

# High Mortality in Patients with Rheumatoid Arthritis and Atlantoaxial Subluxation

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**ABSTRACT. Objective.** To study relationships between atlantoaxial subluxation (AAS) and total mortality in patients with rheumatoid arthritis (RA).

**Methods.** Radiological reports and clinical files of patients with RA were reviewed for the presence of cervical spine involvement verified by cervical radiographs.

**Results.** Among 241 patients with cervical radiographs, anterior AAS  $\geq 4$  mm was found in 5% [95% confidence interval (CI) 2–8] of patients. Vertical and posterior subluxations were found in 1.4 and 0.5%, respectively. The mean observation time from RA diagnosis to AAS was 3.9 years. Patients with AAS had 8 times higher mortality than patients without AAS (95% CI 3–25). According to the death certificate, the patients died from cancer, stroke, and myocardial infarction. Cervical spine disorder was not mentioned on the death certificate. However, an autopsy was not performed.

**Conclusion.** We found high mortality in RA patients with AAS. AAS in the cervical spine developed relatively early in the course of the disease. Analyses adjusted for seropositivity, erosiveness, and glucocorticosteroids did not reduce the mortality rate ratio. Our results underline the need for careful evaluation of patients with RA with respect to development of AAS. (J Rheumatol 2001;28:2425–9)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS  
ATLANTOAXIAL SUBLUXATION

MORTALITY  
SUDDEN DEATH

Patients with rheumatoid arthritis (RA) have 2–3 times higher total mortality than the general population<sup>1,2</sup>. A high risk group may be patients with involvement of the cervical spine. This may cause severe complications, including neurological morbidity such as paresthesia, cervical myelopathy, vertebrobasilar insufficiency, and even sudden death due to brainstem and spinal cord compression<sup>3</sup>.

The rheumatoid inflammatory process may affect any cervical spine segment. The most common abnormality is atlantoaxial subluxation (AAS), which is due to destruction of the transverse ligament, with subsequent laxity. Destruction may cause anterior, posterior, lateral, or vertical subluxation<sup>3</sup>. Cervical subluxation may develop within 2 years of onset of peripheral erosive disease, but more often, such manifestations develop rather late in the course of disease<sup>4</sup>.

The prevalence of cervical abnormalities in RA and the associated neurological complications are still debated. The prevalence of such features has been reported in 17–88% of patients, and neurological complications are found in 11–70%<sup>3–8</sup>. This large variation in prevalence may be due to

the different populations examined and different neurological and radiological classification systems employed<sup>3,9</sup>. Autopsy studies report cervical damage in 30–46% of patients with RA<sup>5,7,10</sup>, and it has been estimated that about 10% of patients with RA die from undiagnosed spinal cord or brainstem compression<sup>11,12</sup>.

We evaluated relationships between AAS and total mortality in patients with RA.

## MATERIALS AND METHODS

**Patients.** All records of 2282 patients registered at the Department of Rheumatology at the University Hospital of Tromsø between 1987 and 1996 with an ICD-9 diagnosis of 714.0 through 714.9 were reviewed. Some patients had records from the start of the Department of Rheumatology in 1978. When ascertaining the diagnosis of RA, we carefully excluded patients with other rheumatic diseases such as juvenile RA (714.3), undifferentiated polyarthritis (714.9), cases that could not meet the 1987 American Rheumatism Association (ARA) criteria of RA<sup>13</sup>, and misfiled records. Altogether 1154 patients satisfied the ARA 1987 criteria. Patients above the age of 16 at the time of diagnosis in 1987 or later with residential address in the 2 northernmost counties (Troms and Finnmark) were selected for this study. To ensure a representative mortality of patients, we had to restrict the study to patients diagnosed after data registration had started in 1986 in our hospital. Thus, a total of 463 patients were included in the analysis. Cervical radiographs were done in cases that had symptoms of the neck, in cases prior to surgery, and occasionally merely as a routine procedure in RA.

For most of the period, our Department of Rheumatology was the only specialist referral center of rheumatology in this region with a population of 225,000 over a vast area of 74,624 km<sup>2</sup>. The policy of the general practitioners is to refer all patients with suspected RA. Part of the time there was one private practitioner of rheumatology in the area, for whom the department served as a tertiary center. Thus, the large majority of patients with RA in the region were diagnosed and followed by us.

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Submitted May 31, 2000; revision accepted June 15, 2001.

**Methods.** All our patients' projections of cervical spine were taken in full extension and flexion, including vertical projections. All radiographs were initially examined by 2 radiologists. Data for this study were collected retrospectively from radiology reports. In addition, an experienced radiologist and one of the authors (TR) reexamined the images of the patients with AAS. Anterior atlantoaxial subluxation (AAAS) was defined as an atlanto-dental interval (ADI)  $\geq 4$  mm, in neutral position. This was measured from the posterior surface of the anterior arch of the atlas to the anterior aspect of the dens along a perpendicular line to the dental axis<sup>14</sup>. AAAS was also diagnosed if a normal ADI in neutral position increased to  $\geq 4$  mm during flexion. In addition, the posterior dental interval (PDI), which is the diameter of the canal, was measured from the posterior border of dens axis to the posterior arch of atlas. A PDI  $< 14$  mm was considered pathological<sup>15</sup>. A perpendicular distance  $< 13$  mm from the center of the pedicles of the axis to the line connecting the anterior and posterior arch of atlas was defined as vertical subluxation (VS)<sup>9</sup>.

For this study we reexamined the radiographs of the patients with AAS present — we were able to find 7 of the 11 radiographs. Images from 4 patients could not be reevaluated because films are destroyed after a certain time if the patient has died or moved. Data from the patients whose radiographs could not be found come from the original radiology reports. As time of diagnosis of RA and AAS was recorded in whole years, we assumed the diagnosis to be set July 1 of the corresponding year.

The Data Inspectorate in Norway gave permission for record linkage and the Norwegian Board of Health permitted access to death certificates, which consist of date and cause of death of patients, through record linkage to Statistics Norway. All inhabitants of Norway have since 1961 had a personal registration number. Patients who died were identified automatically by using their personal identification numbers. From this register we could assemble time and cause of death. The 463 patients with RA were followed from diagnosis until death or to December 31, 1996. We have used the WHO International Classification of Diseases (ICD-8, ICD-9, and ICD-10)<sup>16-18</sup>.

**Statistical analysis.** All analysis was performed with the EPI-Info statistical package<sup>19</sup> and SAS<sup>20</sup>. A  $p$  value  $< 0.05$  was considered significant. To test for any relation between AAS and risk of death, the Cox proportional hazards model (time to event analysis) was applied<sup>21</sup>. AAS was entered in the model as a time-dependent covariate, being 0 before the subluxation was diagnosed or if subluxation was never diagnosed, and 1 after subluxation was diagnosed.

## RESULTS

Among the 463 patients selected for study, 241 cases (52%) had cervical radiographs available, as radiographs were not taken in 222 patients. Demographic features of patients are shown in Table 1. Of 241 patients with cervical spine radiographs, 11 cases of AAS were found (5%) [95% confidence

interval (CI) 2–8]. Although the patients with RA who developed AAS were 6 years older at diagnosis than patients who did not have AAS, this was not statistically significant (sex adjusted  $p = 0.2$ ). The mean observation period from year of diagnosis for patients with AAS was 6.1 years, of which 3.9 years were before the diagnosis of AAS. The 230 patients without AAS were followed for a mean of 5.4 years. The difference between the 2 groups with regard to total length of followup was not, however, statistically significant (sex and age adjusted  $p = 0.3$ ). Patients with unknown AAS status were older at diagnosis than patients without AAS (sex adjusted  $p = 0.006$ ), and they were followed for only 3.9 years (sex and age adjusted  $p \leq 0.004$  for comparison with both the 2 other groups of patients). The frequency of general erosive disease was higher in RA patients with AAS than in patients without AAS (sex and age adjusted  $p = 0.06$ ), but the occurrence of serum rheumatoid factors and use of corticosteroids were similar in the groups with available radiographs (sex and age adjusted  $p \geq 0.6$ ). The frequency of erosive disease and use of corticosteroids (but not seropositivity) were lower in patients with unknown AAS status than in patients without AAS (sex and age adjusted  $p < 0.01$ ).

**Combinations of dislocation.** AAAS was found in all 11 patients with ADI  $\geq 4$  mm (Table 2). One patient also had a PDI  $< 14$  mm (Patient 4), and 3 had a VS  $< 13$  mm (Patients 5, 9, 10), but only one of these (Patient 10) had a superior migration of the dens. Thus, vertical and posterior subluxations were found in 1.4 and 0.5%, respectively, of patients with available radiographs.

No patient had lateral subluxation. Six patients had ADI in the range 4–9 mm, whereas ADI  $\geq 10$  mm was found in 5 patients. The greatest ADI in our series was 12 mm, in 2 patients. One patient underwent surgery due to cervical subluxation.

**Mortality related to cervical luxations.** Table 3 shows that patients who had AAS diagnosed during the followup had higher total mortality than subjects with a normal cervical spine radiograph or patients who never had a cervical radiograph. In analysis adjusted for sex and age, but not taking

Table 1. Demographic and clinical data of patients with RA according to presence of atlantoaxial subluxation.

|   | AAS<br>Diagnosed       | AAS Not<br>Diagnosed   | AAS<br>Unknown         |
|---|------------------------|------------------------|------------------------|
| No. of patients                                 | 11                     | 230                    | 222                    |
| % Women   | 55                     | 65                     | 62                     |
| Age at diagnosis, yrs, mean (SD)<br>(range)     | 62.3 (11.7)<br>(40–77) | 56.2 (14.4)<br>(19–88) | 60.1 (15.5)<br>(20–87) |
| Duration of followup, yrs, mean (SD)<br>(range) | 6.1 (2.5)<br>(1.9–9.5) | 5.4 (2.5)<br>(0.5–9.5) | 3.9 (2.7)<br>(0.1–9.5) |
| % with erosive disease                          | 100                    | 72                     | 58                     |
| % Seropositive                                  | 64                     | 57                     | 48                     |
| % Ever used corticosteroids                     | 73                     | 74                     | 61                     |

Table 2. The 11 patients with RA and AAS.

| Patients | Sex | ADI, mm | PDI, mm | VS, mm | Sudden Death |
|----------|-----|---------|---------|--------|--------------|
| 1*       | M   | 6       | > 14    | > 13   |              |
| 2        | F   | 4       | > 14    | > 13   |              |
| 3*       | F   | 10      | > 14    | > 13   |              |
| 4        | F   | 10      | 13      | > 13   | No           |
| 5        | F   | 11      | > 14    | < 13   |              |
| 6        | M   | 12      | > 14    | > 13   |              |
| 7        | M   | 7       | > 14    | > 13   |              |
| 8        | F   | 5       | > 14    | > 13   | Yes          |
| 9        | F   | 5       | > 14    | < 13   |              |
| 10*      | M   | 12      | > 14    | < 13** | Yes          |
| 11*      | M   | 4       | > 14    | > 13   | No           |

ADI: atlantodental interval, PDI: posterior dental interval, VS: vertical subluxation. \* Radiographs were not available for 4 patients (destroyed after a certain amount of time if the patient had died/moved). Data are from radiology reports. \*\* The dens had penetrated foramen magnum with medulla oblongata riding over the top of the dens.

Table 3. Total mortality in RA patients with and without AAS and AAS status unknown.

|  | AAS Present    | AAS Not Present | AAS Unknown   |
|--|----------------|-----------------|---------------|
| No. of patients                        | 11             | 230             | 222           |
| No. of deaths                          | 4              | 18              | 34            |
| Mortality per 100 patient-yrs (95% CI) | 5.9 (1.6–15.1) | 1.4 (0.8–2.2)   | 3.9 (2.7–5.4) |
| MRR adjusted for age and sex (95% CI)  | 2.9 (0.9–8.9)  | 1.0 (ref.)      | 1.9 (1.1–3.4) |

MRR: mortality rate ratio.

into consideration when the AAS was diagnosed, the patients who developed AAS had 3 times higher mortality than patients without AAS (mortality rate ratio, MRR = 2.9, 95% CI 0.9–8.9). As well, patients with unknown AAS status had an increased mortality compared to patients without AAS (MRR = 1.9, 95% CI 1.1–3.4).

Using the Cox proportional hazard model, analysis was restricted to the 241 patients with available radiographs of the cervical spine. Adjusted for age at diagnosis and sex, the MRR was 8 ( $p = 0.0004$ ). However, the 95% CI was very wide (3–25). Adjustments for seropositivity, erosiveness, and glucocorticosteroid use did not reduce the MRR estimate.

There were 4 deaths among the 11 patients with AAS. According to death certificates the causes of death were cancer (2 patients), stroke, and myocardial infarction. Unfortunately, no patient had an autopsy. Cervical spine disorder was not mentioned on the death certificates. The patient with both vertical and anterior subluxation (Table 2, Patient 10) had a magnetic resonance imaging (MRI) inves-

tigation 5 months before his sudden death. It showed a dens penetrating the foramen magnum with medulla oblongata riding over the top of the dens.

## DISCUSSION

We analyzed total mortality in patients with cervical spine rheumatoid subluxation verified by cervical radiographs in a cohort of patients with RA. To our knowledge, this is the first survey dealing with total mortality in patients with AAS compared to other RA patients. As our department is responsible for all rheumatic care in a population of 225,000, it is likely that the vast majority of patients diagnosed between 1987 and 1996 were registered in our hospital records. A few patients with relatively mild RA have, however, been treated by a private rheumatologist in a remote part of the region. Thus, this RA cohort appears to represent patients with RA in the 2 northernmost counties in Norway.

The frequency of AAS in RA in this study was 5% (95% CI 2–8). This is low compared to the prevalence of 17–88% reported previously<sup>3,5,7</sup>. There are many possible reasons for this discrepancy. Different studies have applied different criteria for AAS (in our study  $\geq 4$  mm), and the length of followup has varied. The most important reason is probably that we treat the great majority of patients with RA in the population, thus we see a lower prevalence of AAS than hospitals that treat only the most severe cases. An additional problem is that a large proportion of the patients were never examined for AAS. Thus, the prevalence of AAS in our RA patients is currently unknown, but lower than in most previous studies, as there is no reason to believe that the prevalence of AAS in patients with unknown AAS status is much higher than in patients with known AAS status.

However, determining the prevalence of AAS in RA was not our purpose — the aim was to investigate the mortality of patients with and without AAS. A relevant question is therefore whether the lack of information about AAS status in a part of the population influenced the mortality rate ratios, quite apart from the fact that it increased the 95% CI due to the lower number of cases. We do not, however, find it likely that the relationship between AAS and mortality is different in a population with known and unknown AAS status. Even if we assume that no RA patient with unknown AAS status had AAS, the relationship between total mortality in patients with AAS was increased more than 6 times (95% CI 2–17). One should also keep in mind that there may be patients with AAS included in the patients that we classified as being without AAS, as AAS may have developed after the last radiograph was taken. If AAS increased the mortality, as our results clearly indicate, this misclassification has reduced the MRR found in our study.

The average length of time between the diagnosis of RA and the diagnosis of AAS was 3.9 years. The first patient with AAS was diagnosed the same year as the diagnosis of

RA was established. AAS is usually a late development in the course of the disease<sup>22</sup>. Our figures, however, correspond to findings of Weissmann and co-workers<sup>4</sup> and Winfield and co-workers<sup>23</sup>, who found that AAS may develop as early as within 2 years of RA disease onset. AAAS is recognized as the most common rheumatoid abnormality in the cervical spine<sup>3</sup>, and such a manifestation was found in all RA patients with AAS in this study. In this respect our findings are in agreement with results from hospital and population studies<sup>3,24</sup>. AAAS was in most cases of rather moderate severity, but 5 out of 11 cases had subluxation of 10 mm or more.

According to some workers<sup>15</sup>, there is a strong correlation between posterior dislocation and neurological manifestations. It is suggested that pathological PDI and vertical subluxation are better correlates to neurological deficit in RA. However, PDI is more difficult to evaluate on plain radiographs than the ADI. Also, a normal ADI may conceal a vertical subluxation. On the other hand, ADI was chosen since it was a readily available measurement given in the radiological report. As only one patient in this series had a PDI < 14 mm, a possible relationship with mortality could not be analyzed further.

There have been some case reports of sudden death in RA patients with AAS<sup>25-27</sup>. Davis and Markley in 1951 were the first to document the relationship between AAS in RA and sudden death<sup>28</sup>. In 1975, Mikulowski and co-workers, in a postmortem study of 104 patients with RA, listed cervicomedullary compression from AAS as the cause of death in 11 patients, of whom 7 died suddenly<sup>11</sup>. Our report is the first systematic analysis of mortality of patients with AAS and RA.

A major bias would have been introduced if patients with a high risk of dying were preferentially subjected to radiographs and thereby having a greater chance of obtaining an AAS diagnosis. A number of studies have found that the majority of cervical subluxation is clinically silent<sup>6,9,11</sup>. In all 4 patients with AAS who died, the AAS was diagnosed during followup of their RA, not because of radiographs taken, for example, due to surgery. Therefore, the increased risk of dying in patients with AAS can probably not be explained by a higher likelihood of detecting AAS in RA patients with known serious comorbidity (Berksonian-like bias)<sup>29</sup>.

We found high mortality in RA patients with AAS. No deaths caused by rheumatoid cervical spine deformities were found in the official death statistics, as AAS (ICD classification)<sup>16-18</sup> is very rarely used as a cause of death. If AAS is recognized by the attending physician as cause of death, the diagnosis registered will most probably be RA. If a patient dies suddenly, "sudden death" may be a diagnosis of choice. This diagnosis, however, initiates investigation by public authorities, and doctors may therefore be reluctant to apply such a diagnosis. It is even possible that the death of

a person may be attributed to another known coexisting nonrheumatic disease, although the real cause of death was cervical spine deformities. In this study, of the 4 patients with AAS who died, all had sustained high RA disease activity — 2 died suddenly and stroke was registered as the cause of death in one of them. This was the same patient who had MRI investigation 5 months before death; the MRI showed a dens penetrating the foramen magnum with medulla oblongata riding over the top of the dens. We tentatively conclude that death certificates do not appear useful as instruments estimating causes of sudden death in RA, unless based on autopsy results.

It has also been reported that severity of cervical spine destruction correlates to the severity of the peripheral joint disease<sup>30</sup>. Glucocorticoid therapy has been linked to rheumatic cervical spine changes in a number of investigations<sup>31</sup>. Kauppi and co-workers in Finland showed, however, that low dose glucocorticoid treatment is not involved in the development of rheumatoid changes in the upper cervical spine<sup>32</sup>. We did not find a higher proportion of ever-users of glucocorticoids in cases with AAS, compared to those without AAS. Patients with diagnosed AAS tended to have radiological erosions more often ( $p = 0.06$ ), possibly indicating more severe disease.

It is also our clinical impression that patients with AAS as a group are among the RA patients with the highest disease activity. All 11 patients with AAS had severe RA with erosions and elevated erythrocyte sedimentation rate. We have adjusted the relationship between AAS and mortality for some possible confounders (seropositivity, erosiveness, glucocorticosteroids), and this did not reduce the mortality rate ratio. It is also difficult to see how any confounder alone could explain the very high MRR observed. The 95% CI is, however, very wide. Because of the paucity of cases, the point estimate from the Cox proportional hazard model also varies depending on how the model is specified. The figures given in the Results are those from the model that gave the lowest MRR estimate.

Our results call for larger studies to confirm our findings. As well, we believe there is a special need for autopsy in deaths of patients with RA. Our claim is that RA patients with AAS may have a high mortality. Our results underline the need for careful monitoring of the disease course in RA with respect to development of cervical spine involvement.

## ACKNOWLEDGMENT

The authors thank Eva A. Jacobsen, MD, PhD, Department of Radiology, University Hospital of Tromsø, for valuable comments to improve our manuscript.

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