Original article

ATLANTO-AXIAL INSTABILITY IN RHEUMATOID ARTHRITIS

Kuchi Avni¹ and Perchinkova Mishevskia Snezhana²

¹PHO City Health Centre Skopje, ²University Clinic of Rheumatology, Skopje

Abstract

Introduction. Rheumatoid arthritis (RA) causes persistent synovitis which could lead to bone erosion, loss of joint cartilage and loose of ligament. In cervical spine this could cause instability, atlanto-axial joint subluxation and medulla spinalis compression.

The aim of this paper was to establish the differences in clinical manifestations between patients with RA and atlanto-axial instability and patients with RA but without atlanto-axial instability.

Methods. A total of 60 patients with a diagnosis of classical and definite rheumatoid arthritis according to the ACR criteria, divided into two groups, participated in this study since 1988. Thirty patients with RA and detected atlanto-axial instability, with expressed cervico-occipital symptomatology participated in the first group. The second group comprised 30 patients with RA but without detected atlanto-axial instability. All patients underwent native and functional x-ray of cervical spine in neutral and lateral position, in flexion and extension as well as CT images. MRI was realized in majority of patients. For assessment of rheumatoid arthritis activity, all patients underwent DAS 28 score test as well as laboratory immunologic tests: RF, CRP and anti-CCR. Statistical analysis was made with appropriate statistical methods.

Results. The mean patients' age in the RA group and atlanto-axial instability was 56.9±12.2 years, which was insignificantly smaller than the mean participants' age from the group with RA. Females dominated in both groups. The mean time duration of the disorder in the RA group and atlanto-axial instability was 17.9±7.8 years, while in the group with RA only it was 6.9±4.2 years. The high SE, RF, anti-CCR as well as DAS28 values were significantly more frequently present in patients with atlanto-axial subluxation (AAS). The results from the investigation showed that the joint deformities as well as the neurologic symptoms were registered significantly more frequently in the patient group with RA and AAS.

Conclusion. In patients with long-lasting active RA due to persistent synovitis at the level of the atlanto-axial joint comes to subluxation of the same joint which could cause significant neurologic symptoms.

Key words: rheumatoid arthritis, atlanto-axial instability

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder which main manifestation is persistent synovitis that could bring to bone erosion, loss of joint cartilage and loose of ligament. It has a prevalence of 1% and appears more frequency in women than in men (females/males ratio of 3/1). RA could start at any age, but the onset peak is at the fourth or fifth decade in males. The cause is unknown. Predisposition towards RA has been genetically determined [1,2].

RA potentially targets any segment of cervical spine. Chronic synovitis of the synovial membrane around the dens causes destruction of transversal and apical ligament, as well as the alar ligaments, and afterwards looseness which causes anterior, posterior and vertical subluxation. Anterior atlanto-axial subluxation (aAAS) (has also been named anterior atlanto-axial luxation) is the most frequent type of cervical involvement in RA. aAAS prevalence ranges greatly, from 5 to 61%, in RA patients [3]. Characteristic finding in the aAAS has been the abnormal division between arcus anterior of atlas in relation to dens. Distance longer than 2.5 mm has been considered abnormal, especially when it changes significantly between flexion and extension [4].

Frequency determination of cervical involvement depends on the patients being studied as well as on the applied radiographic techniques and the criteria being used [5]. Clinical variable which is in the closest correlation with cervical spine involvement in RA patients is presence of hand deformities especially on meta-carpal-phalangeal subluxation [5]. From the aspect of the biological marker investigations as predictive factors in occurrence of atlanto-axial instability the following are included: high erythrocyte sedimentation values (SE), RF, anti CCP and, according to some authors, high CRP values as well [6-8]. When cervical spine is involved, the anatomical manifestation and clinical symptoms and signs are different [5]. Neurologic symptoms are not in direct correlation with the extent of subluxation but could be linked with the individual variations in the spinal canal width. The symptoms of the spinal cord compression which need an intervention include: altered consciousness, syncope and loss of the sphincter control. Dysphagia, dizziness,

Correspondence to: Avni Kuchi, PHO City Health Centre, Skopje, R. Macedonia; E-mail: avnikuqi@yahoo.com

convulsions, hemiplegia, dysarthria, nystagmus, and peripheral paresthesia are additional symptoms which require urgent care [4]. Although subluxation could include any level, the upper part of cervical spine is the most frequently involved, and is also clinically the most significant region [5].

The aim of this study was to establish the differences in clinical manifestations between RA patients and atlanto-axial instability and patients with RA but without atlanto-axial instability.

Material and methods

This investigation represents a cross-sectional study of a prevalent type and has been performed at the University Clinic of Rheumatology.

The cohort of the participants consisted of 60 patients with diagnosis of classical and definite rheumatoid arthritis according to the ACR criteria from 1988, treated in the Outpatient Clinic within the period from 2012 to 2014. The patients were divided into two groups. Thirty patients with RA and detected atlanto-axial instability, with pronounced cervico-occipital symptomatology compared the first group. The second group consisted of 30 patients with RA but with no detected atlanto-axial instability. All patients underwent native and functional x-ray of cervical spine in neutral and lateral position, in flexion and extension as well as CT images. In majority of patients MRI was realized.

For x-ray diagnostics of the atlanto-axial instability the following criteria were used: distance of the rear boundary from the first cervical vertebra arch and the front side of the dens, in spine in flexion, greater than 2.5 mm (represents front instability); the rear atlanto-axial subluxation was demonstrated by the dens placement before the front arch of the atlas; vertical subluxation was established when the dens pick was placed more than 3 mm above the Chamberlaine's line (a line which connects the hard palate to the interior cortex of the rear edge of foramen magnum); lateral atlanto-axial subluxation of the dens occurs when the lateral masses of the first cervical vertebra are placed 2 mm or more laterally than those of the second cervical vertebra; and subaxial subluxation was detected by appearance of cascade spine, when each sliding of 4 mm or more, in relation to the adjacent vertebral body was considered as significant. Also, DAS 28 score test and immunologic tests such as RF, CRP and anti-CCP were made for assessment of rheumatoid arthritis activity in all patients. Other clinical manifestations were present and registered in all patients: joint deformities, legs and arms paresthesias, shoulder joint pains, limited movements of shoulder joints, as well as presence of clinical signs of central origin (vomiting, dizziness, diplopia, transitor vision loss, disathria, dysphagia). Then, comparison of the parameters between both groups was made.

Statistical analysis of data was made with the statistical program SPS 13.0 for Windows. Data categories were presented in absolute frequencies and percentages; quantitative data was made with descriptive statistics (mean, SD, median, minimum, maximum). Fisher exact test, t-test for independent samples and Mann-Whitney Z test were used for testing the difference among determined variables. Bi-variant Pearson's correlation was used to determine the connection between two variables. $P < 0.05$ value was taken as statistically significant.

Results

This investigation was performed on 60 patients with rheumatoid arthritis (RA) divided into two groups. The analysis of the x-ray images in all patients from the first group proved the existence of the atlanto-axial instability. Female patients (76.7 vs 90%) dominated in both groups. As to the ethnic structure, this study included Macedonians, Albanians, Turkish and Romas. Macedonians (80% of the participants) dominated in both groups. The participants from the first group gave data for rheumatic disorder in their families non-significantly more frequently than the participants from the second group (35.7% vs 30%).

Fig. 1a. x-ray-neutral

Fig. 1b. x-ray-flexion

Fig. 1c. CT

Fig. 1d. MR position

Fig.1. Atlanto-axial instability

Table 1. DAS 28 score

Variable	RA with atlanto-axial instability (%)	PA n (%)	p-value
DAS ≤ 3.2	2(6.7%)	7(23.3%)	Fisher exact, two tailed p=0,001**
DAS 3.3 $\leq$ 5.1	6(20%)	19(63.3%)	
DAS > 5.1	22(73.3%)	4(13.3%)	
RF > 12 IU/mL	21(70%)	11(36.7%)	Fisher exact p=0,019*
Anti CCP > 25 IU/ml	16(53.3%)	5(16.7%)	Fisher exact p=0,006**
CRP > 6 mg/L	15(50%)	16(53.3%)	Fisher exact p=1,0

*p<0.05, **p<<0.01

Participants' mean age from the first group was 56.9 ± 12.2 years, which was non-significantly lower than the mean age of the participants from the second group ($p=0.7$). Disorder time duration in the participants from the first group ranged from 5 to 37 years (mean time duration 17.9 ± 7.8 years), while in the second group the disorder had a mean time duration of 6.9 ± 4.2 years, with minimal duration of 6 months, maximal 13 years. In the group

with atlanto-axial instability, RA had highly significantly longer time duration ($t=6.2$ $p<0.01$). Time duration of the disorder in the group with atlanto-axial instability was significantly longer ($t=6.2$, $p<0.01$).

In the first group mean sedimentation value was 33.96 ± 20.2 mm/1h, while in the second group 23.3 ± 14.7 mm/1h ($p>0.05$).

Table 2. Clinical characteristics of the participants

Variable	RA with atlanto-axial instability n (%)	PA N (%)	p-value
Joint deformities			
no	1(3.3%)	11(36.7%)	Fisher exact, two tailed p=0.025*
yes	29(96.7%)	19(63.3%)	
Leg Paresthesia			
no	6(20%)	24(80%)	Chi-square=10.4 df=2 p=0.000006**
no constantly	10(33.3%)	0	
has temporary	14(46.7%)	6(20%)	
Hand paresthesia			
no	3(10%)	25(83.3%)	Fisher exact. two tailed p=0.001**
has constantly	9(30%)	0	
has temporary	18(60%)	5(16.7%)	
Shoulder joints/pain			
no	4(13.8%)	7(23.3%)	Chi-square=0.8 df=1 p=0.3 NS
yes	25(86.2%)	23(76.7%)	
Shoulder joints/movements			
limited	24(82.8%)	5(16.7%)	Chi-square=0.8 df=1 p=0.000**
non-limited	5(17.2%)	25(83.3%)	

*p<0.05, **p<0.01

DAS 28 score greater than 5.1, which indicated high activity of rheumatoid arthritis, was registered highly significantly, and more frequently in the group with atlanto-axial subluxation (73.3% vs 13.3%).

In the first group (RA and atlanto-axial subluxation), the rheumatic factor >12IU/mL had 70% of the participants, i.e. significantly more frequently than the participants with RA without atlanto-axial subluxation ($p=0.019$). Anti CCP>25 IU/mL more frequently and highly significantly was present in the patients who, beside RA, had atlanto-axial subluxation (53,3% vs 16,7%), while both groups of participants differed non-significantly in relation to registration of frequency of the CRP values higher than 6mg/L ($p=1,0$) (Table 1).

Results from the investigation showed that the joint deformities were registered significantly more frequently in the first group (96.7% vs 63.3%). About 33.3% of

the patients with RA and atlanto-axial subluxation had a constant leg paresthesia, and none of the group with RA, while the percent of the participants with temporary leg paresthesia in both groups was 46.7% and 20%, respectively. These differences between both groups were statistically highly significant ($p=000006$).

Hand paresthesia highly significantly and more frequently was also found in the group with RA and atlanto-axial subluxation. The patients with RA and atlanto-axial subluxation significantly more frequently had limited shoulder movements for $p<0.01$ (82.8% vs 16.7%) (Table 2).

In the first group of patients 10% vomited frequently, 23.3%, occasionally, dizziness developed almost 96.6% of the patients, 36.7% had diplopia, transitory loss of vision 43.3%, dysarthria 46.7%, while 36.7% of the patients had dysphagia. These symptoms were found in none of the second group (Table 3).

Table 3. Clinical manifestations of central origin

Variable	RA with atlanto-axial instability n (%)	PA n(%)	p-value
Vomiting			
no	19(63.3%)	30(100%)	
frequent	3(10%)	0	
temporary	7(23.3%)	0	
has an instinct	1(3.3%)	0	
Dizziness			
no	1(3.4%)	30(100%)	Fisher exact, two tailed $p=0.001^{**}$
yes	29(96.6%)	0	
Diplopia			
no	19(63.3%)	30(100%)	Chi-square=13.5 df=1 $p=0.0002^{**}$
yes	11(36.7%)	0	
Transit. vision loss			
no	17(56.7%)	30(100%)	Chi-square=16.6 df=1 $p=0.00005^{**}$
yes	13(43.3%)	0	
Dysarthria			
no	16(53.3%)	30(100%)	Chi-square=18.2 df=1 $p=0.00002^{**}$
yes	14(46.7%)	0	
Dysphagia			
no	19(63.3%)	30(100%)	Chi-square=13.5 df=1 $p=0.0002^{**}$
yes	11(36.7%)	0	

* $p<0.05$, ** $p<0.01$

Discussion

Atlanto-axial instability occurs almost in half of the RA patients. Joints between the occipital bone and atlas and axis are solely synovial and hence are subjected to RA affection. The joints of C1-C2 are placed in horizontal plane and there is no bony protective mechanism from subluxation. Stability at this level depends on the ligament and capsular apparatus [5]. The difference in atlanto-axial distance between flexion and extension of the neck measured in radiography has been named as atlanto-axial instability [9].

Three rheumatoid deformities occur on the cervical spine:

1. C1-C2 subluxation could appear due to incompetence of the transversal ligament or due to dens ero-

sion. This usually happens as an anterior subluxation, but could be both posterior and lateral.

2. Impairment of the longitudinal distance between dens and brain stem could be caused by erosion of occipital-C1 articulation or C1-C2 or of both. From here arises deformity which has been most variously delineated as pseudo-bulbar invagination, a vertical sliding of the dens or the superior migration of dens.
3. Sub-axial subluxation (under the C2 level) is caused by facet joint erosion and ligament incompetence, and could occur at one or several levels [5].

Crockard supposes that the looseness of the atlanto-axial ligaments and the sub-axial post-inflammatory ankylosis are the two main factors for cervical spine deformity in RA. Looseness of the atlanto-axial ligaments plays a dominant role at the beginning of RA [10].

Recent literature has documented involvement of cervical spine at the beginning of RA, frequently within the first two years after the diagnosis [11,12]. Craniocervical complications develop in 30% to 50% of the patients who have had RA for more than 7 years, while AAS with myelopathy developed in 2.5% of those with RA for more than 14 years (14).

Riise *et al.* reported that the patients with AAS had a mortality rate 8-times greater than that of the patients without AAS (14).

According to the literature data, the longer duration of RA, positivity of biological markers such as RF, anti CCP, CRP, elevated values of erythrocyte sedimentation (SE) as well the joint deformities are predictive factors for the development of the atlanto-axial instability in patients with RA. Involvement of cervical spine has been in correlation with the high disorder activity, for which the obtained high values of DAS 28 score go in favor [6-8,15,16].

According to Isdale and Conlon's report, the cervical spine involvement develops within the period of 15 years since the onset of RA, after which it reaches its plateau [17]. Kontinen *et al.* in their presented series assessed that the median interval between the onset of RA and the first diagnosis of the front atlanto-axial instability was 12 years. Majority of patients had ulnar deviation and a swan neck-deformity of fingers as diagnostic signs which could be linked with peripheral ligament looseness with tendencies to subluxation [18].

According to our study, there was statistically significant association between the RA time duration and the atlanto-axial instability.

In the group with the atlanto-axial instability, RA had highly significantly longer time duration ($p < 0.01$).

Magarelli *et al.* (2010) in their study which included 20 patients, 16 women and 4 men (mean age 55.0 ± 12.9 years), made a comparative analysis between 5 patients (25%) with RA in whom atlanto-axial instability was registered compared to 15 (75%) patients in whom the same disorder was not detected after corresponding radiographic investigations. Erythrocyte sedimentation (SE) had significantly higher mean value in 5 patients with RA and atlanto-axial instability compared to 15 patients who did not have atlanto-axial subluxation (77.0 mm/1h vs 33.0 mm/1h). CRP reached a highly mean value in the first group compared to the second (53.6 mg/L vs 14.0 mg/L), while higher mean value of DAS 28 score was found in the first group compared to the second one (4.2 vs 3.2). Four (80%) of 5 patients with atlanto-axial instability had a positive finding of anti CCR and RF, while all 5 patients had erosion changes on the hand joints proved by X-ray. The mean time duration of the disorder was 6.7 ± 3.0 months [7]. This study pointed to the early beginning of cervical spine involvement in patients with active and evolving RA. Chellapandian *et al.* in their study included 75 patients with RA, with a mean age of 42.1 years. The cohort of

the participants was divided into two groups and comparison was made of the clinical characteristics between the patients with and without the involvement of the cervical spine. The first group consisted of 32 patients with RA and involvement of the cervical spine, while the second group consisted of 43 patients with RA but without cervical spine involvement. In the first group the time duration of the disorder was 104 months, the average of sensible joints was 19.53, the average of swollen joints was 7.4, rheumatoid nodules were registered in 9 cases, joint deformities occurred in 12 patients, out-of-joint manifestations were present in 4 patients, rheumatoid factor was positive in all cases. In the second group, the mean time duration of the disorder was 20.9 months, the average of sensible joints was 12.46, the average of swollen joints was 3.0, rheumatoid nodules were registered in 3 cases, joint deformities occurred in 7 patients, out-of-joint manifestations were not present. Rheumatoid factor was positive in all 23 cases. On the palms x-ray, erosions were found in 32 cases of the first group, and in 22 cases of the second one. SE values were elevated in 65 patients, and the CRP values were elevated in 60 patients [8].

The results obtained in our study coincided with the previously cited ones. Among the participants, women predominated, with a mean age of 56.0 ± 12.3 and 58.0 ± 11.5 years. Erythrocyte sedimentation (SE) had a mean value of $33.9658.0 \pm 20.2 \text{ mm/1h}$ in the group with RA and the atlanto-axial subluxation, and $23.3 \pm 14.7 \text{ mm/1h}$ in the group without atlanto-axial instability ($p > 0.05$). DAS28 score greater than 5.1 which pointed to high RA activity, and highly significantly more frequently was registered in the group with the atlanto-axial subluxation (73.3% vs 13.3). In the group with RA and the atlanto-axial subluxation the participants had significantly more frequently RF $> 12 \text{ IU/mL}$ (70%) ($p = 0.019$), anti CCP $> 25 \text{ IU/mL}$ 53.3%. Also, in these patients significantly more frequently were registered joints deformities (96.7%). Majority of them had ulnar deviation and swan-like neck deformity.

Pathological changes could cause a compression on the second cervical nervous root causing pain which was extending to neck and occiput. Neuralgic abnormalities could cause radial pain or paresthesia, posterior column dysfunction as well as sphincter dysfunction, which spoke for spinal cord compression that could progress to quadriparesis or quadriplegia [19].

Also in our study, the first group of patients with RA and atlanto-axial instability had more pronounced cervical-occipital pain, while in the second group they had milder symptomatology of the same pain. Thirty-three percent of patients with RA and atlanto-axial subluxation had leg paresthesia constantly, and temporary 46.7%, which was a statistically significant difference compared to the second group ($p = 0.000006$).

Patients with RA and atlanto-axial subluxation had significantly more frequently limited shoulder move-

ments (82.8% vs 16.7%) for $p < 0.0$, but these could be linked in part to the cases with longer duration of RA, and with the activity and evolution of RA.

Oda *et al.* reported patients with a slight form of RA who did not have atlanto-axial instability; vertical instability developed in 52% of patients with moderate disorder, and this existed also in 88% of patients with severe erosion disorder [21].

The patients with RA and atlanto-axial subluxation were found to have symptoms of tinnitus, dizziness, visual disturbances, loss of balance, diplopia, dysphagia, which could occur due to vertebrobasilar insufficiency or due to mechanical compression of the craniocerebral junction (20).

In our study, in the group with RA patients and atlanto-axial subluxation, 10% of the patients most frequently vomitted, temporary 23.3%, dizziness occurred in even 96.6% of the patients, 36.7% had diplopia, transitory vision loss 43.3%, dysarthria 46.7%, while 36.7% of the patients had dysphagia. These symptoms were not registered in none of the patients in the group with RA but without atlanto-axial subluxation.

Conclusion

In patients with long-lasting active RA due to persistent synovitis at the level of the atlanto-axial joint comes to subluxation of the same joint that could cause significant neurologic symptoms.

These patients have high values of SE, RF, anti CCP, CRP, pronounced clinical manifestations and joints deformities. Due to danger for life of antero-posterior instability between atlas and axis, which has also been a cause for invalidity, it is necessary to take corresponding stabilizing procedures (from carrying the stiff-collar to surgical intervention).

In order to achieve more optimistic results, the atlanto-axial subluxation requires multidisciplinary approach including rheumatologist, neurologist, neurosurgeon, orthopedic surgeon and physiatrist.

Conflict of interest statement. None declared.

References

- Papadakis MA, McPhee SJ. Current Medical Diagnosis & Treatment. 52 ed. New York: McGraw-Hill 2013; 826-827.
- Vrhovac B, *et al.* Interna medicina. ZAGREB, Cetvrto, promijenjeno i dopunjeno izdanje, 2008; 1371-1378.
- Naranjo A, Carmona L, Gavrilu D, *et al.* Clinical and experimental Rheumatology 2004; 427-432.
- Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR, KELLEY'S Textbook of Rheumatology. 9 ed Philadelphia: Elsevier Saunders 2013; p: 832-83, 1116-1117.
- Monsey DR. Rheumatoid Arthritis of the Cervical Spine. *J Am Acad Orthop Surg* 1997; 240-248.
- Kuchi A, Perchinkova MS. Types of atlanto-axial subluxation in patients with rheumatoid arthritis, *Acta Morphol* 2014; 11(2): 42-48.
- Magarelli N, Simone F, Amelia R, *et al.* MR imaging of atlantoaxial joint in early RA. *Radiol Med* 2010; 115: 1111-1120.
- Chellapandian D, Panchapekesa RC, Rukmangatha S, *et al.* Cervical Spine Involvement in Rheumatoid Arthritis and its Correlation with Disease Severity. *J Indian Rheumatol Assoc* 2004; 12: 2-5.
- Kauppi M, Anttila P. A stiff collar restrict atlantoaxial instability in rheumatoid cervical spine in selected cases. *Ann Rheum Dis* 1995; 54(4): 305-307.
- Crockard HA. Surgical management of cervical rheumatoid problems. *Spine* 1995; 20: 2584-2590.
- Paimela L, Laasonen L, Kankaanpää E, Leirisalo-Repo M. Progression of cervical spine changes in patients with early rheumatoid arthritis. *J Rheumatol* 1997; 24(7): 1280-1284.
- Moskovich R. Inflammatory arthritis of the cervical spine. In: Spivak JM, Di Cesare PE, Feldman DS, *et al.* (eds): Orthopaedics: A Study Guide. New York: McGraw-Hill, 2011; p. 373-380.
- Moskovich R, Shott S, Zhang ZH. Does the cervical canal to body ratio predict spinal stenosis? *Bull Hosp Jt Dis* 1996; 55: 61-71.
- Riise T, Jacobsen BK, Gran JT. High mortality in patients with rheumatoid arthritis and atlantoaxial subluxation. *J Rheumatol* 2001; 28: 2425-2429.
- Canale ST, Beaty JH. In: Campbell's Orthopaedics. Other Disorders of the Spine. 11 ed, New York: Elsevier 2007.
- Mathews JA. Atlanto-axial subluxation in rheumatoid arthritis. A 5-year follow-up study. *Ann Rheum Dis* 1974; 33(6): 526-531.
- Isdale IC, and Conlon PW. Atlanto-Axial Subluxation. A six-Year Follow-up Report. *Ann Rheum Dis* 1971; 30: 387-389.
- Konttinen YT, Santavirta A, Kauppi M, *et al.* Atlantoaxial laxity in rheumatoid arthritis. *Acta Orthop Scand* 1989; 60(4): 379-382.
- Pellici PM, Ranawat CS, Tsairis P, Bryan WJ. A prospective study of the progression of rheumatoid arthritis of the cervical spine. *J Bone Joint Surg Am* 1981; 63(3): 342-350.
- Wasserman R B, Moskovich R, Razi EA. Rheumatoid Arthritis of the Cervical Spine: Clinical Considerations. *Bull NYU Hosp Jt Dis* 2011; 69(2): 136-148.
- Oda T, Fujiwara K, Yonenobu K, *et al.* Natural course of cervical spine lesions in rheumatoid arthritis. *Spine* 1995; 20: 1128-1135.