

# Prevalence and associated factors of anterior atlantoaxial luxation in a nation-wide sample of rheumatoid arthritis patients

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## Abstract

### Objective

To estimate the prevalence of anterior atlantoaxial subluxation (AAS) in patients with rheumatoid arthritis (RA), and to analyse its association with disease markers.

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### Methods

Cross-sectional analysis of a cohort of RA patients randomly selected from the clinical registries of 34 centres. AAS, defined as an atlantoaxial displacement in cervical spine X-rays greater than 3 mm on flexion films, was actively searched for. Bivariate and multivariate analysis was performed to examine its association with clinical, functional, and treatment variables.

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### Results

AAS was found in 88 out of 736 patients with available cervical radiographs, (prevalence and 95% confidence interval [CI]: 12% [9.7–14.2]). The presence of AAS was highly associated with a Larsen score (0–150) over 50 (OR and 95% CI: 5.31 [2.68–10.55]), RA duration of more than 10 years (4.48 [2.70–7.44]), disease onset before age 50 (4.15 [2.42–7.12]), eye involvement (3.93 [1.63–9.46]), and previous RA related surgery (3.90 [2.46–6.19]). No association was found with rheumatoid factor. Multivariate analysis showed that a disease onset before the age of 50, the number of previous DMARD, and, above all, a Larsen score greater than 50 were important independent factors associated with AAS. There is a 33% increased risk for AAS every 10 units up in the Larsen score.

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### Conclusion

AAS is frequent in RA patients, particularly in those with markers of erosive disease.

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### Key words

Rheumatoid arthritis, cervical spine, atlantoaxial luxation.

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## Introduction

Cervical spine involvement in rheumatoid arthritis (RA) potentially affects any vertebral segment of the neck. Chronic synovitis at the synovial membrane surrounding the odontoid process leads to destruction of the transverse, alar, and apical ligaments, and the subsequent laxity causes anterior, posterior or vertical subluxation. Anterior atlantoaxial subluxation (AAS), also called anterior atlantoaxial luxation, is the most frequent type of cervical involvement in RA, as it is present in 50–70% of the cases (1–4). The prevalence of AAS ranges widely from 5% and 61% of RA patients (1–4), with differences in the occurrence of AAS between studies being mainly due to the methodological approach (5).

The relevance of AAS is the potential neural impairment due to instability of the odontoid process. Therefore, the elucidation of risk markers that alert rheumatologists on the development of AAS is of great importance. The purpose of this study was to determine the prevalence of AAS and its associated factors in a representative cohort of Spanish RA patients.

## Patients and methods

The EMECAR cohort (Estudio de la Morbilidad y Expresión Clínica de la Artritis Reumatoide) has been described in detail elsewhere (6–8). All patients included in EMECAR fulfilled the American College of Rheumatology 1987 criteria for the classification of RA (9) and were randomly selected from patient registries at 34 participating centres. All patients who entered the cohort signed a written consent form after being informed about the details of the study. The study protocol was reviewed and approved by the Research Ethics Committees of the principal investigators' participating centres.

Participant rheumatologists were instructed to collect the data and were trained in the performance of joint counts and other measurements. Data regarding current and previous treatments with disease modifying anti-rheumatic drugs (DMARD) were collected from the medical records and confirmed by the patient during the study visit.

Corticosteroid use was recorded as a categorical variable: never, less than 1 year, 1 to 5 years, 5 to 10 years, or more than 10 years of cumulative corticosteroid treatment. The number of RA-related surgical interventions, such as total joint replacements (TJR) or synovectomies, was also recorded.

All patients went through a physical exam, laboratory tests, and X-rays of both hands. Additionally, chest and cervical spine X-rays were performed if none were available for the period within one year previous to the baseline visit. An atlantoaxial displacement greater than 3 mm on flexion films was considered abnormal. Remission was defined as by Pinals and colleagues (10). The radiological damage was assessed in hand and wrist X-rays, which were read centrally by a trained radiologist blinded to the patient's record, and scored by the Larsen method with the Scott modification (range 0–150) (11). All patients completed a form with the Spanish version of the HAQ (12) to assess functional capacity.

## Statistical analysis

The data presented were obtained from a cross-sectional analysis of the baseline year of the EMECAR cohort (November 1999 to November 2000).

Mean differences between groups regarding continuous and non-parametrically distributed variables were analysed using the Student's *t* test and the Mann-Whitney *U* test, respectively. Association with categorical variables was tested with chi-squared or Fisher exact tests. Odds ratios were obtained from contingency tables. All estimates and confidence intervals were adjusted to the cluster sampling design using the *svy* commands of Stata (Stata 7.0, Stata corporation, Texas, 2001). Logistic regression was modelled in order to assess the independent effect of dummy variables on the presence or absence of AAS. In the logistic models, all variables which reached a *p* < 0.005 were added. A final logistic model was reached by using stepwise backward estimation, removing all variables with a *p* < 0.02.

## Results

A total of 1,329 patients were randomly

selected from an eligible population of 13,260 subjects. The final EMECAR sample comprised 788 patients, after discarding non-RA patients ( $n=135$ ), deceased persons ( $n=96$ ), non-located persons ( $n=238$ ), and those who refused participation ( $n=82$ ). A total of 562 (72.1%) of the patients included were women, with an average age of  $61 \pm 13$  years and a disease duration of  $10 \pm 8$  years (14.4% of the patients had less than two years of disease duration).

AAS was found in 88 out of 736 patients with available cervical radiographies, yielding a prevalence of 12% (95% CI: 9.7–14.2). Table I shows a description of the patients studied according to the presence of AAS. Patients with RA and AAS have a longer disease duration despite their younger age, reflecting an earlier onset of RA. The strongest associations with AAS in the bivariate analysis (first column in Table II) were a Larsen score over 50, a

disease duration longer than 10 years, a disease onset before 50, eye involvement, and previous RA-related surgery. The AAS prevalence increased with the duration of RA, from 3% in the group of patients with less than 5 years of RA to 26% in patients with more than 15 years of disease (Fig.1). AAS was not associated with gender or rheumatoid factor. Few patients were in remission in the AAS group (2.2% versus 4.7% in the non-AAS group), although the difference did not reach statistical significance (Table I).

Multivariate analysis (Table II, second column) showed that a Larsen score of 50 or greater (OR 4.03; 95% CI: 1.99–8.19) was the independent variable with the strongest association, followed by the number of DMARDs used (OR per DMARD used 1.32; 95% CI: 1.09–1.58). A disease onset before 50, even though it was selected for the stepwise models, did not reach a  $p$  value under

0.01, probably because an early onset is related to the Larsen score and the number of DMARDs, the other two variables included in the final model. The rest of the variables that reached statistical significance in the bivariate analysis were dropped from the final model by stepwise estimation.

In order to better quantify the effect of the radiological damage over the presence of AAS, a logistic model was carried out in which the Larsen score was categorized in 10 unit increments. The following variables were also included in this model for adjustment: the HAQ score, the presence of rheumatoid nodules, and the disease duration. The odds ratio for the Larsen score categorized in 10 unit increments was 1.33 (95% CI: 1.17–1.51), indicating a 33% increase in the possibility of presenting with AAS for every 10 unit increase in the Larsen score.

**Table I.** Description of patients with RA according to the presence or absence of anterior atlantoaxial subluxation (AAS).

	All patients	AAS present	AAS absent	p
No. of patients (%)	736 (100)	88 (12.0)	648 (88.0)	
Women, no. (%)	530 (72.0)	66 (75.0)	464 (71.6)	NS*
Age, mean years (SD)	61.4 (13.1)	58.2 (12.1)	61.8 (13.0)	0.01†
Age at RA onset, mean (SD)	48.3 (14.6)	39.7 (12.9)	49.4 (14.4)	< 0.001†
Disease duration, median years (P <sub>25</sub> -P <sub>75</sub> )	9 (4-13)	12.5 (9-19)	8 (4-12)	< 0.001‡
RF positive, N (%)	541 (73.6)	68 (77.3)	473 (73.1)	NS*
Remission, N (%)				
5 criteria, N (%)	31 (4.5)	2 (2.4)	29 (4.7)	NS**
4 criteria <sup>‡</sup> , N (%)	59 (8.5)	2 (2.4)	57 (9.3)	0.04**
HAQ, mean (SD)	1.2 (0.9)	1.5 (0.9)	1.2 (0.8)	< 0.001†
Larsen score, mean (SD)	54.6 (26.3)	74.4 (27.4)	52.3 (25.0)	< 0.001†
Rheumatoid nodules, N (%)	184 (25.0)	38 (43.2)	146 (22.5)	< 0.001*
Carpal tunnel syndrome, N (%)	81 (11.1)	11 (12.8)	70 (10.8)	NS*
Secondary Sjögren's syndrome, N (%)	121 (17.0)	21 (24.7)	100 (16)	0.04*
Interstitial lung disease, N (%)	25 (3.4)	4 (4.7)	21 (3.3)	NS**
Rheumatoid vasculitis, N (%)	9 (1.2)	2 (2.3)	7 (1.1)	NS**
Amyloidosis, N (%)	4 (0.6)	2 (2.3)	2 (0.3)	0.07**
Felty syndrome, N (%)	2 (0.3)	0 (0)	2 (0.3)	NS**
Serositis, N (%)	19 (2.6)	3 (3.5)	16 (2.5)	NS**
Eye involvement, N (%)	24 (3.3)	8 (9.1)	16 (2.5)	0.001*
Years with glucocorticoids, N (%)				
< 1	91 (14.2)	2 (2.4)	89 (16.0)	
1-5	278 (43.5)	27 (32.9)	251 (45.0)	
> 5	270 (42.3)	52 (64.2)	218 (39.1)	< 0.001*
Number of DMARDs used, mean (SD)	3.8 (2.0)	4.6 (2.1)	3.6 (1.8)	< 0.001‡
Number of TJR or synovectomies, mean (SD)	0.4 (0.9)	1.0 (1.3)	0.3 (0.8)	< 0.001‡

\*Chi-squared test; †Student's t-test; \*\*Fisher test; ‡Mann-Whitney test. <sup>‡</sup>Fatigue excluded.

AAS: atlantoaxial luxation; RA: rheumatoid arthritis; RF: rheumatoid factor; HAQ: health assessment questionnaire; DMARD: disease modifying antirheumatic drug; TJR: total joint replacement.

**Table II.** Measures of association (odds ratio and 95% confidence interval) of variables with the prevalence of atlantoaxial luxation (AAS) in patients with RA.

Variable	n	OR (95% CI)	p	Adjusted OR (95% CI)	p	Final model OR (95% CI)	p
Female gender	530	1.91 (0.71-1.98)	NS				
Disease onset before 50	383	4.15 (2.42-7.12)	*	2.20 (1.11-4.36)	0.02	2.37 (1.23-4.56)	0.010
10+ years with RA	326	4.48 (2.70-7.44)	*	1.15 (0.55-2.41)	0.38		
Positive rheumatoid factor	540	1.42 (0.82-2.45)	NS				
5+ years with corticosteroids	270	2.80 (1.72-4.54)	*	1.39 (0.69-2.77)	0.35		
HAQ score 1.5	307	2.01 (1.28-3.14)	0.002	1.04 (0.53-2.06)	0.90		
Larsen score 50	245	5.31 (2.68-10.55)	*	3.07 (1.43-6.59)	0.004	4.03 (1.99-8.19)	*
Rheumatoid nodules	184	2.61 (1.65-4.14)	*	1.48 (0.76-2.88)	0.251		
Carpal tunnel syndrome	81	1.21 (0.61-2.38)	NS				
Secondary Sjögren's syndrome	121	1.73 (1.01-2.95)	0.05				
Eye involvement	24	3.93 (1.63-9.46)	0.002	2.37 (0.57-9.92)	0.24		
Remission (4 criteria)	59	0.24 (0.06-1.02)	0.05				
DMARDs (per DMARDs used)	736	1.28 (1.15-1.42)	*	1.25 (1.02-1.52)	0.02	1.32 (1.09-1.58)	0.004
At least one RA-related surgery	165	3.90 (2.46-6.19)	*				

\*p &lt; 0.001

## Discussion

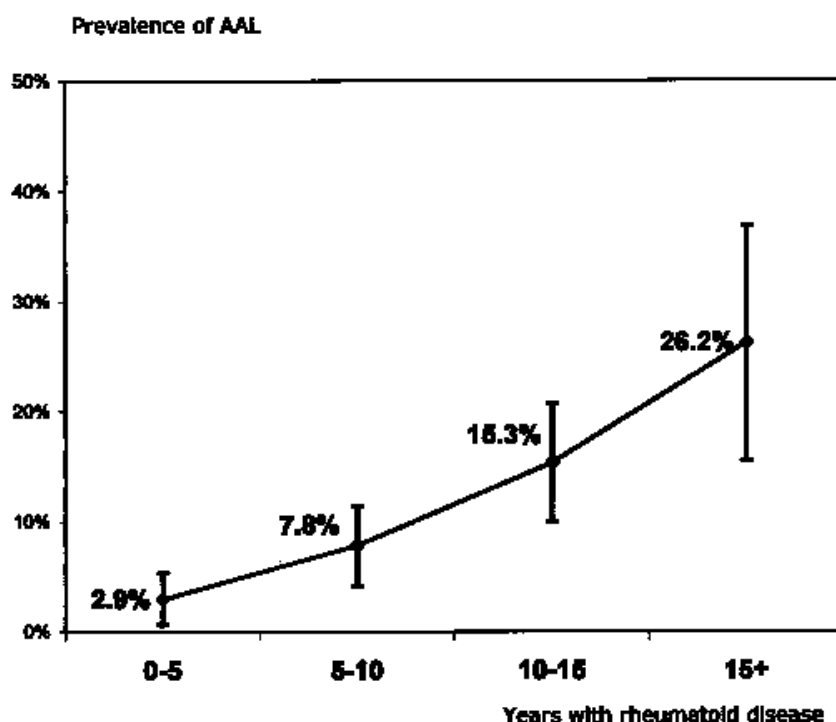
AAS is the most frequent presentation of atlantoaxial subluxation. The pathogenetic mechanism and clinical consequences are common to other types of cervical involvement (1-4), but AAS is easier to diagnose than the others, and most published studies focus on AAS, making comparisons between studies

less difficult.

We estimated the prevalence of AAS in a large and representative sample of Spanish RA patients (6-8), finding a realistic estimate of the actual occurrence of RA AAS in Spain of 12%. In other settings, the prevalence of AAS in RA patients has been found to fluctuate between 5% and 61% (13-22). Such

a wide range in AAS prevalence may be explained on the basis of the sample studied as well as on the different radiological classification systems used (e.g. 3 or 4 mm). Riise *et al.* found AAS (greater than 4 mm) in 11 of 241 (5%) RA patients in whom a cervical radiograph had been performed for neck symptoms, or prior to surgery, or, in an unknown proportion of cases, as a routine procedure (14). However, these authors did not actively search for AAS, as we did in the EMECAR cohort, and their population had suffered RA for a shorter time. A community-based study in Finland found a prevalence of several cervical complications in one-third of their patients, more than twice our estimate (18). However, the Finnish patients were older and had a longer disease duration than the EMECAR patients, in whom we have confirmed that the prevalence increases with the time from the diagnosis. The prevalence of AAS in Spanish RA patients is, nevertheless, similar to that found in 70 consecutive Malaysian patients (11%) and in 70 British matched control patients (6%), although the samples in this study were too small to draw any reliable estimate (20).

In the EMECAR study, AAS was associated with the duration of RA, and with the presence of rheumatoid nodules and other markers of severity, especially with radiographic damage, but no as-

**Fig. 1.** Prevalence of anterior atlantoaxial subluxation (AAS) in rheumatoid arthritis (RA) according to the disease duration.

sociation was observed with the presence of rheumatoid factor. As expected, few patients with AAS were in remission. Also, in patients with AAS the disease onset occurred a mean of 10 years earlier than in patients without AAS. Other studies have previously found an association with the duration of RA and with signs of aggressive disease, such as the presence of multiple joint involvement, rheumatoid nodules, high rheumatoid factor levels, severe erosive disease, high use of steroids, decreased bone mineral density, and vasculitis (16,19,21-23). Furthermore, Riise *et al.* found an 8-fold increased mortality in RA patients with AAS compared to patients without AAS (14). Secondary amyloidosis, a likely consequence of maintained inflammation, was not clearly associated with AAS in the results of our study, although Laiho *et al.* (25) showed AAS in 59 of 147 (40%) patients with RA and secondary amyloidosis.

The association of AAS with erosive RA and with extra-articular manifestations observed in our study and in previous studies could be considered a consequence of the longer disease duration in the AAS group. However, multivariate analysis shows that AAS is independently associated with more severe erosive RA, regardless the duration of RA. Riise *et al.* (14) found in their population that AAS occurred a mean of 3.9 years from the diagnosis of RA. Other authors have found an early occurrence of AAS (21, 26) and retardation of the development of rheumatoid atlantoaxial subluxations with DMARD combination therapy (27). Our study confirms and quantifies the large influence of the erosion score in the development of AAS.

In summary, AAS is present in a moderately high proportion of RA patients, especially in those with erosive disease. In view of our results, it would appear reasonable to conclude that avoiding or slowing radiological damage might reduce the risk of this potential life-threatening complication. The results of the EMECAR cohort over time will throw light on the effect of new approaches to disease management on AAS.

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