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**Prevalence and Predictors of Atlanto-Axial Subluxation in Rheumatoid Arthritis after
12-Years' Follow-Up (ESPOIR Cohort)**

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Conflict of interest statement

None of the authors has any conflicts of interest to declare.

All authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for

authorship and take responsibility for the integrity of this work.

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ABSTRACT

Objectives: Anterior atlanto-axial subluxation (AAS), defined as an anterior atlanto-dental interval (aADI) ≥ 3 mm, can occur in rheumatoid arthritis (RA) and carries a risk of severe neurological impairments. Our objective was to determine the prevalence and baseline predictors of radiographic aAAS after 12 years' follow-up of patients with early polyarthritis.

Methods: We studied patients enrolled in the early-polyarthritis cohort ESPOIR between 2002 and 2005 (at least two swollen joints for >6 weeks and <6 months, no other diagnosis than RA, and no previous exposure to glucocorticoids or disease-modifying anti-rheumatic drugs). All patients still in the cohort after 12 years had dynamic cervical-spine radiographs taken then read by two blinded observers. To evaluate how well combinations of tests predicted aAAS after 12 years, univariate analysis and multiple logistic regression procedure were applied.

Results: Of 323 patients followed for 12 years, 15 (4.6%; 95% confidence interval: 2.8 to 6.4) had aAAS. Among baseline variables, only IgA rheumatoid factors were associated ($p < 0.05$) to aAAS (sensitivity 60%, specificity 75%). Among data collected after 10 years, oral corticosteroid therapy during the 10-year interval, treatment by DMARDs, CRP (mg/dl), and positive tests for RFs were associated with aAAS after 12 years, but only CRP and RFs remained in a model of logistic regression (combination predicted aAAS with a sensitivity of 60% for a specificity of 90%).

Conclusion: In conclusion, the prevalence of aAAS after 12 years was 4.6% in the ESPOIR cohort, with no patients having severe aAAS. No factors were found statistically associated to AAS at baseline, while CRP and RFs at 10 years are predictive factors of aAAS after 12 years

Keywords

Rheumatoid arthritis. Cervical spine. Radiography. Atlanto-axial subluxation.

Key messages

What is already known on this topic?

- Atlanto-axial subluxation occurs in patients with rheumatoid arthritis. Whether screening for cervical-spine lesions in all patients with RA for at least 10 years or in a subset of these patients characterised by risk factors might decrease the occurrence of neurological impairments is unknown.

What this study adds?

- This study found a prevalence of anterior atlanto-axial subluxation diagnosed by routine dynamic radiography (defined as an anterior atlanto-dental interval ≥ 3 mm) in patients followed up for 12 years after a diagnosis of early polyarthritis consistent with rheumatoid arthritis at 4.6% .
- No patient had severe anterior atlanto-axial subluxation defined as an anterior atlanto-dental interval ≥ 9 mm.

How this study might affect research, practice or policy?

- Given that atlanto-axial subluxation is uncommon, routine screening of all patients would have a low yield.

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INTRODUCTION

Atlanto-axial subluxation (AAS) chiefly occurs in patients with rheumatoid arthritis (RA), in whom chronic inflammation of the synovial membranes leads to bone erosions, ligament laxity, and spinal instability with a risk of neurological damage.^{1,2}

Anterior AAS (aAAS) is defined as an anterior atlanto-dental interval (aADI) ≥ 3 mm and severe aAAS as an aADI ≥ 9 mm and/or a posterior atlanto-dental interval (pADI) < 14 mm. Severe aAAS is associated with potentially severe neurological complications and requires surgical advice and radiological monitoring.^{3,4} Vertical atlanto-axial subluxation (vAAS) is defined by a Clark station grade 2 or 3 and/or a Sakaguchi-Kauppi grade 2 to 4.^{5,6}

Radiographic cervical-spine involvement has been reported in about 50% of patients with RA.⁵⁻¹⁰ However, when radiography, computed tomography (CT), and magnetic resonance imaging were combined, up to 80% of patients had some degree of cervical-spine involvement.^{1,11-13} The most common radiological abnormality was AAS, with 7.0% to 42.5% of patients.^{2,5,6,10,12,14,15}

There is general agreement that cervical-spine involvement with RA should be sought only in patients with suggestive symptoms.¹⁶ The symptoms lack specificity, however. Thus, C1-C2 involvement may manifest as neck pain, headache, nausea¹⁷ or, far more rarely, a progressive neurological deficit.¹⁸ Moreover, cervical-spine instability is very often asymptomatic.^{8,17,19,20} In one study, pain intensity at the C1-C2 level decreased significantly as anterior vertebral slippage increased.⁹ Cervical myelopathy, although rare,²¹ carries a poor prognosis with persistent disability despite surgery.¹⁷

Therapeutic advances in recent decades have significantly improved the course of RA, thereby decreasing the complication rate. Thus, decreases in destructive lesions of the cervical spine have been reported^{1,12,21-23} A 2015 meta-analysis showed a reduction in the prevalence of

aAAS from 36% (95% confidence interval [95%CI], 30% to 42%) before the 1980s to 24% (95%CI, 13% to 36%) in the 2000s ($p=0.004$).²¹

Cervical-spine involvement by RA has been described in studies with follow-ups of more than 5 years,¹⁰ 10 years,¹⁵ or 12 years.²⁴ A disease duration greater than 10 years may be the strongest predictor of cervical-spine damage.¹⁷ Other factors significantly associated with cervical involvement are onset before 45 years of age, neck pain, neurological symptoms, C-reactive protein (CRP) elevation, structural joint damage at the hands and/or feet, Sharp score alteration, prolonged corticosteroid therapy, failure of disease-modifying anti-rheumatic drugs (DMARDs), cervical instability at study enrolment, and presence of rheumatoid factors (RFs).^{6,15,17,18} Whether screening for cervical-spine lesions in all patients with RA for at least 10 years or in a subset of these patients characterised by risk factors might decrease the occurrence of neurological impairments is unknown.

The objectives of this ancillary study of the ESPOIR cohort of patients with early polyarthritis consistent with RA was to define the prevalence of aAAS after 12 years and to identify predictors of aAAS present at baseline.

METHODS

ESPOIR cohort

The ESPOIR cohort is a French prospective multicentre cohort of patients with early arthritis consistent with RA (clinicalTrial.gov NCT03666091).²⁵ Adults aged 18 to 70 years with possible early RA were referred by rheumatologists and general practitioners to one of 14 regional centres in France, which included 813 patients between 2003 and 2005. The main inclusion criteria were at least two inflammatory joints for at least 6 weeks but no more than 6 months, a definite or probable clinical diagnosis of RA, and no previous DMARD or

glucocorticoid therapy (except prednisone for less than 2 weeks in a dosage no greater than 20 mg/day or as a single intra-articular injection within 4 weeks before inclusion). The main exclusion criterion was a definite diagnosis of another inflammatory joint or connective-tissue disease. Patients were treated and monitored by their rheumatologists according to the standard of care, without predefined therapeutic strategies. Study visits at the relevant regional centre occurred every 6 months during the first 2 years then annually. At baseline and at each study visit, clinical and laboratory variables recommended for the management of early arthritis were recorded. For each patient at baseline, blood samples were sent to a central laboratory for determination of the CRP level (normal <5 mg/L), IgM and IgA RFs, anti-citrullinated peptide antibodies (anti-CCP2), and human leukocyte antigen (HLA)-DRB1* alleles which has been described as associated to radiological evolution of RA²⁵. At each visit, each patient completed the Health Assessment Questionnaire Disability Index (HAQ DI). After 10 years, CRP level, RFs (yes/no), and anti-CCP2 tests were done at the relevant centre. Radiographs of the hands and feet taken at baseline then 10 years later were used for a centralised determination of the van der Heijde-modified total Sharp score (mTSS). The ESPOIR cohort study protocol was approved in July 2002 by the ethics committee of Montpellier, France (N° 020307). All patients gave their signed informed consent before inclusion. Only patients meeting 2010 ACR/EULAR criteria for RA²⁶ (at any time) were included in the current study.

Cervical radiographs

Dynamic standard radiographs of the cervical spine in the fully flexed position were obtained 12 years after patient inclusion, digitised, and included in the ESPOIR database in .bmp and .jpeg formats. The odontoid sagittal diameter (O), aADI, Clark station, and Sakaguchi-Kauppi grade were measured in pixels (Figure 1).

The radiographs were read blindly by a junior radiologist (TG) and a junior rheumatologist (ALQ). The intraclass correlation coefficients indicated excellent inter-observer and intraobserver agreement (>0.8).²⁷ Each reader performed two measurements of each study variable. When the two readers disagreed about the presence of aAAS, they performed a second reading. If the disagreement persisted, the two readers and a more experienced reader worked together to achieve a consensus.

Each reader measured the distance from the anterior to the posterior border of the dens (O) and the distance from the posterior border of the anterior ring of C1 to the anterior margin of the odontoid (aADI). The Clark station of the atlas was determined by dividing the odontoid process into three equal parts in the sagittal plane; the anterior ring of the atlas being level with the middle and caudal third defined stations II and III, respectively. The Sakaguchi-Kauppi grade was determined based on the location of the superior facets of C2 relative to the line drawn along the inferior borders, midpoints, or superior borders of the arches of C1.

As digitised radiographs in .bmp and .jpeg formats did not allow usual measurements, we used proportions as previously described²⁷ to obtain the aADI from aADI/O, with aADI/O \geq 0.23 indicating aADI \geq 3 mm and aADI/O >0.74 indicating aADI \geq 9 mm (Figure 1). We defined vertical AAS (vAAS) as Clark station II or III and/or Sakaguchi-Kauppi grade 2 to 4.

Statistical analysis

Categorical data were described as n (%) and continuous data as mean (SD). Comparisons were with the χ^2 test or Fisher's exact test for binary variables and the Mann-Whitney U test for continuous variables.

We studied the prevalence of aAAS after 12 years of follow-up then compared patients with and without aAAS. Univariate analyses were carried out to look for associations linking aAAS to the baseline variables listed in Table 1. We built the same method to assess the ability of data collected after 10 years (listed table 2) to predict aAAS after 12 years.

The statistical analyses were performed using SPSS software version 25.0 (IBM, Armonk, NY) and the R programme for logistic regression. Values of p smaller than 0.05 were considered significant, and all tests were two-sided.

To evaluate how well combinations of tests predicted aAAS after 12 years, 2 different procedures were developed. First, all tests with P values lower than 0.2 in the univariate analysis were combined by pairs; then the pair with the best diagnostic value was combined with a third selected laboratory test to determine the best combination of 3 tests and receiver operating characteristic curves were plotted. Second, a logistic regression procedure was applied to tests with P values lower than 0.20 in the univariate analysis using R++ (the next step, 2022, France).

Finally, we evaluated the correlation between the mean DAS28 and aAAS using spearman coefficient correlation.

RESULTS

Patients and prevalence of aAAS and vAAS

Figure 2 is the patient flow chart. Table 1 reports the main characteristics of the 323 patients. All patients had a diagnosis of RA, which was established at a mean age of 47.9 (SD 11.2) years.

For 8 patients, the two readers agreed that aAAS was present. The two readers disagreed about 18 other patients at the first reading but agreed for 16 patients at the second reading; 5 of these 16 patients were diagnosed with aAAS. For the 2 patients with persistent disagreement, the consensus reading established the presence of aAAS. Thus, aAAS was found in 15 (4.6%; 95% confidence interval [95%CI,] 2.8 to 6.4) patients. No patient had severe aAAS.

Both readers agreed that 5 (1.5%) patients had vAAS defined as Sakaguchi-Kauppi grade 2 and that no patients had Clark station II or III.

Factors associated with aAAS at baseline

Among baseline variables, mean IgA rheumatoid factors were associated with aAAS ($p=0.03$) but their binary evaluation (yes or no) was not significantly associated to aAAS ($p=0.06$), predicting it with a sensitivity of 60% for a specificity of 75% (table 1).

Factors associated with aAAS after 12 years

At 10 years, 2 received a biologic and / or targeted DMARD (one etanercept and one rituximab) among the 15 patients with aAAS versus 51/308 in the group without aAAS ($p=1.00$) but more patients received steroids in the group with aAAS (8/15) than in the group without aAAS (83/303) ($p=0.03$). Zero patients in the group with AAS and 20 in the group with AAS developed anti CCP, and only 4 in the group in the group with AAS and 19 in the group with AAS developed RF ($p= NS$). Among data collected after 10 years, oral corticosteroid therapy during the 10-year interval, CRP (mg/l), and positive tests for RFs were associated with aAAS after 12 years (table 2).

Only CRP and RFs remained in the model of logistic regression and their combination predicted aAAS with a sensitivity of 60% for a specificity of 88% (figure 3) with a moderate predictive value (positive predictive value 69% and negative predictive value 80%).

Correlation between the mean DAS28 and change in aAAS

We did not find any correlation between DAS28 and AAS at inclusion ($r=0.05$, $p=0.88$) and at 10 years ($r=-0.23$; $p0.66$).

DISCUSSION

Among patients with early RA, 4.6% had aAAS after 12 years. None had severe aAAS.

This prevalence is lower than in earlier studies: aAAS was found in 36% of patients before the 1980s and 24% in the 2000s.²¹ Inclusion in the ESPOIR cohort began in 2003, at a time when biological therapies were already available, allowing better disease control compared to earlier years. Of our patients, 33.4% of patients received a biological DMARD within the first 10 years, including 23.5% within the first 5 years.

Radiographs should be obtained routinely in patients with neurological manifestations.^{30,31} Cervical spine imaging is also necessary before anaesthesia, as neck manipulation during anaesthesia may cause neurological injury if the spine is unstable.^{32,33} Outside these two situations, screening radiographs might be useful in patients at high risk for AAS. Thus, predictors of AAS would help to identify patients for screening.

At inclusion, only IgA RF predicted aAAS in our population. Anti CCP give close results but the difference was not statistically significant. These factors are of adverse prognostic significance and indicate a higher risk of unresponsiveness to TNF antagonists.³⁴ The predictive value as assessed in our patients was nevertheless too limited to serve in everyday practice.

At 10 years, CRP elevation was the best test to predict aAAS 12 years later, although RFs positive tests, and previous treatment by oral corticosteroids were associated with aAAS after 12 years. Earlier studies also found an association between RFs and cervical-spine involvement by RA.^{15,17} A gradual decline in RF levels has been reported to accompany the decrease in clinical activity in patients given DMARDs³⁵ or biologic agents.³⁶⁻³⁹ However, RF assays have not been found helpful for monitoring disease activity⁴⁰ or the treatment response.⁴¹ Structural damage to the hands and/or feet and mTSS changes were associated with cervical-spine involvement by RA in several studies.^{6,15,17,18} Nevertheless, these factors did not predict aAAS in our cohort. Another risk factor was failure of DMARD therapy, sometimes with persistent CRP elevation.¹⁸

The evaluation of the risk of aAAS at inclusion was useful to justify a systematic evaluation of aAAS during the follow up, and the evaluation of at 10 years of the risk of aAAS a 12 years to justify an evaluation 2 years later. Another study could evaluate the area under the curve of inflammation and treatment course to estimate their impact on the risk but the number of patients seems to small for relevant data.

One limitation of our study is that some of the initially included patients left the cohort within the first 10 years. The baseline characteristics did not differ significantly between these patients and those remaining in the cohort.⁴² Another limitation is that patients in the ESPOIR cohort may be treated more aggressively than the general population of patients with RA (33.4% received a biological DMARD within the first 10 years) but this cohort started 20 years ago and the treatment of RA is now more standardized.. AAS was sought using only standard radiographs, and more sensitive imaging techniques might have produced a higher prevalence. Cervical radiographs were not performed at inclusion and we cannot exclude fortuitous aAAS preexisting to rheumatoid arthritis, although the risk is very low as the prevalence in the normal population is very low. Finally, we did not confirm our cases by imaging follow up including MRI.

In conclusion, the prevalence of aAAS after 12 years was 4.6% in the ESPOIR cohort, with no patients having severe aAAS. Although some factors were found statistically associated to AAS at 10 years, given that aAAS is uncommon, routine screening of all patients would have a low yield. Indeed, the best combination of tests allowed predictive value (positive predictive value 69% and negative predictive value 80%) not good enough to select patients justifying radiographs. So, systematic radiographs are not justified in RA after 12 years, but remained necessary for patients with cervical pain or neurological sign, peculiarly in patients with RF and elevated CRP.

Figure 1: Standard lateral radiograph of the cervical spine in full flexion used to measure Schematic representation of the anterior atlanto-dental interval (aADI) and odontoid sagittal diameter (O) measurements (a) and of Clark station determination (b)

Figure 2: Flow chart of the study patients

Figure 3: Receiver operating characteristic curve at baseline at 10 years. The curves show the relationships between sensitivity and 1-specificity of each test at baseline [IgA rheumatoid factor assays] and at 10 years [for C Reactive protein, rheumatoid fr assays, and their combination] in discriminating between patients with and without aAAS at 12 years.

Footnote: We included in the model tests with *P* values lower than 0.20 in the univariate analysis which remained in a model of logistic regression

Table 1: Main features at baseline and at 10 years of the study patients and univariate comparisons of patients with vs. without anterior atlanto-axial subluxation (aAAS) after 12 years in the cohort

	aAAS n=15	No aAAS n=308	p value
At baseline			
Females, n (%)	11 (73.3)	239 (77.6)	0.70
Age (years), mean (SD)	43.6 (11.2)	48.1 (11.2)	0.12*
Height (cm), mean (SD)	166 (6.2)	164.9 (8.3)	0.43
Smokers (current or past), n (%)	9 (60.0)	144 (46.8)	0.43
Alcohol abuse, n (%)	2 (13.3%)	51 (16.6%)	0.99
Tender joint count (/28), mean (SD)	9.5 (7.2)	8.7 (7.0)	0.59
Swollen joint count (/28), mean (SD)	7.1 (6.3)	7.7 (5.2)	0.37
CRP mg/dL, mean (SD)	2.6 (3.9)	2.0 (2.9)	0.82
DAS 28, mean (SD)	5.2 (1.2)	5.1 (1.3)	0.68
HAQ, mean (SD)	1.0 (0.6)	1.0 (0.7)	0.74
IgM RF, n (%)	10 (66.7)	167 (54.2)	0.34
IgA RF, n (%)	9 (73.3)	161 (52.3)	0.06*
Anti-CCP antibodies, n (%)	9 (73.3)	83 (26.9)	0.12*
HLA-DRB1 shared epitope, n (%)	10 (76.9)	171 (57.8)	0.25
van der Heijde-modified total Sharp score mean (SD)	3.7 (4.2)	2.2 (5.2)	0.28
at 10 years			
Tender joint count (/28), mean (SD)	2.9 (7.4)	2.1 (4.3)	0.90
Swollen joint count (/28), mean (SD)	1.2 (1.9)	0.9 (2.2)	0.39
CRP mg/dL, mean (SD)	1.4 (1.7)	0.63 (1.9)	0.001**
DAS 28, mean (SD)	2.8 (1.5)	2.5 (1.3)	0.23
HAQ, mean (SD)	0.74 (0.61)	0.51 (0.59)	0.07*
RF n/N (%)	13/15 (86.7%)	152/299 (50.8%)	0.007**
Anti-CCP antibodies, n (%)	9/15 (60%)	141/308 (45.8%)	0.54
Seropositivity (RF or Anti-CCP antibodies), n (%)	13/15 (86.7%)	161/286 (56.3%)	0.02**
van der Heijde-modified total Sharp score, mean (SD)	19.2 (25.9)	12.9 (19.1)	0.76
Radiographic abnormalities, n/N (%)	9/15 (60%)	116/300 (38.7%)	0.11*
Oral corticosteroids n/N (%)	8/15 (53.3%)	83/303 (27.4%)	0.03**
DMARDs n/N (%)	14/15 (93.3%)	227/303 (74.9%)	0.13*

*p<0.02 but>0.05 statistically insignificant but included in the evaluation to determine the best tests ** p<0.05 statistically significant in the univariate analysis

aAAS, anterior atlanto-axial subluxation; VAS, visual analogue scale; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; RF, rheumatoid factor; CCP, cyclic citrullinated peptide

Table 2: Logistic regression using features at 10 years associated with anterior atlanto-axial subluxation (aAAS) after 12 years in the cohort

	OR (95% CI)	p
Rheumatoid factors (positive vs negative)	5.4 (1.2-24.7)	0.03
CRP (elevated versus normal)	5.5 (1.7-18.1)	0.005

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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DATA SHARING STATEMENT

The study data are available upon reasonable request to the principal ESPOIR-cohort investigator Alain Saraux (Brest).

AUTHORS' CONTRIBUTIONS

Substantial contributions to study conception and design: ALQ, TG, GCA, FG and AS ; substantial contributions to analysis and interpretation of the data: ALQ, TG, GCA, GM, YC, ARW, RMF, FG and AS; drafting the article or revising it critically for important intellectual content: ALQ, TG, GCA, GM, YC, ARW, RMF, FG and AS ; final approval of the version of the article to be published: ALQ, TG, GCA, GM, YC, ARW, RMF, FG and AS

DISCLOSURES

None

ETHICAL APPROVAL INFORMATION

The ESPOIR study was approved by the appropriate ethics committee (Montpellier, France; N° 020307) and was conducted according to good clinical practice guidelines (NCTO 164 8907). All participants gave written informed consent before inclusion.

PATIENT AND PUBLIC INVOLVEMENT

Patients and members of the public were involved in the design, conduct, and reporting of the research via a detailed description of the protocol available at <http://www.lacohorteespoir.fr>

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