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Atlanto-Axial Subluxation in Iraqi Patients With Rheumatoid Arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic multisystemic disease which can lead to significant deformities and functional disability.
Objectives: To assess atlanto-axial subluxation (AAS) in Iraqi patients with RA; and to evaluate its correlations with patients characteristics if present.
Patients and methods: A cross sectional study was conducted on 109 patients with RA diagnosed according to the American College of Rheumatology Criteria for the classification of RA. Patients' baseline characteristics included: age, sex, duration of RA illness, functional status, hand deformities, symptoms and signs suggestive of cervical myelopathy, and drugs related history, Disease Activity Score for 28 joints (DAS 28), erythrocyte sedimentation rate (ESR), and Rheumatoid Factor (RF). X-ray of cervical spines lateral view, involving both flexion and extension was done. AAS was diagnosed when the separation between atlas and axis >3 mm during flexion part.
Results There were 109 RA patients included in this study, the mean age of them was (45.85± 10.35) years. Ninety seven patients (89%) were females. AAS was present in 30 (27.52%) patients and it was significantly associated with longer disease duration (p=0.01), RF positivity (p=0.014), lower functional class (p=0.03), hand deformities (p<0.01), and advancing disease progression stage (p=0.01). No significant relationship between AAS with: patients' age, gender, DAS 28, VAS of the patient, and smoking.
Conclusions: AAS was common in patients with RA. In patients with RA, AAS was significantly associated with: longer disease duration, RF positivity, lower functional class, hand deformities, and advancing disease progression.

Keywords: Rheumatoid arthritis, atlanto-axial subluxation, cervical spine, baseline characteristics

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder affecting multiple organ systems, joints, ligaments, and bones and commonly involves the cervical spine [1]

Atlanto-axial subluxation (AAS) is characterized by excessive movement at the junction between the atlas (C1) and the axis (C2) as a result of either a bony or ligamentous abnormality [2]. Symptomatic AAS occurs when subluxation causes the odontoid process, or posterior arch of the atlas, to impinge on the spinal cord and cause neurologic manifestations [3]. The mechanism of AAS in RA is that the rheumatoid process affects the articular cartilage of the apophyseal joints and the transverse ligaments [4]. In addition, the rheumatoid pannus and the associated inflammation can weaken the transverse ligaments, alar ligaments, and facet capsules early in the disease process [5].

Many studies have investigated the progression of cervical spine instabilities in RA [6-9] however up to our knowledge there is no study in Iraq. This study aimed to evaluate AAS in RA in Iraqi patients with RA.

2. Patients and Methods

2.1 Study design

A cross sectional study was conducted in the outpatient consultation clinic of rheumatology Unit in Baghdad Teaching Hospital from December 2012 to April 2013. Patients with RA, diagnosed on base of American College of Rheumatology Criteria for the classification of RA [10].

This study was granted full ethical approval from the local ethics committee and all the patients have given informed written consents prior to the commencement of our study.

Patients were excluded from the study if there were evidences of overlapping connective tissue disease, or pregnancy.

2.2 Clinical, laboratory, and radiological evaluation

Patients data were obtained via face-to face interview with the researcher. Focused history was taken including: age, sex, duration of RA ,smoking , patients self-assessment of disease activity or Visual Analogue Scale for the patient (Patient s VAS), functional status was assessed according to the criteria for classification of functional status in rheumatoid arthritis [11], and symptoms suggestive of cervical myelopathy: (neck pain and their radiation ,weakness or sphincteric disturbances) ,and drug related history (corticosteroids, disease modifying antirheumatoid drugs (DMARDS),and biologic agents).

Each patient was examined for detecting tender and swollen joints, rheumatoid nodules, hand deformities, and neurological examination for any sign of cervical myelopathy (spastic quadriparesis, sensory loss in the hands, and sphincteric disturbances).

A blood sample was taken for the measurement of Erythrocyte sedimentation rate (ESR) was measured (usingWestergren's method, in mm/ hour) and rheumatoid factor (using latex fixation test) . Disease activity was assessed according to Disease Activity Score for 28 joints (DAS 28). DAS28 was calculated from the number of tender and swollen joints (28-joint count), patient s self-assessment of disease activity (VAS) , and ESR according to the following formula [12]:

DAS28 = (0.56 * tender joint count $^{1/2}$) + (0.28 * swollen joint count $^{1/2}$) + (0.7 * ln [ESR]) + (0.014*VAS).

X-rays of both hands in postero-anterior view (PA view) were obtained ,and the progression of rheumatoid arthritis patients was classified according to steinbrocker classification [13]. The cervical spine was radiographed using antero-posterior, and lateral (extension/flexion) views and read by single radiologist. A diagnosis of AAS is made if the distance between the anterior aspect of the dens and the posterior aspect of the anterior arch of atlas is more than 3 mm during flexion.

2.3 Statistical analysis

Data of 109 recruited patients in this study were checked for any errors or inconsistencies and transferred into computerized database software with analytic facilities; Statistical package for social sciences (SPSS) was used in all statistical analysis and procedures. Descriptive statistics for age, duration of RA, DAS28 and VAS of the patient were presented as mean ± standard deviation (SD). Duration of use and doses of medications were presented as median and inter-quartile range (IQR). Other variables were presented as numbers and percentages. Student's t test was used to compare two means to assess the significance of difference. Chi square was used to assess the significance of variation in frequencies of variables. P-values less than 0.05 were considered significant.

3. Results

A total of 109 RA patients were involved in the study. The mean age of patients was 45.85 ± 10.35 years and 97 (89%) were females. Other baseline characteristics were shown in table 1.

Atlanto-axial subluxation was present in 30 (27.52%) patients (Figure 1).

In addition, atlanto-axial subluxation was significantly associated with longer disease duration (p=0.01), rheumatoid factor positivity (p=0.014), lower functional class (p=0.03), hand deformities (p<0.01), and advancing disease progression stage (p=0.01). There was no significant relationship between atlanto-axial subluxation in rheumatoid arthritis patients with: patients age, gender, DAS 28,VAS of the patient ,and smoking as in table 2.

Table 1: Baseline characteristics of study group (N=109)

Variable		value
Age (years), Mean ± SD (Range)		45.85 ± 10.35 (21-70)
Gender Male n (%)		12 (11.0)
Female n (%)		97 (89.0)
Smokers n (%)		26 (23.9)
Duration of RA illness (years) Mean ± SD (Range)		10.07 ±7.5
RF Positive n (%)		66 (60.9)
Hands deformities n (%)		57 (52%)
DAS28 Mean s± SD (Range)		5.64 ± 1.11(3 - 8)
VAS (0-100) Mean s± SD (Range)		55.4± 23.81 (0 - 100)
Functional class	Class I n (%)	32 (29.4)
	Class II n (%)	52 (47.7)
	Class III n (%)	20 (18.3)
	Class IV n (%)	5 (4.6)
Disease progression stage	Stage I n (%)	27 (24.8)
	Stage II n (%)	23 (21.1)
	Stage III n (%)	46 (42.2)
	Stage IV n (%)	13 (11.9)
Medication n(%)	n.	%
Steroid	94	86.2
DMARDS	106	97.2
MTX	92	84.4
HCQ	39	35.8
SSZ	9	8.3
Azathioporin	9	9.2
Leflunomide	2	1.8
Etanercept	53	48.6

RA, Rheumatoid arthritis; DAS, disease activity score; VAS, visual analogue scale; DMARDs, disease modifying anti-rheumatic drugs; MTX, methotrexate; HCQ, Hydroxychloroquine; SSZ, sulfasalazine; SD, standard deviation.

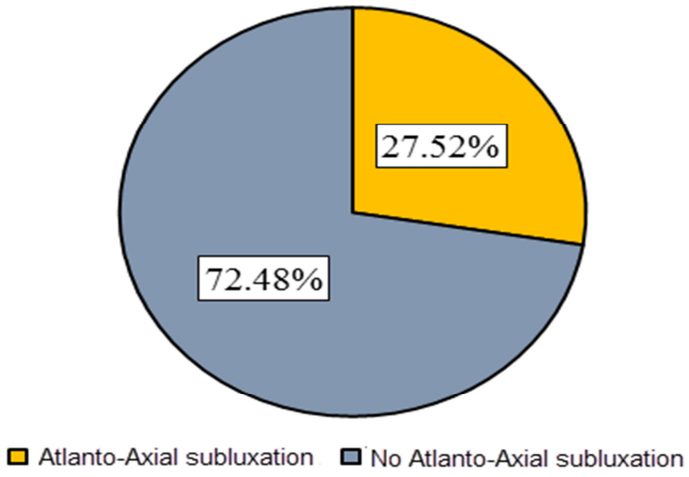

Figure 1. Distribution of Atlanto-Axial subluxation among 109 RA patients

Table 2. Relationship of patients' baseline characteristic's with atlanto-axial subluxation

Variable		Atlanto-axial subluxation				P-value
		Present (n=30)		**Absent** (n=79)		
		No.	%	No.	%	
Gender	Male	4	13.3	8	10.1	0.63
	Female	26	86.7	71	89.9	
Smokers		8	26.7	18	24.4	0.77
RF positive		23	82.1	43	55.8	0.014*
Functional class	Class I	5	16.7	27	34.2	0.031*
	Class II	15	50.0	37	46.8	
	Class III	10	33.3	10	12.7	
	Class IV	0	0.0	5	6.3	
Hand deformities		24	80.0	33	41.8	<0.001*
Disease progression stage	Stage I	1	3.3	26	32.9	0.001*
	Stage II	4	13.3	19	24.1	
	Stage III	19	63.3	27	34.2	
	Stage IV	6	20.0	7	8.9	
Glucocorticoids use		28	96.6	66	85.7	0.173
Duration (mean±SD) (months)		28.14 ± 9.3		22.8 ± 6.7		0.002*
Biologics use(etanercept)		6	20.0	16	20.3	0.161
Duration (mean±SD) (months)		7.3 ± 3.5		5.6 ± 2.7		0.12
DMARDS use		30	100.0	76	96.2	0.56
Duration (mean±SD) (months)		18.4± 10.1		16.2 ± 8.7		0.41

*P<0.05 significant; RF, rheumatoid factor; DMARDs, disease modifying antirheumatic drugs; SD, standard deviation

Table 3.Distribution of neck pain and neurological features among patients with and without Atlanto-Axial subluxation.

Variable		Atlanto-axial subluxation				Total		P-value
		Present (n=30)		**Absent** (n=79)				
		n	%	n	%	n	%	
Neck pain	Yes	25	83.3	57	73.1	**82**	75.9	0.26
	No	5	16.7	21	26.9	**26**	24.1	
	Total	**30**	**100.0**	**78**	**100.0**	**108**	**100.0**	
Neurological features	Yes	2	6.7	3	3.8	**5**	4.6	0.52
	No	28	93.3	76	96.2	**104**	95.4	
	Total	**30**	**100.0**	**79**	**100.0**	**109**	**100.0**	

n, number

4. Discussion

Cervical spine involvement is one of the causes of morbidity and mortality in RA patients [14]. The most important cervical spine involvement in RA is atlanto-axial subluxation (AAS) , significant sub-axial disease is common and usually coexists with the AAS [15]. Although radiological abnormalities may remain asymptomatic for years, patient s are at continued risk of neurological complications and even sudden death from medullary compression [16].

The interesting observation in this study is that the frequency of cervical spine subluxations (AAS) (27.52%) was low compared with historical data. In 1978, USA study [17] reported a 42% prevalence of AAS in patients who had had RA for 15 years. In a 9.5-years follow up study in UK in (1983) [18], cervical spine subluxations were found in 34% of RA patients. Furthermore, in the Heinola Follow-up Survey of RA, 42% of patients exhibited cervical spine subluxations at 20 years [19]. This proportion of AAS in present study was lower than that reported in Finland study in 1996 (32%) [20].In these studies, patients have been treated with traditional DMARDs which were either rather weak (anti-malarials) or often discontinued due to side effects (gold salts). In the present study, the patients were treated with potent DMARDs,e.g methotrexate. Comparisons with historical controls introduce several potential confounding factors. Nevertheless, we suggest that it is possible that the extensive drugs therapy with conventional DMARDs played some role in preventing cervical spine changes, at least in some patients.

No significant difference was observed in age, gender, smoking history, DAS28 and VAS between RA patients with AAS and those without AAS, the significant difference was in the duration of RA ($p = 0.01$). The effect of disease duration on cervical spine involvement is controversial. Cervical spine involvement has been reported within 2 years of RA onset. In a 5 years study in USA on (106) RA patients, radiological evidence of cervical spine involvement was seen in 43% of patients at baseline and 76% at last follow-up [21]. This finding regarding disease duration is inconsistent with result of Finland study (2003) [22].

There was a significant difference between RA patients with AAS and RA patients without AAS regarding RF, functional class, hand deformities and disease progression stage ($p < 0.05$). This finding is consistent with results of Finland study in (2003) [22]. A significant difference in disease duration might lead to significant differences in RF and hand deformities [23].

In the present study, high disease severity of RA patients (measured by the functional class and disease progression stage) was a statistically significant risk factor for later atlantoaxial subluxations [24]. Structural damage at the atlantoaxial region is a potentially life-threatening condition. Severe rheumatoid destruction of the cervical spine and periodontoid pannus formation may cause compression of the spinal cord or brainstem, which may result in myelopathy or sudden death [25]. Therefore, early recognition of patients who may develop or currently have atlantoaxial subluxations is important, in order to apply preventive strategies and early treatment.

There was no significant difference in the treatment history between RA patients with AAS and those without; this finding is consistent with that reported in USA study [17].

From other point of view, a significant difference in treatment duration was observed with glucocorticoids and not with the other medications; patients with subluxation had a history of longer duration of use of glucocorticoids than those without subluxation, the possible explanations are that use of steroids for long period may cause ligament laxity, osteoporosis and decreasing muscle mass, which leads to accelerated subluxation, or that steroid treatments are used in more severe cases which have a higher tendency towards cervical subluxation.

Finally, no significant difference in the frequency of neck pain in patients with AAS and those without, this finding was close to that reported previously in other studies [26,27], in which the study reported 69% of the cases had neck pain and 65% of those without AAS. On the other hand, neurological signs showed no significant difference between both groups, this was also consistent with two other studies [26, 27].Neurologic symptoms and signs may have a weak relationship to the degree of subluxation and this is probably due to individual variation in the diameter of the spinal canal.

This study has some limitations**:** The causal relationship cannot be estimated. Recall bias couldn't be excluded, some data collected were dependent on the memory of the patients. This study cannot be generalized on Iraqi population.

5. Conclusion

Atlanto - axial subluxation is common in patients with rheumatoid arthritis and it was significantly associated with: longer disease duration, rheumatoid factor positivity, lower functional class, hand deformities, and advancing disease progression. This study revealed no significant relationship between AAS in RA patients with: patient's age, gender, DAS 28, (VAS) of the patient, and smoking.

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