Atlantoaxial disorders in rheumatoid arthritis associate with the destruction of peripheral and shoulder joints, and decreased bone mineral density

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Abstract

Objective

To evaluate whether cervical spine changes are associated with the destruction of shoulder or peripheral joints and with bone mineral density (BMD) in patients with long-term RA.

Methods

An inception cohort of 67 patients with seropositive and erosive RA were followed up for 20 years. Cervical spine, shoulder, hand and foot radiographs, and the BMD of the lumbar spine and femoral neck were evaluated.

Results

A positive relationship was detected between the occurrence of atlantoaxial disorders and the destruction of both shoulder ($p < 0.001$) and peripheral ($p = 0.001$) joints. In addition, the severity of anterior atlantoaxial subluxation and atlantoaxial impaction positively correlated with the grade of destruction in the evaluated joints. Furthermore, patients with atlantoaxial disorders presented decreased BMD of the femoral neck ($p = 0.019$). The occurrences of subaxial subluxations (SAS) and subaxial disc space narrowings only associated with higher onset age of RA.

Conclusions

Patients with severe RA and osteoporosis have an increased risk for atlantoaxial disorders. The co-existence of shoulder destruction and cervical spine disorders makes the differential diagnosis of shoulder and neck pain challenging.

Key words

Rheumatoid arthritis, cervical spine, bone mineral density, peripheral joints, shoulder joint, risk factors.

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Introduction

Cervical spine involvement is a common phenomenon in advanced rheumatoid arthritis (RA) (1, 2). Anterior atlantoaxial subluxation (aAAS) and atlantoaxial impaction (AAI) are the most characteristic cervical spine disorders in RA, being detected in 13 - 70% and 4-35% of the patients, respectively (2, 3). aAAS has been reported to develop early in the course of RA (3-5), whereas AAI develops later after sustained inflammation, erosions and collapse of the atlantoaxial joints (6-10). Furthermore, rheumatoid inflammation of the facet joints below the second cervical vertebra may cause subaxial subluxations (SAS) (1). However, the differential diagnosis between subaxial subluxations caused by RA and degeneration of the cervical spine is often difficult.

The occurrence of cervical spine subluxations has been reported to associate with erosiveness of the peripheral joints, HLA status, and the presence of rheumatoid factor (RF) and rheumatoid nodules (3, 6-8, 11, 12). Although pain in the shoulder-neck region is a common symptom caused by both cervical spine disorders and shoulder joint destruction, a relationship between the destruction of cervical spine and shoulder joints has not been previously studied.

Osteoporosis due to RA or corticosteroids has been suggested to promote the development of aAAS and AAI (13, 14). This suggestion is based on the assumption that weakening of the bone structure increases the risk for destruction of bony attachments of the transversal ligament and for collapse of the lateral masses of atlas and/or axis, resulting in aAAS and AAI, respectively. However, the relationship between the rheumatoid cervical spine disorders and bone mineral density (BMD) has not been evaluated. Moreover, the studies concerning the role of corticosteroid treatment as a risk factor for cervical spine disorders in RA have yielded controversial results (6,11,15-17).

Previously, we studied the occurrence of cervical spine changes in a prospective 20-years follow-up study (10). The prevalences of aAAS, AAI and SAS after 20 years of RA were 23%, 26% and 19%, respectively. In the present study, we compared the occurrence of these disorders to severity of peripheral, glenohumeral (GH) and acromioclavicular (AC) joint erosions, BMD of the lumbar spine and femoral neck and the age of patients at disease onset.

Patients and methods

During 1973-1975, 118 patients with recent (≤ 6 months) seropositive RA were admitted to a follow-up study at the Rheumatism Foundation Hospital, Heinola, Finland. The selection criteria, data of the collection strategy and the characteristics of the patients have been described previously (18-20). The follow-up examinations were done at the beginning of the study, and at 1, 3, 8,15 and 20 years from entry. The number of patients who attended the 8-, 15- and 20-year check-ups was 103, 74 and 67, respectively. During the follow-up period 34 patients died and 17 patients failed to attend the 20-year check-up. The protocol of the study was approved by the ethical committee of Rheumatism Foundation Hospital, Heinola, Finland.

The cervical spine radiographs of 67 patients [56 women and 11 men; mean age 61.2 years (range 37 - 86 years)] taken at the 20-year examination were evaluated. Lateral-view cervical spine radiographs (during flexion and extension) were taken using a 150 cm tube-to-plane distance (10). A diagnosis of aAAS was made if the distance between the anterior aspect of the dens and the posterior aspect of the anterior arch of the atlas was > 3 mm. AAI was diagnosed using the Sakaguchi-Kauppi (S-K) method, which has been developed in particular for screening purposes and evaluates the position of the atlas in relation to axis (21). It divides the condition into 4 grades (Grade I represents normal and Grades II-IV abnormal). SAS was diagnosed if a vertebra had moved > 3 mm in relation to the next vertebra when measured from the posterior line of the vertebral bodies. Subaxial disc space narrowings were also evaluated. Because the aAAS and AAI are the most specific cervical spine disorders for RA, they are re-

Table I. Larsen score/grade of peripheral,glenohumeral (GH) and acromioclavicular (AC) joints in RA patients with and without atlantoaxial disorders (aAAS or AAI).

	Patients without atlantoaxial disorders		Patients with atlantoaxial disorders		p value
	N of radiographs available	Median (IQR)	N of radiographs available	Median (IQR)	
Larsen score of peripheral joints (0-100)	45	33 (16,48)	22	68 (47,81)	0.001
Larsen grade of GH joints (0-10)	40	2 (0,3)	21	4 (3,7)	< 0.001
Larsen grade of AC joints (0-10)	40	3 (1,4)	21	5 (4,7)	< 0.001

N: number; IQR: interquartile range.

ferred to atlantoaxial disorders in the text.

Radiographs of the hands and feet of all patients were taken in the antero-posterior projection at the 20-year follow-up. The Larsen grades for the 1st to 5th metacarpophalangeal joints, the wrists, and the 2nd to 5th metatarsophalangeal joints (20 joints) were assigned and added to form a Larsen score of 0 to 100. Shoulder radiographs were taken only at the 15-year check-up, and they were available from 61 patients. The sums of the left and right GH or AC joint Larsen grades were calculated to describe the destruction of these central joints (i.e., the range of joint destruction varied from 0 to 10).

At the 20-year check-up, the BMD of the lumbar spine (L2 – 4) and femoral neck was measured using dual X-ray bone densitometry in 53 and 57 patients, respectively. The BMD of the patients is described as a Z-score, which represents the number of standard deviations (SD) from the mean, weight-adjusted BMD for persons of the same age and sex.

The occurrence and severity of the atlantoaxial disorders and SAS were compared to the age of the patients at disease onset; Larsen grades for GH and AC joints at the 15-year follow-up; and the Larsen score for peripheral joints and BMD of the lumbar spine and femoral neck at the 20-year follow-up.

Table II. Correlation between the severity of atlantoaxial disorders (aAAS and AAI) and Larsen score/grade of the peripheral and shoulder joints.

Larsen score/grade	Atlantoaxial distance (mm) r (95% CI)	Severity of atlantoaxial impaction (S-K grade) r (95% CI)
Peripheral joints	0.44 (0.22 to 0.61)	0.44 (0.22 to 0.61)
Glenohumeral joints	0.46 (0.24 to 0.64)	0.37 (0.13 to 0.57)
Acromioclavicular joints	0.40 (0.17 to 0.60)	0.41 (0.18 to 0.60)

S-K: Sakaguchi-Kauppi method; r: correlation coefficient; CI: confidence interval.

Statistical analysis

The results are expressed as mean and SD, median and interquartile range (IQR) and 95% confidence intervals (95% CI). Statistical comparison between groups was performed using the Student's t-test or Mann-Whitney U-test. Correlations were estimated with Spearman's correlation coefficient method. The normality of variables was evaluated by the Kolmogorov-Smirnov test, with a Lilliefors test or Shapiro-Wilk test.

Results

A positive relationship was observed between the occurrence of atlantoaxial disorders (aAAS and AAI) and the destruction of peripheral, GH and AC joints (Table I). All associations were statistically significant. Moreover, the grade of destruction in these joints correlated to a certain extent with the severity of aAAS and AAI (Table II, Fig. 1, Fig. 2).

The BMD at the femoral neck was significantly decreased in patients with atlantoaxial disorders (Table III). However, the difference in BMD of the lumbar spine between the two groups did not reach statistical significance. The results were similar even if patients with aAAS or AAI were evaluated separately (data not shown). No relationship was found between the occurrence of atlantoaxial disorders and the age of patients at the onset of RA or the gender of the patients.

In contrast to atlantoaxial disorders, no significant relationship was found between the occurrence of SAS and the destruction of peripheral, GH or AC joints, or BMD of the lumbar spine or femoral neck. However, the prevalences of SAS and subaxial disc space narrowings associated with the late onset age of RA. In patients with SAS, the mean age at onset of RA was 48 (SD 8) years and in the other group 39 (SD 12) years ($p = 0.015$).

Discussion

In the present study the cervical spine changes after 20 years of RA were compared to the BMD and the peripheral joint Larsen score after 20 years of RA, and to the shoulder joint erosions after 15 years of RA. Unfortunately, the shoulder joint radiographs were not taken at the 20-year check-up. However, 15 years is already a very long follow-up period and we believe that the results at that point well describe the development of shoulder joint destructions in long-term RA.

Our findings confirm the results of cross-sectional and shorter follow-up studies, which have demonstrated that RA patients with highly erosive peripheral joint disease have an increased risk for cervical spine changes (3, 8, 11). Since severe cervical spine disorders in RA may cause the compression of neu-

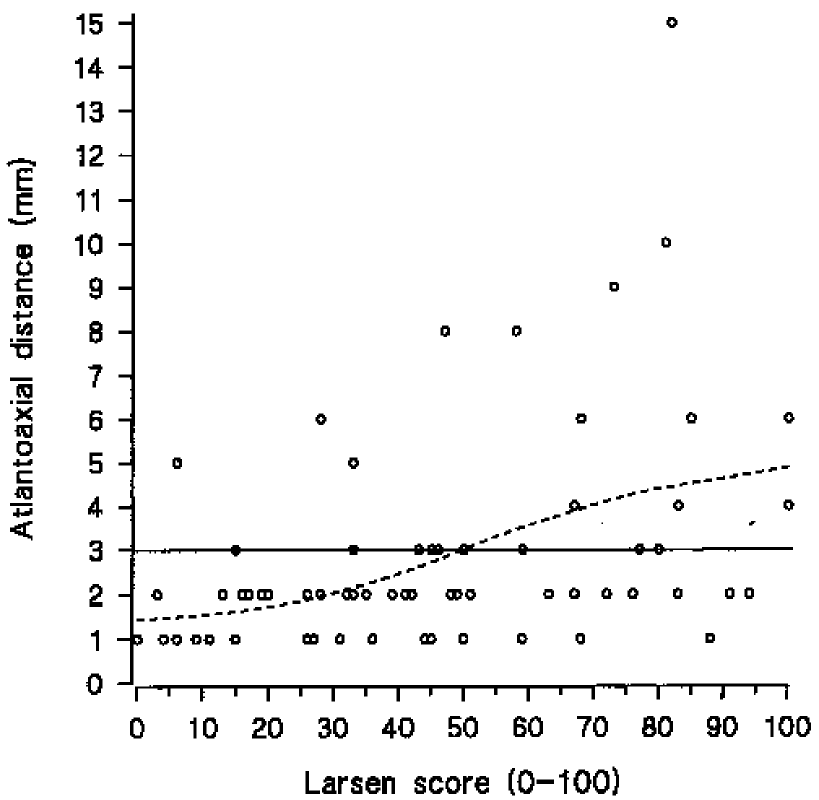

Fig. 1. Scatter diagram of the atlantoaxial distance based on the Larsen score for the peripheral joints (0-100). The straight line demonstrates the limit of normal values for atlantoaxial distance (≤ 3 mm).

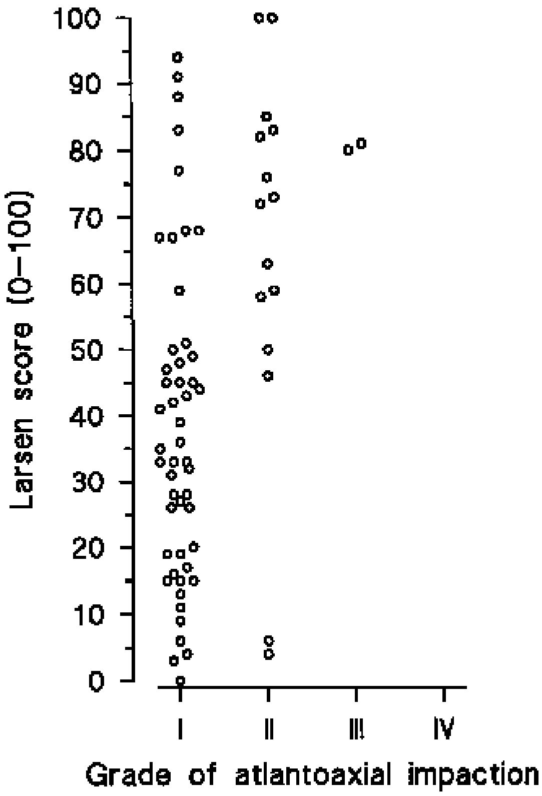

Fig. 2. Scatter diagram of the Sakaguchi-Kauppi grade of atlantoaxial impaction by the Larsen score for the peripheral joints (0-100).

ral and vascular structures in the area of spinal cord and brainstem, and thereby eventually result in quadriparesis or sudden death, patients with severe RA should have cervical spine radiographs taken at regular intervals and the frequency should be determined by the clinical state (22-25). Furthermore, cervical spine radio-graphs should always be evaluated be-fore major surgery to avoid serious complications caused by intubation during anaesthesia (26, 27).

Patients with RA often experience chronic pain in the neck and shoulder region. In our study patients with atlantoaxial disorders also presented destruction in the shoulder joints. Thus, in patients with destruction in either of these areas, both structures, as well as soft tissue surroundings, may be the origin of pain, which should be remembered in clinical work. In addition to careful clinical examination, advanced imaging methods such as ultrasound and magnetic resonance imaging may be needed for the successful treatment of pain in this region (28-30).

Previously, Rasker and Cosh (11) reported that the extent of aAAS is associated with the severity of MCP joint damage in long-term (15 years) RA. We also observed a positive relationship between the atlantoaxial distance and the severity of peripheral or shoulder joint destruction, although the correlation was not very strong (Fig. 1, Table II). However, one has to bear in mind that in patients with severe atlantoaxial facet joint disease, the roughness of the articular surface may reduce atlantoaxial movement or even stabilise the atlantoaxial joint to a certain position (9). For example, in the present study 6 out of 16 patients with aAAS presented "stabilized subluxation" in which aAAS occurred in both the flexion and extension positions of the neck. Because of this phenomenon, a strong correlation between the atlantoaxial distance and the severity of peripheral or shoulder joint destruction should not even be expected. Instead the progression of AAI is more closely related to the activity and duration RA and therefore also to the destruction of the evaluated joints. This correlation can be observed in Figure 2, although in the

Table III. Lumbar spine and femoral neck *Z*-scores of bone mineral density (BMD) in RA patients with and without atlantoaxial disorders (aAAS or AAI).

	Patients without atlantoaxial disorders		Patients with atlantoaxial disorders		p value
	N	BMD *Z*-score Mean (95% CI)	N	BMD *Z*-score Mean (95% CI)	
Lumbar spine	37	0.45 (-0.20 to 1.11)	16	-0.35 (-0.97 to 0.27)	0.13
Femoral neck	40	-0.30 (-0.63 to 0.04)	17	-1.00 (-1.48 to -0.52)	0.019

BMD Z-score: number of standard deviations from the mean BMD of age- and sex-matched healthy controls; CI: confidence interval.

present study the small number of patients with severe AAI prevents extensive analysis.

According to post-mortem examinations and plain radiographs, osteoporosis is commonly observed in rheumatoid cervical spine, and has been suggested to be involved in the development of atlantoaxial disorders (1, 14, 24, 27). Since BMD of the cervical spine is difficult to examine and normal BMD values are not available, BMD of the lumbar spine and femoral neck were used in the present study. Interestingly, patients with atlantoaxial disorders presented lower BMD at the femoral neck than the other patients. However, the decrease in BMD of the lumbar spine in patients with atlantoaxial disorders when compared with the other patients did not reach statistical significance. Previously, osteophytes and end plate erosions have been described to affect the measurement of BMD at the lumbar spine (31). Therefore in older patients, as in our study, it is more reliable to measure BMD of the femoral neck. On the basis of our results, we propose that highly destructive disease with cervical spine changes may cause axial loss of bone due to inactivity and/or inflammation. On the other hand, decreased BMD in the cervical spine may be a contributing factor in the development of aAAS and AAI. To further evaluate the influence of osteoporosis in the development of cervical spine changes, additional studies are needed.

In spite of variability in the diagnostic criteria of SAS, the presence of SAS has been reported to be associated with erosions in the peripheral joints (4, 8, 11). In the present study, no correlation was found between SAS and the destruction of peripheral or shoulder joints. Instead, the occurrence of SAS and subaxial disc space narrowings was associated with late onset age of RA, indicating that patients with these disorders were older and therefore also presented more degenerative changes in their cervical spine. Indeed, subaxial disc space narrowings most frequently occurred in the disc space C5/6, which is more likely to be affected by degenerative disease than RA. In conclusion, we suggest that in the majority of patients, SAS and disc space narrowing were caused by degenerative disease rather than RA itself.

Taken together, the existence of cervical spine disorders in patients with severe peripheral joint disease should be taken into account in clinical work in order to diagnose and effectively treat these disorders. Moreover, rheumatoid patients with severe peripheral joint disease are also likely to have low BMD, which may contribute to further destruction of the cervical spine and thereby increase the risk for complications caused by these disorders.

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