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Progression of rheumatoid arthritis of the cervical spine: radiographic and clinical evaluation

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Abstract: Cross-sectional and longitudinal studies were conducted to observe progression of rheumatoid arthritis in the cervical spine. Two hundred and ninety-seven patients were enrolled in the cross-sectional study. Both upper and lower cervical spine involvement increased with disease duration. The relationship between atlanto-axial motion and the development of subaxial subluxation was inconclusive. Eighty-seven patients were enrolled in the longitudinal study and were followed for at least 5 years. In about half of these patients, rheumatoid changes started from the upper cervical spine, with rheumatoid changes beginning from the lower cervical spine in about 8% of patients. Neurological deficits were correlated with radiographic changes but neck pain did not correlate with radiographic changes. As to the upper cervical spine, the parameter most influencing neurological deficits was found to be the minimum value of the atlanto-axial angle in flexion, by multivariate analysis using a multiple logistic model. Neurological deficits were seen in more than half the patients when the atlanto-axial angle in flexion was 5° or less.

Key words: rheumatoid arthritis, cervical spine, radiographic evaluation, clinical evaluation

Introduction

The natural history, mechanism of symptoms, and treatment of cervical spinal changes in rheumatoid arthritis remain topics of controversy. Upper cervical changes are easily detectable and are well described in the literature. Lower cervical changes are said to occur after upper cervical changes, although the relationship between them is still not clear.

As to symptoms and treatment, Rana[12] recommends preventive surgery if the anterior atlanto-axial subluxation exceeds 10 mm, although not all patients with significant rheumatoid changes show clinical symptoms. Boden et al.[1] took the sagittal diameter of the spinal canal as their reference, recommending surgery when it measured less than 14 mm. Saito et al.[14] have reported that myelopathy takes place when the angle between the atlas and axis is less than 5°. Thus, although numerous methods have been adopted to evaluate the rheumatoid cervical spine, it remains unclear which is most effective. The purpose of this study was to clarify both the efficacy of these various methods, and the factors producing clinical symptoms by analyzing the disease progression both radiographically and clinically.

Patients and methods

Our subjects were 297 of 307 patients with rheumatoid arthritis who had radiographs of the cervical spine taken at Niigata University Hospital between 1976 and 1995. The 10 excluded patients included 9 patients with an age of onset of the disease of 16 years or less (juvenile rheumatoid arthritis) and 1 patient with a posterior dislocation of the atlas. There were 46 men and 251 women and the average age at the time of this study was 57 years (range, 23 to 79 years), and the average duration of the disease was 13 years (range, 0 to 44 years). They were studied retrospectively.

Radiographic evaluation

We used the following methods to define upper and/or lower rheumatoid cervical spine involvement.

Upper cervical spinal lesion. A lateral-functional radiograph was used to measure the following

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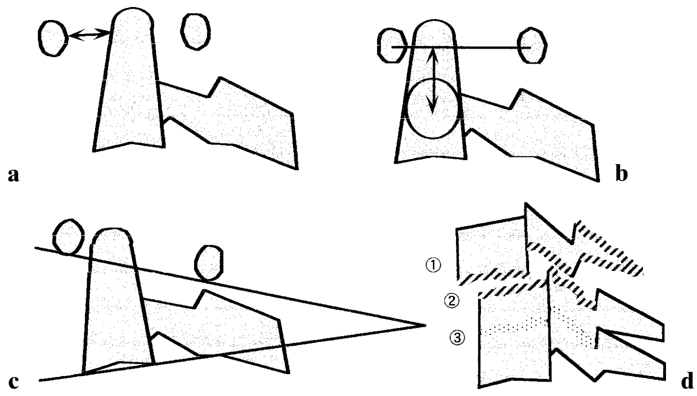

Fig. 1a–d. Radiographic evaluation. **a** Atlanto-dental interval (ADI, distance between the posterior margin of the anterior arch of the first cervical vertebra and anterior margin of dens of the second). ADI values greater than 3 mm were taken as indicating anterior atlanto-axial subluxation. The ADI was measured both in flexion (flexion-ADI) and in extension (extension-ADI). **b** The technique described by Ranawat et al.[13] measures the distance between the center of the pedicle of the second cervical vertebra and the coronal axis of the first. The coronal axis of the first cervical vertebra is determined by connecting the center of the anterior arch of the atlas with its posterior arch. Males with Ranawat values of 14 mm or less and females with values of 13 mm or less were considered to have vertical subluxation. **c** Atlanto-axial angle (AAA, angle between the line drawn from the anterior arch to the posterior arch of the first cervical vertebra, and the line drawn along the inferior margin of the second). AAA was measured both in flexion (flexion-AAA) and in extension (extension-AAA). **d** Lower cervical lesion: ①Subaxial subluxation of more than 2 mm; ②erosion of either endplate, facet joint, spinous process, or a combination of the three; ③fusion of either spinal body, facet joint, or both

parameters (Fig. 1). Anterior atlanto-axial subluxation and/or vertical subluxation were classified as upper cervical changes. Anterior atlanto-axial subluxation was determined by measuring the atlanto-dental interval (ADI, distance between the posterior margin of the anterior arch of the first cervical vertebra and the anterior margin of the dens of the second) and defined as an ADI greater than 3 mm (Fig. 1a). The ADI was measured both in flexion (flexion-ADI) and in extension (extension-ADI). Vertical subluxation was evaluated using the technique described by Ranawat et al.,[13] measuring the distance between the center of the pedicle of the second cervical vertebra and the coronal axis of the first. The coronal axis of the first cervical vertebra is determined by connecting the center of the anterior arch of the first cervical vertebra with its posterior arch (Fig. 1b). Males with Ranawat values of 14 mm or less and females with values of 13 mm or less were considered to have vertical subluxation. Antero-inferior tilt of the atlas was measured using the atlanto-axial angle[19] (AAA, angle between the line drawn from the anterior arch to the posterior arch of the first cervical vertebra, and the line drawn along the inferior margin of the second; Fig. 1c). The AAA was measured both in flexion (flexion-AAA) and in extension (extension-AAA). Instability between the first and the second cervical vertebra was evaluated by subtracting the flexion-AAA value from the extension-AAA value to determine the range of motion of the first cervical vertebra.

Lower cervical spinal lesion. From C2/3 through C7/Th1 we defined lower cervical spinal changes as the presence of one or more of the following three criteria: subaxial subluxation of more than 2 mm (Fig. 1d①); erosion of either endplate, facet joint, spinous process, or a combination of the three (Fig. 1d②); and fusion of either spinal body, facet joint, or both (Fig. 1d③). Disc space narrowing with osteophytes was considered as a spondylotic change and excluded. Sharp et al.[16] have reported that disc space narrowing without osteophytes was specific to rheumatoid cervical spine. However, we did not include disc space narrowing without erosion as a lower cervical lesion criterion because it was difficult to recognize subtle disc space narrowing.

Cross-sectional study

We analyzed the correlation between each of the above-mentioned parameters and the duration of the disease. The correlations between each parameter were also analyzed using multiple regression analysis. Finally, to determine the influence of upper cervical lesions on lower cervical instability (subaxial subluxation), we evaluated atlanto-axial instability in three groups. Group 1 had only anterior atlanto-axial subluxation, group 2 had vertical subluxation without lower cervical spinal changes, and group 3 had subaxial subluxation with upper cervical spinal changes. The groups were compared using one-way analysis of variance (ANOVA).

Longitudinal study

Eighty-seven patients were followed for at least 5 years and entered into the longitudinal study. There were 7 men and 80 women. The average age was 58 years (range, 31 to 77 years), the average duration of the disease was 17 years (range, 6 to 42 years), and the average follow-up period was 9 years (range, 5 to 21 years). In studying the progression of the cervical lesions, radiographs were examined in the same manner as in the cross-sectional study.

Symptomatic patients

Clinical symptoms in the longitudinal study group were evaluated using Ranawat and colleagues' classification.[13] The group with pain in the occipitocervical region was defined as Ranawat grade 1 or more and the neurological deficits were defined as Ranawat class II or more. Some pain occurred in 72 patients (83%) during the follow-up period. Neurological deficits were seen in 22 patients but 5 were considered to be secondary to peripheral nerve disorders. The remaining 17 patients (21%) had neurological deficits (cord signs) which were related to rheumatoid changes and entered in the study.

To study the relationship between neurological deficits and upper cervical lesions, we used the flexion-ADI, extension-ADI, Ranawat value, flexion-AAA, and extension-AAA. Multivariate analysis with a multiple logistic model was used to study the parameters which most influenced neurological deficits within the longitudinal study group. Seven patients with neurological symptoms caused by lower cervical lesions were excluded, leaving 80 patients to be studied.

To study the relationship between neurological deficits and lower cervical lesions, we evaluated patients with criteria for lower cervical spine changes. For the lower cervical spine, we used the maximum value of subaxial subluxation and the duration of the disease when erosion or fusion first took place.

Statistical analyses

Pearson's correlation coefficient (r) or the Spearman rank correlation method (ρ) was used according to the characteristics of the data for the correlation analysis between duration of disease and each parameter. A P value of 0.05 or less was considered significant, even if the correlation coefficient was low. Multiple regression analysis was used to study the relationship between the parameters. One-way analysis of variance (ANOVA) was used for analysis of atlanto-axial instability. χ^2 tests were used to compare the cross-sectional and longitudinal study groups. The Mann-Whitney U-test was used to study comparisons between the groups. A multiple logistic model was used to determine the parameters that most influenced the development of neurological deficits.

Results

Cross-sectional study

No rheumatoid changes were seen in 114 patients (38.4%), upper cervical changes were seen in 110 patients (37.0%), lower cervical changes were seen in 16 patients (5.4%), and both upper and lower cervical changes were seen in 57 patients (19.2%: Table 1).

A Positive correlation was observed between upper cervical spine involvement and duration of the disease ($r = 0.73$, $P < 0.0001$). The flexion-ADI and extension-ADI were positively correlated with the duration of the disease, although the correlation coefficients were very low ($\rho = 0.197$, $P < 0.001$, and $\rho = 0.153$, $P < 0.01$, respectively). The Ranawat value, flexion-AAA, and extension-AAA were all negatively correlated with the duration of the disease ($r = -0.37$, $P < 0.0001$; $r = -0.234$, $P < 0.0001$; and $r = -0.301$, $P < 0.0001$, respectively). Multiple regression analysis was used to study the relationship between the parameters. The Ranawat value correlated with the extension-ADI and extension-AAA (Fig. 2; Ranawat value = 11.199 − 0.603 × (extension-ADI) + 0.135 × (extension-AAA), $r = 0.605$, $P < 0.0001$).

A positive correlation was observed between patients with lower cervical spine involvement and the duration of the disease ($r = 0.485$; $P < 0.05$). Erosion of the lower cervical spine was positively correlated with disease duration ($r = 0.559$; $P < 0.005$), although there was no correlation between subaxial subluxation and fusion ($r = 0.321$, $P = 0.1$; and $r = 0.211$, $P = 0.3$, respectively).

Atlanto-axial instability was compared in the three groups described under "Cross-sectional study in Methods", using the value derived by subtracting the flexion-AAA from the extension-AAA. Group 1 consisted of 67 patients, group 2 consisted of 44 patients, and group 3 consisted of 30 patients. With one-way analysis of variance (ANOVA), no significant difference was found between these groups (Fig. 3;

Table 1. Comparisons between cross-sectional study group and longitudinal study group

	No rheumatoid changes	Upper cervical changes	Lower cervical changes	Both upper and lower cervical changes	Total	Mann-Whitney U-test
Cross-sectional study group (%)	114 (38.4)	110 (37.0)	16 (5.4)	57 (19.2)	297	$P < 0.05$
Longitudinal study group (%)	23 (26.4)	35 (40.2)	6 (7.0)	23 (26.4)	87	

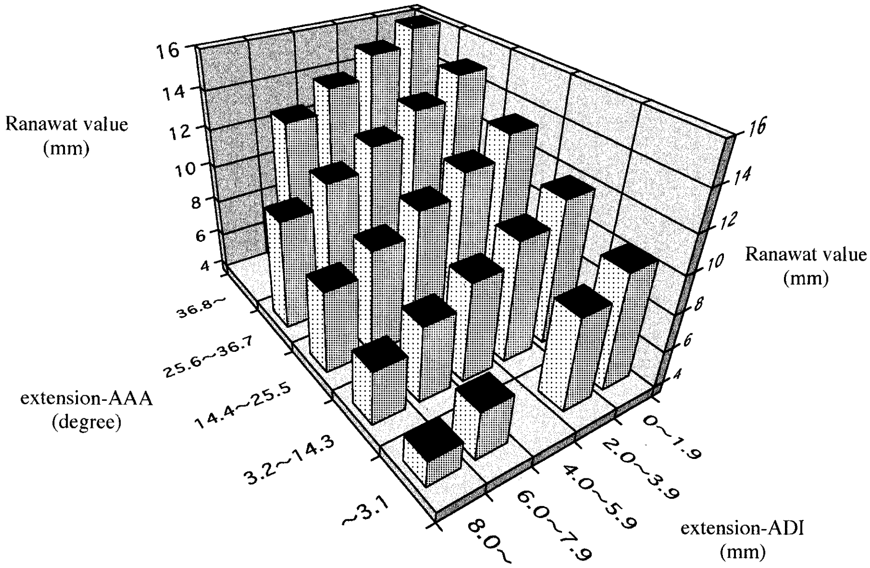

Fig. 2. Relationship between parameters. On multiple regression analysis, the Ranawat value correlated with extension-ADI and with extension-AAA ($r = 0.605$, $P < 0.0001$)

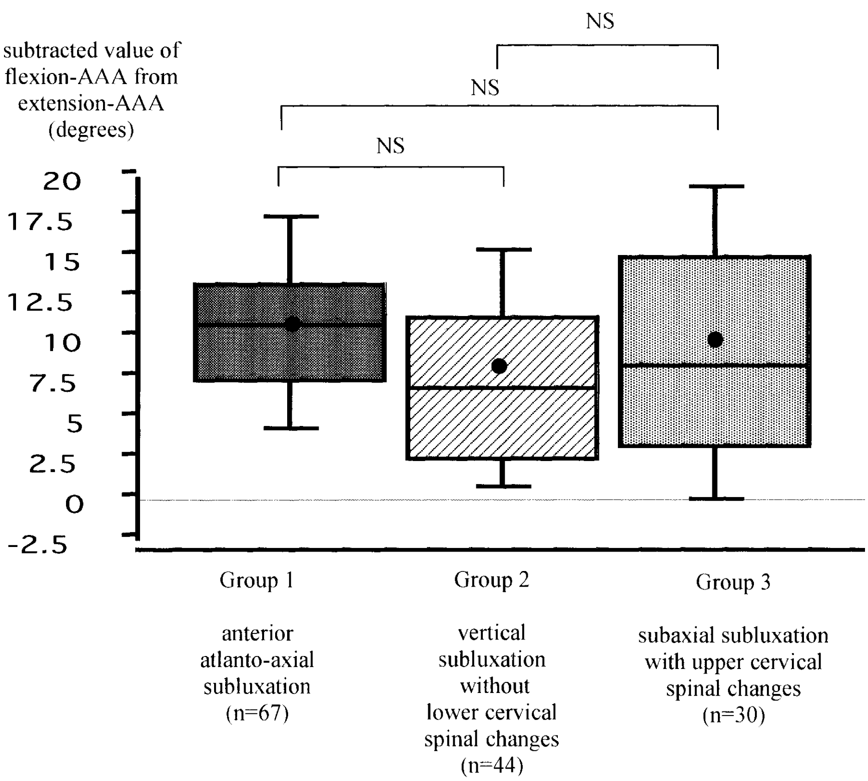

Fig. 3. Atlanto-axial instability was compared in three groups, using the value of flexion-AAA subtracted from extension-AAA. Group 1 consisted only of patients with anterior atlanto-axial subluxation ($n = 67$, 10.5 ± 4.9°), group 2 consisted of patients with vertical subluxation without lower cervical spinal changes ($n = 44$, 8.1 ± 8.0°), and group 3 consisted of patients with subaxial subluxation with upper cervical spinal changes ($n = 30$, 9.3 ± 7.7°). With one-way analysis of variance (ANOVA), no significant difference was found between these groups (*NS*)

group 1, 10.5 ± 4.9°; group 2, 8.1 ± 8.0°; group 3, 9.3 ± 7.7°).

Longitudinal study

Rheumatoid cervical changes were observed on the initial radiograph in 38 of the 87 patients (44%). At the time this study was performed, 64 patients (74%) showed rheumatoid cervical changes. The longitudinal study group had more patients with rheumatoid changes than the cross-sectional study group, according to the Mann-Whitney *U*-test (Table 1, $P < 0.05$).

The course of the rheumatoid cervical changes is shown in Fig. 4. Initially, anterior atlanto-axial

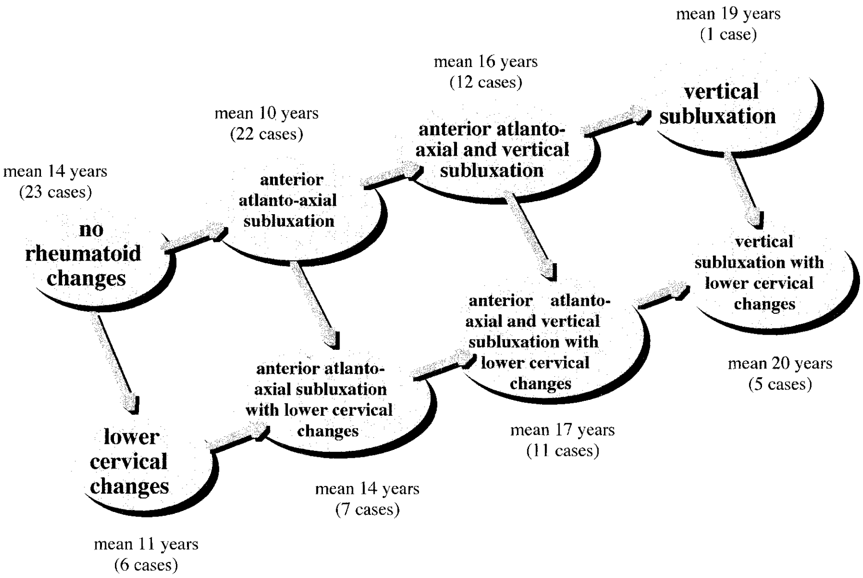

Fig. 4. The course of rheumatoid arthritis in the cervical spine. The number of patients and the mean duration from the onset of rheumatoid arthritis until the occurrence of each radiographic change are shown. Anterior atlanto-axial subluxation or lower cervical change was seen first. With regard to the upper cervical spine, vertical subluxation followed anterior atlanto-axial subluxation and progressed to the point where it existed alone. Combinations of upper and lower cervical changes were also observed

subluxation or lower cervical change occurred. With regard to the upper cervical spine, vertical subluxation followed anterior atlanto-axial subluxation and progressed to the point where it appearred to exist alone. Combinations of upper and lower cervical changes were also observed. In one rare situation, vertical subluxation occurred without prior obvious manifestation of anterior atlanto-axial subluxation, and in 4 patients the atlanto-axial joint fused spontaneously. In 23 patients (26%) no rheumatoid cervical changes were seen, in 46 patients (53%) changes started from the upper cervical spine, in 7 patients (8%) changes started from the lower cervical spine, and in 11 patients (13%) it was not clear which came first. The mean duration from the onset of rheumatoid arthritis until the occurrence of anterior atlanto-axial subluxation was 10 years (range, 3 to 33 years). The mean disease duration for lower cervical changes was 11 years (range, 3 to 16 years); for anterior atlanto-axial subluxation with lower cervical changes, 14 years (range, 5 to 24 years); for both anterior atlanto-axial and vertical subluxation, 16 years (range, 3 to 31 years); for both anterior atlanto-axial and vertical subluxation with lower cervical changes, 17 years (range, 2 to 37 years); for vertical subluxation, 19 years (range, 6 to 27 years), and for vertical subluxation with lower cervical changes, 20 years (range, 10 to 30 years).

Symptomatic patients

Neck pain was found in 72 patients in the longitudinal study group. With the onset of neck pain, radiographic changes were seen in 35 patients (49%), and there was no correlation between radiographic changes and pain ($\chi^2 = 2.1$, $P = 0.14$). Neurological deficits were seen in 17 patients, and at the onset of the neurological deficits radiographic changes were seen in 16 patients (94%). The radiographic changes and neurological deficits were found to correlate ($\chi^2 = 3.9$, $P < 0.05$).

Among the 58 patients with upper cervical spinal changes, neurological deficits were seen in 14 patients. The minimum value of the flexion-AAA during the follow-up period was significantly lower in the group with neurological deficits (6.9 ± 10.4°) than in the group without them (14.9 ± 6.7 °, $P < 0.05$). The minimum value of the extension-AAA during the follow-up period was significantly lower in the group with neurological deficits (17.4 ± 11.8°) than in the group without them (25.0 ± 9.0°, $P < 0.05$). We did not find any relationships between neurological deficits and the other parameters. Based on multivariate analysis using a multiple logistic model, the parameter that most influenced neurological deficits was the minimum value of flexion-AAA (Table 2). Neurological deficits were found in more than half the patients when the minimum value of the flexion-AAA was 5° or less (Fig. 5).

Among the 29 patients with lower cervical spinal lesions, neurological deficits were found in 16 patients. Of the 11 patients with fusion, 5 had neurological deficits. Comparing the duration of the disease in relation to the time fusion was first seen, patients with neurological deficits fused earlier (11 years compared with 20 years, $P < 0.05$). Of 19 patients with subaxial subluxation, 10 had neurological deficits. Of 16 patients with erosion, 7 had neurological deficits. We did not find any relationship between neurological deficits and either subaxial subluxation or erosion. We could not perform multivariate analysis because these 29 patients

Table 2. Parameters that most influenced the development of neurological deficits in 80 patients with rheumatoid changes of the cervical spine (longitudinal study group)

Variable	*P* value	Odds ratio	95% Confidence interval
Maximum value of flexion-ADI	0.88	1.057	0.529–2.113
Maximum value of extension-ADI	0.28	0.549	0.185–1.630
Minimum value of Ranawat value[13]	0.08	0.538	0.274–1.058
Minimum value of flexion-AAA[a]	0.03	0.457	0.230–0.908
Minimum value of extension-AAA	0.05	1.690	1.007–2.836

See text for explanations of ADI and AAA
Based on multivariate analysis using the multiple logistic model
Seven patients with neurological symptoms caused by lower cervical lesions were excluded
[a] The parameter that most influenced the development of neurological deficits was the minimum value of the flexion-AAA

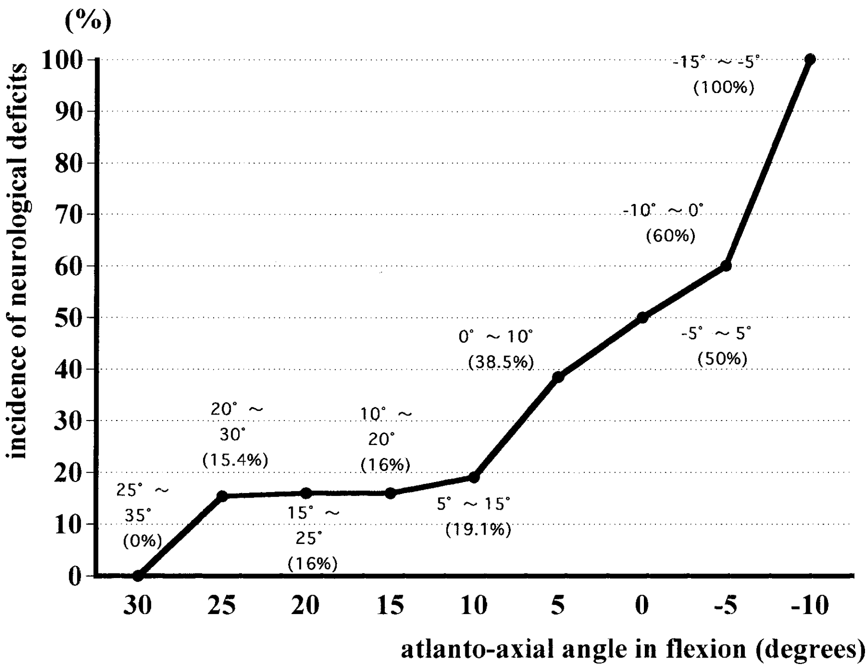

Fig. 5. Neurological deficits and the atlanto-axial angle. Neurological deficits were found in more than half of the patients when the minimum value of the flexion-AAA was 5° or less

did not have all three lower cervical radiographic changes, and not enough data were obtained for a multiple logistic model.

Discussion

Progression of rheumatoid arthritis of the cervical spine

It is known that anterior atlanto-axial subluxation occurs first, followed by vertical subluxation. As vertical subluxation progresses, the atlas begins to tilt antero-inferiorly.[21] Anterior atlanto-axial subluxation, vertical subluxation, and antero-inferior tilt of the atlas correlated with one another (Fig. 2). The severity of anterior atlanto-axial subluxation decreases as the atlas moves downward,[9,12,17] because the base of the second cervical vertebra is wider in sagittal diameter than the dens. This may be the reason for the correlation coefficient of the ADI and the duration of disease being low. However, the AAA, which appeared to decrease with the progression of rheumatoid changes, may be a suitable parameter for reflecting spinal cord compression.

There has been little discussion in the literature about the relationship between the upper and lower rheumatoid cervical spine. Yamauchi et al.[22] postulated that, as the motion of the upper cervical movement decreases, increasing stress is transmitted to the lower cervical spine, thereby causing subaxial subluxation. Kraus et al.[7] compared cases patients occipito-cervical fusion with patients with atlanto-axial fusion. Only 2.6 years after the index procedure, 36% of the occipito-cervical fusion group required additional surgery as a result of subaxial subluxation. In contrast, no more than 5.5% of the atlanto-axial fusion group had developed subaxial subluxation 9 years postoperatively. It is believed that by confining the loss of motion to the atlanto-axial joint, the risk of subaxial subluxation can be greatly reduced. However, if the motion from the occiput to the cervical spine is lost, this can result in the creation of a longer lever arm that generates higher forces at the lower cervical level, and ultimately results in subaxial subluxation. Hiraizumi et al.[3] compared an atlanto-axial fusion group with a conservatively treated group, and reported no differences with respect to progression of subaxial subluxation. Atlanto-axial motion is not the main factor in determining the progression of subaxial subluxation. We subtracted the flexion-AAA value from the extension-AAA value to assess atlanto-axial instability. No differences were observed between the group with upper cervical changes and the group with subaxial and upper cervical spinal changes (Fig. 3). In following the course of rheumatoid arthritis of the cervical spine (shown in Fig. 4), we found that subaxial subluxation occurrred not only in patients with vertical subluxation but also in those patients without it. We cannot definitively conclude that mechanical stress is the main cause of subaxial subluxation, because atlanto-axial motion does not play an important role in this subluxation.

Clinical findings

The general consensus is that the rheumatoid cervical spine should be treated conservatively, since many patients are asymptomatic despite findings of radiographic change.[5,11] Weissman et al.[21] have reported an association between neurological deficits and flexion-ADI values in excess of 9 mm. Rana[12] has reported a similar finding for flexion-ADI over 10 mm. Our data showed no correlation between neurological deficits and flexion-ADI. Boden et al.[1] used the sagittal diameter of the spinal canal instead of the ADI, and recommended surgery if it was 14 mm or less, regardless of the presence of neurological deficits.

Toyama and Kamata[20] stressed the importance of dynamic factors, rating specifically, that neurological deficits tended to be seen in patients with atlanto-axial instability. According to these authors, the average range of motion of the atlas is 13° in normal subjects, and if it exceeds 20°, myelopathy is seen. Our own results contrasted sharply with these findings, since both flexion-AAA and extension-AAA during the follow-up period were significantly lower in the group with neurological deficits than in the group without them, and no correlation of neurological deficits with atlanto-axial instability was seen. Saito et al.[14] compared 13 patients with myelopathy with 23 patients without myelopathy. They found that if the flexion-AAA was 5° or less, the spinal cord was pinched between the posterior arch of the atlas and dens, causing myelopathy. Our data are consistent with their results, with neurological deficits occurring in more than half the patients when flexion-AAA was 5° or less. We believe operative intervention is indicated in patients with flexion AAA less than 5°.

Regarding lower cervical changes and myelopathy, Yonezawa et al.[23] used multivariate analysis to demonstrate the influence of a number of factors on the onset of this disease, reporting findings that included destruction of the spinous process, shorter neck, narrow spinal canal diameter, younger patients, and longer duration of the disease. Our study revealed that in patients with neurological deficits, fusion of the lower cervical spine took place significantly earlier. Santavirta et al.[15] reported on 16 patients in whom subaxial subluxation was managed operatively; in 3 patients (20%) subaxial subluxation developed at another level. The patient reported by Ogata et al.[10] showed spontaneous spinal fusion adjacent to the level of cord compression. According to these reports, it appears that mechanical force arises at the adjacent vertebra causing instability or deformation, leading to neurological deficits. We found that erosion of the lower cervical spine was positively correlated with disease duration, but no correlation with neurological deficits was found. Although fusion of the lower cervical spine was not correlated with disease duration, such fusion is an important factor for predicting neurological deficits. Prudent observation is necessary in patients with early spontaneous fusion of the lower cervical spine.

Pain was experienced by more than half of our study population, although they had no detectable rheumatoid changes. Stevens et al.[18] reported that, among patients without atlanto-axial subluxation, 58% had neck pain. Kontinnen et al.[6] explained that neuropeptides near blood vessels in the atlanto-axial interspinous ligament, as well as synovitis, caused pain before the development of atlanto-axial subluxation. As to neurological deficits, not all patients with such deficits showed radiographic changes. Stevens et al.[18] reported on patients with neurological deficits, and in 21% of these patients neither rheumatoid nor spondylotic changes were seen. Castro et al.[2] studied the rheumatoid cervical spine with plain radiographs, magnetic resonance imaging (MRI), and somatosensory evoked potentials. They reported that, in the upper cervical spine, cord compression was due to pannus around the dens or vertical subluxation, and the correlation with anterior atlanto-axial subluxation was low. Hopkins[4] and Kudo et al.[8] found two major causes of cord compression at the lower cervical level. The first was bony compression, such as subaxial subluxation, and the other was soft tissue compression, such as the presence of extradural granulation tissue or dural thickening.

It is therefore necessary to study the natural history of this disease with radiographs in combination with MRI, because in some patients the clinical symptoms cannot easily be explained by radiographs alone. Nonetheless, in many patients in whom MRI has not been evaluated by a functional view method, the plain radiograph has its raison d'etre, and neurological deteriolration can be predicted by the flexion-AAA.

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