Relevant incidence of cervical arthritis in patients with erosive seropositive rheumatoid arthritis even today

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Abstract

Objectives

This paper aims to investigate adherence to, and outcome of, radiographic screening of patients with rheumatoid arthritis (RA) for cervical involvement, given the availability of state of the art disease-modifying anti-rheumatic drug (DMARD) and biological therapies.

Methods

Cervical screening results and clinical information were obtained from the charts of 395 consecutive patients with rheumatoid arthritis who attended an academic rheumatology outpatient clinic in a 3-month interval. This sample was combined with eight patients who underwent C1-C2 fusion at the Department of Orthopaedic Surgery.

Results

Reports on cervical spine x-ray films were not found in the charts of 67 patients (17 %), including 21 (8 %) of the 257 patients with a disease duration of ≥5 years. Nevertheless, 17 (7%) of these 257 patients had an increased atlantodental distance. An additional 4 RA patients of the Department of Orthopaedics were added for a total of 21 patients with cervical arthritis, 13 of whom had no cervical symptoms. All 21 patients with cervical arthritis had erosive peripheral arthritis with at least 10 years of disease duration, and were positive for rheumatoid factor. Almost half of these patients were not under adequate DMARD therapy when cervical instability was diagnosed, and none were on biological response modifiers.

Conclusion

Screening for cervical arthritis is still of importance, especially in patients with erosive seropositive disease. In view of the documented incidence, adherence to screening protocols was disappointing.

Key words

rheumatoid arthritis, rheumatoid spine, screening, erosive disease, rheumatoid factor

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Introduction

Rheumatoid arthritis (RA) is well known to also affect the uppermost portion of the cervical spine, most commonly between cervical vertebrae C1 and C2. While this has been a leading cause of death in RA patients in former times (1-3), novel surgical approaches today allow for fusing the first two cervical bodies with good functional outcome (4-7). Cervical instability is often asymptomatic (8-11), and symptomatic disease may be beyond repair without sequelae (12). Accordingly, it is even more important that early, asymptomatic cervical spine involvement will not go unnoticed, and radiographic screening for atlantodental instability has been the current guideline in our division.

On the other hand, RA therapy has considerably changed in the last two decades (13-17), and the impression is that cervical involvement has become rather uncommon. Despite an absence of clear data on this question, there is some tendency to reduce adherence to screening recommendations because of such thoughts.

We therefore undertook to evaluate the adherence to the current guideline with regard to screening for cervical spine involvement, to investigate the actual occurrence of this complication, and to search for parameters that would predict an increased risk of a new diagnosis of cervical arthritis. Based on published experience and clinical experience, we explicitly analysed seropositive disease, long disease duration, high disease activity, and inadequate DMARD or biological response modifier medication (18-21).

Patients and methods

At the Rheumatology outpatient clinic of the University Clinical Centre of Dresden, informed consent to pseudonymised workup of clinical routine data is obtained from all consenting patients. Data of patients who chose not to consent are excluded. Data of patients who have not been asked (before this approach became standard) and cannot be asked because they are no longer in the care of the outpatient clinic are added in a pseudonymised way by the treating physician. This approach is in agreement with the German Laws and the Declaration of Helsinki, and approval was obtained from the Ethics Committee of the Clinical Centre and the Medical Faculty.

For a period of three months (November to February), the consecutive charts of patients with a diagnosis of seropositive (ICD M05.*) or seronegative (M06.*) RA were assessed. In addition, in order to enrich the sample for patients with cervical arthritis, information was obtained on all eight patients who had undergone C1:C2 fusion for RA cervical involvement at the Department of Orthopaedics. In the latter patients, in particular, the information on clinical disease activity and on serology was not always entirely complete, and, with missing documentation of physician global assessment, CDAI/SDAI values were not available on visits before 2007.

Whenever available, in addition to the reports of conventional x-ray films of hands and feet as well as the cervical spine in anteflexion, sex, age, and disease duration, all components of disease activity scores (swollen and tender joints, patient and physician global assessment, CRP and ESR), rheumatoid factor and anti-CCP antibodies were recorded.

Statistics

Categorical data were analysed by Fisher's exact test (for 2x2 tables) or χ^2 test. All group data were submitted to D'Agostino's K^2 test. If samples followed Gaussian distributions, Student's *t*-test was used, and data are represented as mean±SD. Otherwise, the Mann-Whitney U-test was employed, and data are given as median and range. *p*-values <0.05 were considered significant. Disease duration, seropositive and seronegative disease, disease activity (as measured by DAS28), erosive peripheral disease on hand and feet x-ray, and actual DMARD (none/conventional/biological) were predefined and were corrected for multiple comparisons (p_c). All other statistics are descriptive only.

Results

Patient sample

The total patient sample consisted of 395 patients with RA according to ACR

classification criteria (22) who had had a visit in the Rheumatology outpatient clinic from November 2009 to January 2010, partially overlapping with 8 RA patients who had undergone C1:C2 fusion for atlantodental instability at the Department of Orthopaedic Surgery, for a total of 399 RA patients. Three-hundred and five of the RA patients were female (76%), median patient age was 64 (17–90) years, median disease duration was 9 (0.7–55) years.

Compliance with local guideline

Despite a local guideline to perform radiographs of both hands and feet and of the cervical spine, including an x-ray film in anteflexion, documented reports of cervical spine radiographs were missing in 67/395 (17%), and even reports of hand and feet films were missing in 9 (2%) of the charts evaluated. Thereafter, 19 additional patients (all of them within their first five years of disease) had been sent for radiographs until August 2011, so that complete data of a total of 347 patients were available for evaluation (Fig. 1). When we took into account the fact that patients within their first five years of disease are unlikely to develop atlantodental instability, still 21 (8%) of the 257 patients with a disease duration of ≥5 years had no cervical films documented first.

Prevalence of cervical involvement

For 17 (5%) of the 347 RA patients with radiographs, *i.e.* 7% of the 236 patients with ≥5 years disease duration, a pathological anterior atlantodental distance of more than 3 mm was reported. Of the 17 patients, 12 patients (71%) had not reported symptoms suggestive of cervical spine involvement, while 3 reported neck pain, and one each headaches and dizziness. Three patients had had a first diagnosis of cervical arthritis before the year 2000, 6 between 2000 and 2004, and the remaining 8 since 2005. Of these 17 patients, 4 underwent cervical fusion surgery, while the remainder of the patients under modified DMARD therapy (methotrexate in 10, leflunomide in 1, and biologicals [±methotrexate] in 6 patients) remained stable for 6±3 years after the first diagnosis of atlantodental instability. This sample was increased by those 4 patients of the Department of Orthopedic Surgery who had not been cared for at the Rheumatology outpatient clinic, for a total of 21 patients with atlantodental instability (Fig. 2).

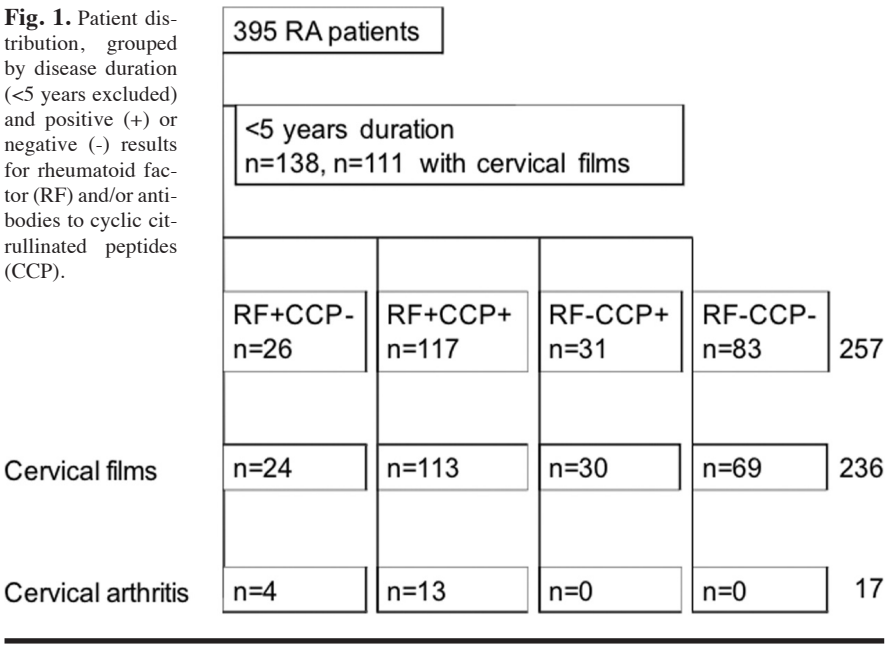

Fig. 1. Patient distribution, grouped by disease duration (<5 years excluded) and positive (+) or negative (-) results for rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptides (CCP).

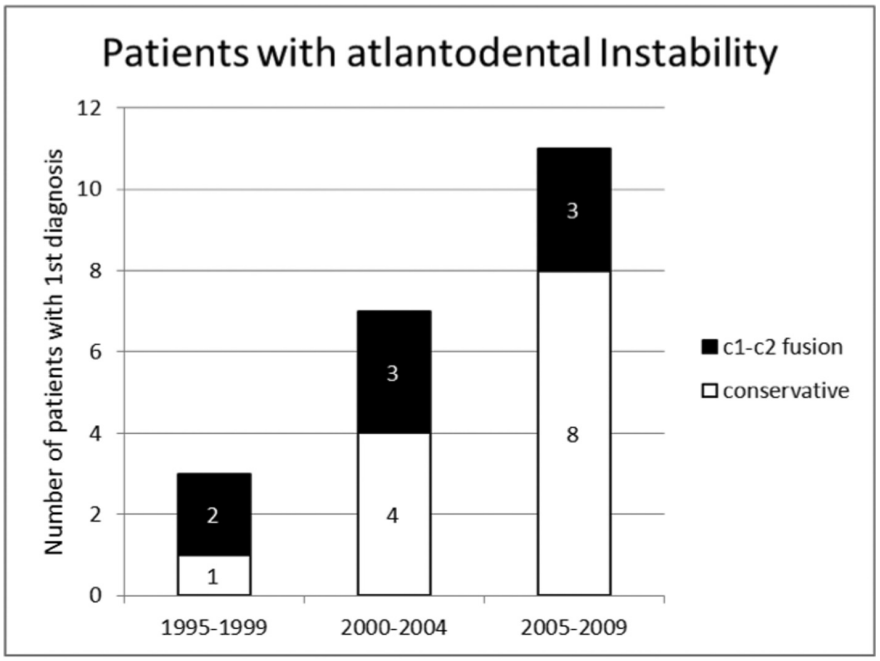

Fig. 2. Numbers of patients with a new diagnosis of an increased atlantodental distance in 5-year intervals, and relation to necessary, C1:C2 fusion (in black).

Characteristics of the patients with cervical spine involvement

We further analysed the characteristics of these 21 patients and compared them to those patients with normal atlantodental distance on cervical radiographs in anteflexion (Table I).

Patients with cervical involvement were older (69±9 years, median 69 [54–87] years) than patients without cervical involvement (median 64 [17–90] years, p=0.032), and had a significantly longer disease duration of 26.7±12.4 years (median 24 [10–55] years) than those without cervical arthritis (median 10 [0.7–55] years, p<0.0001, p_c<0.0005).

Table I. Clinical and laboratory variables of patients with and without atlantodental instability.

Patients	With cervical involvement		Without cervical involvement		*p*-value
	Mean±SD*	Median (25%/75%)	Mean±SD*	Median (25%/75%)	
Age (years)	69.2±8.8	69.0 (64.5/74.0)		64.0 (51.0/73.0)	0.0321
RA duration	26.7±12.4	24.0 (16.0/34.5)		10.0 (4.0/18.0)	<0.0001
RF (IU/mL)		122 (54/201)		32 (19/100)	0.0003
CCP (IU/mL)	943±1112	529 (94/1510)		103 (3/788)	0.0117
DAS28	4.2±1.8‡#	3.8 (2.5/6.3)‡#		2.7 (2.2/3.5)	0.0061
CRP (mg/L)		6.6 (3.6/10.9)‡		3.1 (1.1 7.0)	0.0090

*only if following a Gaussian distribution, ‡at the time of a first diagnosis of cervical arthritis, #DAS28 available for n=14.

Age and disease duration were significantly correlated, as expected (r=0.27, $p<0.0001$). Age at disease onset was not associated with an increased risk of developing spinal involvement: patients with increased atlantodental distance were a mean of 63±11 years, median 61 (46–86) years, at disease onset, patients with normal atlantodental distance 64 (17–90) years ($p=0.91$). All patients with cervical involvement in our sample had a disease duration of at least 10 years and were older than 50 years (Table I). In a subset of patients, normal radiographs of the cervical spine in anteflexion were available 3.5±1.2 years (maximum 5 years) before atlantodental instability was diagnosed. The percentage of female patients was not significantly different

All patients with cervical spine involvement had seropositive disease, whereas 151 of the 330 patients without cervical spine involvement (46%) were seronegative, a significant difference ($p<0.0001$, $p_c<0.0005$).

Most of the patients with atlantodental instability were positive for both rheumatoid factor (RF) and anti-CCP antibodies (ACPA). However, 4 of these patients (19%) had positive RF in the absence of ACPA, as compared to 33/330 patients (10%) without cervical spine disease. In contrast, no patient with ACPA, but no RF had a pathological cervical spine radiograph (as compared to 35/330 patients [11%] without cervical involvement).

Similarly, all 21 patients with cervical spine involvement had erosive disease at the hands and/or feet, while 105/330 patients (32%) with normal cervical spine radiographs had no erosions ($p=0.0008$). As expected, non-erosive patients were more frequently negative for RF and ACPA (61/105 and 62/105 patients, respectively), as compared to erosive patients (RF negative 90/246, $p=0.0003$; ACPA-negative 91/245, $p=0.0002$).

Disease activity and medication

Next, the disease activity of patients at the time of diagnosis of cervical arthritis (DAS28 available for 14 patients) was compared to the disease activity of patients without cervical involvement (DAS28 available for 327/330 patients). RA disease activity was higher in those patients who had developed atlantodental instability. These patients had higher DAS28 (4.2±1.8; median 3.8 [1.8–6.7] *vs*. 2.7 [0.3–6.2], $p=0.0061$, $p_c=0.035$), CRP (6.6 [1.0–52.6] *vs*. 3.1 [0–64.2] mg/L, $p=0.009$), and RF (122.3 [19–661.5] *vs*. 31.7 [0–763.5] U/ml, $p=0.0003$).

According to DAS28 cut-off values, 0/14 patients with increased *vs*. 144/327 with normal atlantodental distance were in remission and 4/14 (*vs*. 87/327) were in low disease activity, while 5/14 (*vs*. 90/327) were in moderate and 5/14 (*vs*. 6/327) in high disease activity ($p<0.0001$ in a χ^2 test). None of the patients with newly diagnosed cervical spine involvement met the new ACR/EULAR remission criteria (23), in contrast to 52/327 patients without cervical arthritis ($p=0.054$).

Cervical spine arthritis was newly diagnosed in 8/21 patients (38%) without current DMARD therapy (as compared to 5/330 in the control group), mostly after longer intervals of not having been seen by a rheumatologist. The 13 other patients with a new diagnosis of atlantoaxial instability were on conventional DMARDs (methotrexate in 10, and leflunomide, i.m. gold, and hydroxychloroquine, in one each). None of the patients with newly diagnosed cervical arthritis were treated with biological response modifiers at this time. In comparison, 272/330 patients without cervical arthritis were on conventional DMARDs and 66/330 patients (20%) on biological response modifiers (χ^2 $p<0.0001$, $p_c<0.0005$; categorised as no, conventional, or biological DMARD).

Discussion

In this study on RA patients of an academic centre's outpatient clinic, we have found a somewhat shocking discrepancy between the adherence to screening for upper cervical spine instability and the actual incidence of this condition. In fact, reports on cervical x-ray films in anteflexion were not found in the charts of 17% of patients. While this number dropped to 8% in patients with a disease duration of at least five years, and while some of that may have been due to failure to retrieve reports from patients, the actual finding is not reassuring.

After all, despite all advance in RA therapy, one in 15 patients with long-standing RA still had a pathological atlantodental distance. Although this number includes patients with disease onset well before effective drugs became available, approximately half of the patients were diagnosed with cervical arthritis during the last five years, when TNF blockade had long become standard.

On the other hand, there are also indications that the current approach to RA therapy (17) indeed reduces cervical involvement. Seven percent of patients with longer disease duration are clearly lower than what was reported in earlier cohorts, with prevalence ranging from 12 to 27% (18, 24-27). Approximately half of the patients had not taken any adequate DMARD in the period before cervical arthritis was detected, and no single patient with new onset cervical involvement was treated with a biological response modifier. Moreover,

instability often remained stable after adapting DMARD therapy, and C1:C2 fusion has so far not become necessary in the majority of patients.

In line with several other reports (8-11), the majority of patients had not reported symptoms suggesting cervical spine involvement. In fact, one of the patients undergoing C1:C2 fusion had been completely asymptomatic, when she had a syncope in the initiation phase of anesthesia for knee surgery, and C1:C2 fusion had to be performed on an emergency basis. Therefore, radiographic screening of asymptomatic patients is warranted.

In order to identify the RA patient population at particular risk of developing cervical instability, we compared the patients with cervical involvement to those without. In addition to the above-mentioned importance of consequent DMARD therapy, we have identified seropositivity for RF, erosive disease in hand and feet, high disease activity, and long disease duration, as risk factors for newly developing atlantodental instability.

Age and disease duration will always correlate to some degree. In our sample, the correlation was rather obvious, and both disease duration and age were associated with an increased risk for cervical arthritis. However, the more robust association was with disease duration rather than age. Moreover, if cervical arthritis were associated with age, one would expect some influence of the age at disease onset, which was not found. Therefore, at least ten years of RA disease duration appeared to be the more relevant parameter for predicting risk. Given that up to five years had passed since the last normal radiographs before diagnosis, this would again largely exclude patients of up to five years of disease duration.

The finding that cervical arthritis was associated with erosive peripheral disease came to no surprise (18, 21, 27). However, and while not securely excluding exceptions, it appears relevant that no single patient with non-erosive arthritis was found to have an increased atlantodental distance.

Since erosive disease has long be known to more commonly be seropositive disease (28-32), some association of seropositive disease with an increased risk was likewise expected. However, we have again not identified a single seronegative patient with upper cervical instability. While this does not firmly exclude that seronegative patients could develop C1/C2 arthritis, as occasionally reported in the literature (33, 34), the higher risk is with seropositive patients.

Much less expected (28, 35), however, was the finding that RF was superior to anti-CCP in predicting atlantodental disease. On the one hand, RF was significantly associated with an increased atlantodental distance, and anti-CCP antibodies were not. On the other hand, among patients with a disease duration of at least five years, one in six patients with cervical involvement had a positive RF only, in the absence of ACPA, while none of 30 patients with positive anti-CCP in the absence of RF had atlantodental instability (Fig. 1). Since disease activity was significantly higher in the patients with a new diagnosis of cervical arthritis, this better association with RF could stem from the fact that, in contrast to anti-CCP antibody levels, RF levels are known to fall when disease is controlled (36-39).

The results of this study are somewhat limited by its moderate sample size in that we can neither exclude that patients with seronegative or non-erosive diseases or patients under biological response modifiers might still develop cervical arthritis. However, our sample size has been sufficient to investigate important risk factors. In addition, the sample is completely unbiased in reflecting daily life in an academic outpatient clinic. Therefore, while one would hope that adherence be more complete elsewhere, we feel that non-adherence to screening for cervical arthritis probably is an issue, and when looking at the actual incidence in particular.

In conclusion, despite novel therapeutic approaches, we have found cervical arthritis in approximately five percent of the patients with rheumatoid arthritis seen at the division's outpatient clinic. More than two thirds of these patients were asymptomatic. Erosive seropositive rheumatoid with longer disease duration and inadequately controlled disease activity predicted increased risk. For this patient group, in particular, adherence to screening schedules for cervical arthritis is still essential, and regular monitoring for adherence to screening recommendations may be advisable.

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