Original Article

Prevalence of Atlanto-axial Subluxation in Patients with Rheumatoid Arthritis

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Objective: To determine the prevalence and associated factors of atlanto-axial subluxation in patients with rheumatoid arthritis (RA).

Materials and Methods: A cross-sectional study using database of patients with RA who visited rheumatologic clinic in the authors' institution between September 2014 and February 2015 was performed. Data collected were demographic, laboratory and imaging data.

Results: During the study period, 231 patients were included. The mean age was 55.2±11.8 years. Majority of patients (92.6%) were female. Atlanto-axial subluxation was found in 40 patients (17.3%): 35 (15.1%) had anterior type only, two (0.9%) had vertical type, and three (1.3%) had combined anterior and vertical subluxation. Factors which were significantly associated with atlanto-axial subluxation were simple disease activity index score (p = 0.024), health assessment questionnaire score (p<0.001) and modified total sharp score (p = 0.002). There was no association among atlanto-axial subluxation and age, sex, anti–cyclic citrullinated peptide antibody, rheumatoid factor, duration of disease, extra-arthricular manifestation, drug use, disease activity score 28, clinical disease activity index, C-reactive protein, IL-6 and procalcitonin.

Conclusion: Atlanto-axial subluxation is highly prevalent in RA patients. Factors associated with atlanto-axial subluxation represent high disease activity, high degree of functional disability and radiological severity of RA.

Keywords: Atlanto-axial subluxation, Disease activity, Functional disability, Radiological severity, Rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that is prevalent in Thailand, especially in adult women. The disease is characterized by synovial hyperplasia and progressive destruction of articular cartilage and bony part of joints. The most commonly affected joints are the small joints of the fingers, wrists, feet, and ankles. However, other sites including large joints and spines have also been reported to be involved.

Recent attention has focused on RA involving cervical spines as it leads to atlanto-axial subluxation. This subluxation is classified as anterior or vertical types, with its overall reported rates varying from 14% to 80% in RA patients[1-3]. The clinical manifestations of atlanto-axial subluxation are not only severe pain, numbness and weakness in upper extremities, but it can also compromise the integrity of the spinal cord leading to quadriplegia, stroke, obstructive hydrocephalus or sudden death when left untreated[4,5]. Hence, rheumatologists should be aware of this disorder in patients who are initially diagnosed with RA, so regular surveillance and early treatment could be provided to lower risks of significant morbidities and mortality.

Previous studies reported that long-standing RA and initial cervical radiological findings were significantly related to atlanto-axial subluxation[6-8]. Nevertheless, these studies were conducted among populations with different backgrounds to Thai people. It is well-recognized that Thai RA patients generally have chronic steroid use. As data suggest that steroid intake is a risk factor for atlanto-axial subluxation[9], the prevalence of this cervical spine disorder among Thai patients might be different to those reported in other population groups. The aim of this study was to determine the prevalence of atlanto-axial subluxation in Thai RA patients. A further aim was to evaluate an association of clinical characteristics with atlanto-axial subluxation.

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Materials and Methods

Study population

This cross-sectional study was undertaken after approval from the Vajira Institutional Review Board (approval No. 60/2557). Written informed consent was obtained from all patients. The inclusion criteria were patients aged 18 years or older who were diagnosed with RA and attended our rheumatology clinic between September 2014 and February

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2015 for the treatment. These patients were offered blood tests and imaging studies for disease activity, functional disability and atlanto-axial subluxation. The exclusion criteria were patients who had other autoimmune diseases including systemic lupus erythematosus, vasculitis or scleroderma; poor verbal communication; loss of sensation; upper-limb lymphedema; and previous cervical spine surgery.

Data collection and outcome assessment

Data collected were: age, gender, duration of RA diagnosis, positivity or negativity of anti-cyclic citrullinated peptide antibody (ACPA), rheumatoid factor (RF), extra-articular symptoms of RA, number of disease modifying antirheumatic drugs (DMARDs) treatment, uses of biologic agents and corticosteroids, RA disease activity measurements, disability index score, blood profiles, presence or absence of atlanto-axial subluxation and radiographic progression of RA in the hands and feet.

The diagnosis of RA was made according to the criteria of ACR 2010[10,11]. The extra–articular symptoms were rheumatoid nodule, anemia, interstitial lung involvement, nerve entrapment, etc. DMARDs included methotrexate, sulfasalazine, antimalarial medication, azathioprine, cyclosporine A and leflunamide, whereas biologic agents were infliximab, etanercept and rituximab. The measurement of RA disease activity was performed using three indices including disease activity assessment 28 (ESR) or DAS-28 (ESR), clinical disease activity index (CDAI) and simplified disease activity index (SDAI). The disability index score was assessed based on the Thai Health Assessment Questionnaire Disability Index (HAQ-DI)[12]. Blood profiles consisted of C-reactive protein (CRP), interleukin-6 (IL-6) and procalcitonin.

The authors made a diagnosis of atlanto-axial subluxation when either anterior or vertical subluxation occurred. The measurement of anterior atlanto-axial subluxation was performed with anterior atlantodental interval (AADI) or posterior atlantodental interval (PADI), which was considered positive when AADI was more than 3.5 mm or PADI was less than 14 mm[4]. The measurement of vertical atlanto-axial subluxation was done using three combined methods: Ranawat, Clark's stations and the Redlund-Johnell method[13]. The diagnosis was made when all the three methods showed positive results. With regard to the evaluation of RA progression in the hands and feet, the modified sharp scoring system was used based on the radiographic pictures of joint damage[14].

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics version 22.0 (IBM corporation, Armonk, NY, USA). Categorical variables were presented as number with percentage and continuous variables as mean with standard deviation (SD) or median with interquartile range as appropriate. Chi-square test was used for categorical variables and student t-test or Mann-Whitney U test was used for continuous variables. The p-value <0.05 was considered statistically significant.

Results

During the study period, a total of 231 patients were included in the study. Of these, 92.6% were female. The mean age of patients was 55.2±11.8 years. The median duration of RA diagnosis was 5 years (range 2 to 9 years). Approximately half of the study population (55.4%) had non-joint symptoms. Among these, the most common clinical extra-articular manifestation was interstitial lung infiltration which was found in 19% of the patients. Almost all patients (97.0%) used any of DMARDs. Other baseline characteristics of the patients are presented in Table 1.

The atlanto-axial subluxation was found in 40 patients (17.3%): 35 patients (15.1%) had anterior type only, two patients (0.9%) had vertical atlanto-axial subluxation, and the remaining three patients (1.3%) had combined anterior and vertical subluxation. Of the 35 patients who had anterior

Table 1. Baseline characteristics of the study population (n = 231)

Characteristic	n (%)
Age, mean (SD)	55.2 (11.8)
Gender, n (%)	
Male	17 (7.4)
Female	214 (92.6)
Positive ACPA, n (%)	132 (58.0)
Positive RF, n (%)	105 (46.0)
Number of DMARD use, n (%)	
0	7 (3.0)
1	31 (13.4)
2	75 (32.5)
3	74 (32.0)
4	36 (15.6)
5	8 (3.5)
Biologic agent use, n (%)	6 (2.6)
Corticosteroid use, n (%)	135 (58.4)
RA disease activity score, median (IQR)	
DAS-28 (ESR)	3.1 (2.5 to 3.9)
CDAI	5.0 (2.5 to 10.0)
SDAI	6.6 (3.6 to 12.5)
HAQ score, median (IQR)	0.3 (0 to 0.8)
Blood profile, median (IQR)	
CRP (mg/L)	9.0 (6.0 to 15.0)
IL-6 (pg/mL)	6.0 (3.7 to 12.8)
Procalcitonin (ng/mL)	0.04 (0.03 to 0.05)
Modified total sharp score, median (IQR)	122.0 (0 to 151.0)

ACPA = anti-cyclic citrullinated peptide antibody; CDAI = clinical disease activity index; CRP = C-reactive protein; DAS-28 (ESR) = disease activity assessment 28 (ESR); DMARD = disease modifying anti-rheumatic drugs; HAQ = health assessment questionnaire disability index; IL-6 = interleukin-6; IQR = interquartile range; n = number; RA = rheumatoid arthritis; RF = rheumatoid factor; SD = standard deviation; SDAI = simplified disease activity index

atlanto-axial subluxation, 34 were diagnosed because AADI measurement was more than 3.5 mm while the other one had positive results of both AADI and PADI measurements. Details of the diagnosis of atlanto-axial subluxation are presented in Table 2.

Table 3 compares demographic and clinical characteristics of patients with and without atlanto-axial subluxation. The results showed that patients who were diagnosed with atlanto-axial subluxation had significantly higher SDAI, HAQ and modified total sharp scores than those without atlanto-axial subluxation. On the other hand, there were no differences in age, sex, ACPA, rheumatoid factor, duration of disease, extra-arthricular manifestation, drug use, DAS-28 (ESR), CDAI, C-reactive protein, IL-6 and procalcitonin between the two groups.

Table 2. Number and rate of atlanto-axial subluxation by type of subluxation (n = 231)

Type of atlanto-axial subluxation	n (%)
Anterior type	35 (15.1)
Positive result of AADI measurement	34 (14.7)
Positive results of AADI and PADI measurements	1 (0.4)
Vertical type	2 (0.9)
Combined anterior and vertical type	3 (1.3)

AADI = anterior atlantodental interval; PADI = posterior atlantodental interval

Discussion

The present study found 17.3% prevalence of C1 and C2 (atlanto-axial) subluxation among Thai RA patients. This figure was in the range of 14% to 80% reported by other authors[1-3]. In the present study population, the anterior subluxation type accounted for 95% (38 out of 40 patients) of atlanto-axial subluxation cases. This proportion was much higher than that observed in the study of Younes et al[15] who also reported that anterior subluxation was the most common atlanto-axial subluxation pattern, but with the proportion of only 25%.

The present study assessed several clinical, laboratory, and imaging parameters possibly associated with the subluxation. We assessed the use of DMARDs, steroid, biologic agents in the RA patients and did not find association of these medication histories with atlanto-axial subluxation.

Table 3. Demographic and clinical characteristics of patients with and without atlanto-axial subluxation by type of subluxation

Characteristic	Atlanto-axial subluxation		*p*-value
	Yes (n = 40)	No (n = 191)	
Age, median (IQR)	58.0 (46.3 to 65.0)	56.0 (47.0 to 62.0)	0.736
Sex, n (%)			0.970
Male	3 (7.5)	14 (7.3)	
Female	37 (92.5)	177 (92.7)	
Positive ACPA, n (%)	23 (57.5)	109 (57.1)	0.800
Positive RF, n (%)	21 (52.5)	84 (44.0)	0.219
Duration of RA diagnosis (years), median (IQR)	6 (2 to 9)	4 (2 to 9)	0.465
Non-joint symptoms, n (%)	24 (60.0)	104 (54.5)	0.523
DMARD use, n (%)	39 (97.5)	185 (97.0)	0.919
Biologic use, n (%)	1 (2.5)	5 (2.6)	0.966
Corticosteroid use, n (%)	24 (60.0)	111 (58.1)	0.827
RA disease activity score, median (IQR)			
DAS-28 (ESR)	3.47 (2.5 to 4.6)	3.05 (2.5 to 3.8)	0.060
CDAI	8.00 (5.0 to 11.5)	4.50 (2.0 to 9.9)	0.102
SDAI	9.55 (5.5 to 14.0)	5.80 (3.0 to 11.7)	0.024
HAQ score, median (IQR)	0.8 (0.4 to 1.4)	0.1 (0 to 0.6)	<0.001
Blood profile, median (IQR)			
CRP (mg/L)	11.0 (6.0 to 23.0)	9.0 (6.0 to 14.0)	0.091
IL-6 (pg/mL)	8.6 (4.8 to 25.7)	5.8 (3.7 to 11.9)	0.053
Procalcitonin (ng/mL)	0.04 (0.04 to 0.05)	0.04 (0.02 to 0.05)	0.148
Modified total sharp score, median (IQR)	157.0 (109.0 to 196.5)	119.0 (98.5 to 141.3)	0.002
Erosion score, median (IQR)	78 (57.8 to 98.0)	61.0 (49.0 to 72.0)	0.001
Joint space narrowing score, median (IQR)	72 (48.5 to 96.8)	57.0 (44.0 to 71.0)	0.003

ACPA = anti-cyclic citrullinated peptide antibody; CDAI = clinical disease activity index; CRP = C-reactive protein; DAS-28 (ESR) = Disease Activity Assessment 28 (ESR); DMARD = disease modifying anti-rheumatic drugs; HAQ = health assessment questionnaire disability Index; IL-6 = interleukin-6; IQR = interquartile range; n = number; RA = rheumatoid arthritis; RF = rheumatoid factor; SDAI = simplified disease activity index

These results were consistent with other studies[16-18]. This may be because drugs used for the treatment of RA are generally prescribed by rheumatologists based on the DAS-28 score, but not the CDAI or SDAI. The DAS-28 scores between the patients with or without subluxation in our studies were not different, so the history of drugs used was not associated with the subluxation. In addition, although symptoms of some patients in our study were in remission, rheumatologists usually prescribe drugs with the aim of preventing disease flare-ups or relapse in routine practice. This is another reason for the similar patterns of drug use between the two groups.

Regarding the other clinical parameters, several studies found the severity of RA was an important factor associated with the C-spine subluxation; however, the extent or degree of association varied depending on means of measurement for the activity scores[19,20]. Two previous studies by Magarelli et al[19] and Kauppi et al[20] found that DAS-28 was significantly associated with atlanto-axial subluxation among patients with early RA who had the diseases for 1 or 2 years. Inconsistent with the findings from the two previous studies by Magarelli et al and Kauppi et al, the authors did not find any difference of DAS-28 scores between the patients who had or had no subluxation. The difference might lie on the characteristic features of the patients included in each study. The two previous studies included only patients who had early RA (mean duration of 1 to 2 years) when their diseases were still in active phase (median DAS-28 scores of 4.2 vs. 3.2 in patients with and without joint involvement, respectively) whereas our study included all affected patients (median duration of 5 years) who had been treated and might already be in remission (median DAS-28 scores of 3.5 vs. 3.1 in patients with and without joint involvement, respectively). Aside from this, our study found a direct association of the SDAI score, but not CDAI, with the atlanto-axial subluxation (p = 0.024). The discordant results between DAS-28 and SDAI scores observed in our study were supported by findings from other studies which showed that the DAS-28 was not accord with CDAI and SDAI scores among patients who were in remission or had low disease activity and low value of ESR (which was one parameter of DAS-28 score)[21,22].

HAQ score reflecting an individual's daily activities was another clinical factor assessed in RA. One study by Kauppi et al evaluated and found a significant direct association of HAQ score with the subluxation in RA patients[20]. This was consistent with our study which found a significant relationship between HAQ score and C-spine subluxation. To be note, patients in the present study of Kauppi et al. had follow-up visits for a 5-year period whereas our study population had a median disease duration of 5 years. The similarity of disease duration between the two studies might be one reason for the concordant findings between our and Kauppi et al's studies.

Concerning imaging parameters, our study had consistent finding with previous studies showing a significant association of the modified total sharp score of peripheral joint as well as each of its components (erosion score and joint space narrowing score) with the C-spine subluxation[2,3,11,15,19,23]. This finding should highly suggest a detailed C-spine clinical evaluation including careful physical examination and appropriate imaging for patients with high total sharp scorer or one of its component scores.

Among the laboratory tests in RA, we evaluated the association of five markers in the present study: two of which are specific to RA (RF and ACPA) and two of which can increase in general inflammatory processes (CRP and IL-6). The authors also assessed procalcitonin as a new marker in acute inflammatory process especially in septic condition[24]. Previous studies found an elevation of ESR, CRP and IL-6 in C-spine involvement with active RA[25,26]. These markers are directly associated with the activity of disease with an increase in active disease and a decline after treatment or remission[25]. The present study did not find an association of any inflammatory markers of RA with the subluxation. This may be explained by the same reason as described with the finding of DAS-28 that our patients were rather in remission phase and any measurement using an inflammatory marker would yield negative findings[27].

One limitation of this study was that it was a cross-sectional study, so it could not establish causal relationship between the three significant factors and the occurrence of atlanto-axial subluxation. In addition, detail of drug used, e.g. duration, dosage, etc. were not included for analysis. These factors might affect the outcomes of the study. Finally, our RA patients with subluxation was only 40 cases. A small number of affected patients might not yield adequate power to determine the significance of some clinical features.

Conclusion

The prevalence of subluxation in our study was 17%. The authors found SDAI, HAQ, and imaging findings of peripheral joints were significantly associated with atlanto-axial subluxation. These markers may be used in other RA patients with similar characteristic features. Nevertheless, the physician should be aware that the severity of RA or phase of disease activity may impact on clinical and laboratory findings for their clinical management.

What is already known on this topic?

RA is a chronic inflammatory autoimmune disease that is prevalent in Thai adult women. One serious manifestation of RA is atlanto-axial subluxation, which can cause pain, numbness, weakness in upper extremities, and more severely spinal cord compression leading to quadriplegia or sudden death. Early detection of this subluxation is important, so prompt treatment could be provided to reduce morbidity and mortality risks of the patients.

What this study adds?

Atlanto-axial subluxation is highly prevalent in Thai RA patients. Factors associated with atlanto-axial subluxation represent high disease activity, high degree of functional

disability and radiological severity of RA.

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Potential conflicts of interest

The authors declare no conflict of interest.

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