Radiological features of 61 patients with longstanding ankylosing spondylitis.

	No	(%)
BASRI-cervical spine score		
0	11	(18.0)
1	12	(19.7)
2	21	(34.4)
3	4	(6.6)
4	13	(21.3)
BASRI-lumbar spine score		
0	1	(1.6)
1	1	(1.6)
2	27	(44.3)
3	12	(19.7)
4	20	(32.8)
BASRI-hip score		
0	2	(3.3)
1	8	(13.1)
2	35	(57.4)
3	14	(23.0)
4	2	(3.3)
Sacroiliitis grading according to the modified New York criteria		
1	0	
2	7	(11.5)
3	20	(32.8)
4	34	(55.7)
Ossification score between the atlas and the dens		
0	24	(39.3)
1	17	(27.9)
2	10	(16.4)
3	10	(16.4)
Zygapophyseal joint score		
0	12	(19.7)
1	20	(32.8)
2	6	(9.8)
3	23	(37.7)

Table III. Correlations between the BASRI-cervical spine score and the radiological or clinical variables.

	r	p-value
Age	0.467	< 0.001
Disease duration	0.484	< 0.001
Atlantodental ossification score	0.585	< 0.001
Zygapophyseal joint score	0.729	< 0.001
Severity of radiological sacroiliitis	0.555	< 0.001
BASRI-lumber spine score	0.496	< 0.001
BASRI-hip score	0.345	0.006

Table IV. Correlations between the atlantodental ossification score and the radiological or clinical variables.

	r	p-value
Age	0.398	0.001
Disease duration	0.560	< 0.001
Zygapophyseal joint score	0.535	< 0.001
BASRI-cervical spine score	0.585	< 0.001
BASRI-lumber spine score	0.316	0.013
BASRI-hip score	0.305	0.017
Severity of radiological sacroiliitis	0.387	0.002

had neurological signs and symptoms for the cervical spine involvement, including vertebrobasilar insufficiency and myelopathy, but SSEPrevealed abnormal findings in 6 patients: all the patients with abnormal SSEP showed prolonged interpeak latencies in N9 and N13 (4 bilateral and 2 unilateral) and 3 patients had prolonged interpeak latencies in N20 (2 bilateral and 1 unilateral).

The characteristics of patients with AAS are summarized in Table V. AAS was observed in 11 patients (18.0%); 5 with anterior AAS, 3 with lateral AAS, 1 with anterior and lateral AAS, and 2 with vertical AAS. Although 4 of the 11 patients with AAS showed abnormal SSEP results, none had clinically significant neurological complications, which might be attributed in part to complete atlantodental ankylosis manifested in 6 patients with AAS and to fusion of the ZA joints seen in 7 patients with AAS. Interestingly, AAS had developed in 3 patients (patients 3, 6, and 7) with minimal or no involvement in the remaining cervical spine other than the atlantoaxial joint. In addition, AAS was associated with abnormal SSEP results ($p = 0.032$), but not with sex, OALL, OPLL, peripheral arthritis, inflammatory back pain, cervical symptoms, peripheral enthesopathy, or uveitis. However, after multiple logistic regression analysis, the statistical significance was lost for all the variables, including abnormal SSEP results (data not shown). In addition, disease duration in patients with AAS was significantly longer than that in patients without AAS (18.0 ± 7.9 versus 13.0 ± 6.5 yrs, $p = 0.029$).

OALL and OPLL in the cervical spine were observed in 16 (26.2%) and 18 patients (29.5%), respectively. Disease duration in patients with OALL was significantly greater than that in patients without OALL(18.3 ± 9.1 versus 12.3 ± 5.3 yrs, $p = 0.024$). Also, patients with OPLLshowed a tendency towards longer disease duration compared with that in patients without OPLL, but the difference was not statistically significant (15.9 ± 6.8 versus 13.0 ± 6.9 yrs, $p = 0.135$).

Discussion

Our data are in line with the previous investigations showing that the cervical spine is frequently affected and that the risk of cervical spine involvement is associated with older age, longer dis-

Table V. Characteristics of 11 patients with atlantoaxial subluxation (AAS).

Pt	Sex/age	Duration (yrs)	Classification of AAS	Distance (mm)	BASRI-cervical score	ZAscore	Ossification score	Nex	SSEP
1	M/52	32	anterior	5.8*	4	3	3	N	Abn
2	F/26	12	anterior	5.8*	1	2	3	N	N
3	M/33	7	anterior	4*	0	1	0	N	Abn
4	M/29	18	anterior	4*	4	3	3	N	N
5	M/40	18	anterior	5.5*	4	3	3	N	N
6	M/25	11	anterior and lateral	6*, 2.4**	1	0	0	N	Abn
7	M/38	16	lateral	2**	0	1	0	N	N
8	M/30	15	lateral	3**	3	3	1	N	N
9	F/71	30	lateral	2.3**	4	3	2	N	N
10	M/27	14	vertical	grade II	2	3	3	N	N
11	M/64	25	vertical	grade II	4	3	3	N	Abn

Pt: patient; *: distance between the posterior margin of the antertior arch of the atlas and the anterior aspect of the dens; **: distance of lateral masses of atlas lying more laterally compared to the lateral masses of axis; ZA: zygapophyseal joint; Nex: neurological examination; SSEP: somatosensory evoked potentials; N: normal; Abn: abnormal.

ease duration, higher BASRI scores of the lumbar spine and the hip joints, and more severe sacroiliitis (4-7). Moreover, we have found that more advanced cervical spine disease is closely associated with greater scores for the atlantodental ossification and the ZA involvement. We were also able to see a trend towards less severe, radiological involvement of the cervical spine in the cases with peripheral enthesopathy. However, since the statistical significance is not strong enough to affirm this negative relationship with peripheral enthesopathy, larger or longitudinal studies are required.

The BASRI was used to evaluate radiographic changes, which are essential for determining the diagnosis and outcome in AS. Recently, the BASRI was devised to assess radiological lesions of the cervical and lumbar spines, and the hip joints, and it has been demonstrated to be reproducible, reliable, and easy to perform (14,15,18,19). In the present data, the unexpected small number of patients with a BASRI-cervical spine score of 3 was observed, and a similar lower frequency of this score has also been reported in another Korean study (6). Considering discontinuity of the frequencies in the percentile distribution of the BASRI-cervical score, a BASRI-cervical spine score ≥ 2 was counted as definite BASRI-cervical spine involvement and it was analyzed with other clinical and radiological variables.

Some investigators have suggested that ZA joint inflammation is the essential element that leads to impaired spinal motion in patients with AS (20-22). The radiographic abnormalities affecting these joints include erosion, sclerosis, and bony ankylosis (23). Moreover, ZA joint ankylosis is known to occur exclusively in patients with spondyloarthropathies and to be especially remarkable in the cervical spine (23-25). In a study performed by de Vlam *et al*., owing to a relatively inaccurate evaluation of the ZA joints by conventional radiographs, they focused on the presence of ZA joint ankylosis, which was seen in 22% of the cervical spine (16). In the current study, the ZA joint lesions of score ≥ 1 and ZA ankylosis were observed in 80.3% and 37.7%, respectively. Additionally, since the presence and severity of ZAjoint involvement could not be finely assessed by the BASRI system, the ZA joints was evaluated using MSCT examination.

The key lesions of AS are noted to consist of a combination of synovitis at apophyseal and sacroiliac joints and enthesitis. The inflammatory process of the synovial and adjacent ligamentous structures initially leads to erosive changes on these elements, which is followed by healing during which ossification or new bone formation occurs, and the final outcome of this inflammatory disorder results in bony ankylosis. (1-3,23,26). It is assumed that similar inflammatory and healing processes could take place in the atlantoaxial region, which contains several ligaments and synovial tissue. In the present study, some degree of ossification was observed between the atlas and the dens in a considerable number of patients with longstanding AS. Moreover, partial or complete atlantodental ankylosis was seen in over 30% of the patients. In addition, higher atlantodental ossification levels were associated with older age, longer disease duration, and more severe structural damage of the spine, the hip joints, and the sacroiliac joints.

AAS has been reported in various rheumatic disorders, such as rheumatoid arthritis (8,27,28), spondyloarthropathies (4, 6, 9, 11, 17, 23, 29), systemic lupus erythematosus (30), and mixed connective tissue disease (31). There are several types of AAS, including anterior, lateral, posterior, ant vertical ones, among which anterior AAS is most frequent (17, 27). The prevalence of AAS in AS is known to be less than that in rheumatoid arthritis (4, 8, 28), and it varies from 0 to 21% according to the reported populations and investigators (6, 7 ,9 , 17). It is important to detect AAS in its early stages, since an unstable displacement may progress and occasionally result in grave neurological complications and even death (27). Fortunately, the frequency of neurological compromise is uncommon in AS, though its frequency may be different according to the discrepancies in clinical expression attributable to the ethnic origin or study design. Some investigators have reported the absence of neurological complications in AS (7, 9, 29), while others have described AAS progressing in a significant proportion of the patients in the following 2 years after its detection (32). In addition, AAS in AS is usually found in the later stages of the disease (23), though it may present as an early complication (33). In the previous investigations, anterior AAS has been associated with increasing radiological sacroiliitis, or the presence of peripheral arthritis, OPLL, or abnormal SSEP results (17, 29).

In our series, as in the previous reports, anterior AAS was the most frequent type, which was found in 6 patients. Four of the AS patients with AAS showed abnormal SSEP results, but no patients in our AS cohort had clinically significant neurological complications. This might have been due to atlantodental ankylosis or ZA joints fusion developed in a considerable proportion of patients with AS, as these could provide joint stability for the cervical spine and prevent further neurological compromise. A close follow-up is required to determine whether SSEPmay be useful for identifying patients likely to develop neurological complications. In addition, AAS in our AS cohort was associated with increasing disease duration, and interestingly, it had developed in 3 patients with minimal or no cervical spine involvement.

OPLLhas been described as an isolated phenomenon in the general population, most frequently in the Japanese race (34, 35), or in patients with AS (9, 17, 23, 36, 37) or diffuse idiopathic skeletal hyperostosis (38, 39). However, it remains to be determined whether this ossified lesion of the posterior ligamentous attachment is closely related to diseases, such as AS. Moreover, little information has been available regarding OALL in AS. In the assessment of AAS in patients with AS, Ramos-Remus *et al.* (17) detected relatively high frequencies of OPLL and OALL, which reached 15 and 16%, respectively. Recently, the same group found that the OPLL was observed in 15.5 to 29.0% of patients with spondyloarth-

ropathies from 3 different geographical areas, and that it was associated with longer disease duration and more severe axial disease. Thus, they suggested that OPLLwould be another manifestation of enthesopathy related to spondyloarthropathies (40). In the current study, OALL and OPLL in the cervical spine were observed in 16 (26.2%) and 18 patients (29.5%), respectively. Moreover, there was a tendency that patients with OALL or OPLL in the cervical spine were associated with longer disease duration or atlantodental ankylosis. Taken all situations into consideration, it is assumed that OALLand OPLL of the cervical spine in AS may be the outcome of ligamentous ossification related to a longstanding disease process rather than an isolated phenomenon.

Although this study was carefully planned, there are some limitations. First, since all the radiographs were evaluated once by one radiologist, information regarding intra- and inter-observer variation could not be obtained. Second, since our study was performed on the patients who were referred to tertiary medical centers, these subjects might represent a relatively severe group with a more progressive disease. To overcome these problems, longitudinal studies and continuous observation of radiographic changes will be required in a greater number of patients.

In summary, cervical spine involvement and atlantodental ossification appear to be frequent in patients with longstanding AS, and particularly more severe in patients with longer disease duration. In addition, the atlantodental ankylosis and the ZA joint fusion were also commonly found in a significant portion of patients with longstanding AS. At present, a longitudinal study is under way to determine whether such atlantodental ankylosis and ZA fusion may provide some degree of stability and thereby prevent further neurological compromise in AS patients with joint dislocation.

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