Is It the Age at Disease Onset or the Disease Radiological Severity That Affects Cervical Spine Involvement in Patients With Rheumatoid Arthritis?

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ABSTRACT

BACKGROUND: Cervical spine involvement in patients with rheumatoid arthritis (RA) can cause pain and disability, with a variety of neurologic signs and symptoms.

OBJECTIVES: To investigate the relationship between structural cervical spine involvement in patients with RA with the age at disease onset and the degree of radiologic severity of RA measured by Larsen scoring.

PATIENTS AND METHODS: This cross-sectional study included 50 adult patients with RA. Patients who complained or not complained from symptoms of cervical spine involvement in RA were included; we did X-ray of the cervical spine, hands, and feet; Larsen scoring method; disease activity score (DAS28); and Neck Disability Index.

RESULTS: The results revealed that patients with cervical involvement tend to be younger at their disease onset than those with no cervical involvement, as detected by cervical X-ray. The relation was significant $P < .05$ regarding all cervical involvements except for basilar invagination. Disease radiological severity (measured by Larsen score) significantly increases the risk for subaxial subluxation, $P = .040$. All other cervical complications of RA tend to have nonsignificant relation with disease severity. Using univariate binary regression analysis for risk factors for cervical involvement showed that the only probable risk factor for cervical involvement (detected by X-ray) in patients with RA is age at disease onset.

CONCLUSIONS: The early age at disease onset tends to affect cervical spine involvement in patients with RA more than the disease radiological severity.

KEYWORDS: Rheumatoid arthritis, Neck Disability Index, Larsen score, cervical X-ray

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Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with a characteristic feature of persistent inflammatory synovitis usually affecting peripheral joints and leads to cartilage destruction and bone erosion. Subsequently, joint deformity occurs. The axial skeleton, except for the cervical spine, is affected later and less frequently.[1]

Cervical spine involvement can lead to pain and disability, with a variety of neurologic signs and symptoms, but some patients with significant radiographic evidence of disease may be asymptomatic.[2] The main affection of cervical spines involvement occurs in its upper portion, causes anterior atlantoaxial subluxation (AAS), atlantoaxial impaction or basilar invagination (also known as vertical AAS), and subaxial subluxation (SAS).[3,4]

Atlantoaxial subluxation may occur within the first 2 years of disease onset. The first neurologic complaint is a headache in the occipital area due to compression of the greater occipital nerve (Arnold's neuralgia), with sensory and motor deficit affecting the arms and legs. Other complaints include neck stiffness, earache, vertigo, gait abnormalities, loss of balance, and tinnitus.[5] In established disease, complications such as quadriparesis, chronic hydrocephalus, cerebral infarction, and sudden death have been reported.[6]

Basilar invagination problems tend to appear later in the progress of the disease and present more commonly in the severe cases of RA. Brain stem compression might result from the upward migration of the odontoid process.[7]

The axial subluxation is presented as an isolated deformity or may affect multiple levels which result in the onset of a deformity with a "staircase" appearance.[8]

The degree of inflammatory changes in hands is known to correlate with cervical spine changes but no detailed data are available on such changes.[9]

Rheumatoid arthritis severity contains elements of disease activity (eg, swollen joints, elevated erythrocyte sedimentation rate [ESR]) and disease disability (eg, functional status, joint deformity). Because RA severity affects treatment and incidence of comorbid conditions, RA severity is considered as an important potential confounder in many pharmaco-epidemiologic studies.[10]

Six rheumatologists[11] compiled a list of 47 potential indicators of RA severity; radiology and laboratory findings with clinical and functional status measures are from the main categories of these potential indicators.

The aim of this study is to compare the association between structural cervical spine involvement in a group of patients with RA, with the age at disease onset and the degree of a radiological damage measured by Larsen score.

Patients

This cross-sectional study included 50 adult patients with RA who were recruited from rheumatology outpatient clinic in Sohag University hospital and were diagnosed per the ACR/EULAR 2010 for RA. Included patients complained or not complained from symptoms of cervical spine involvement in RA. We excluded patients if having any other connective tissue disease (eg, mixed, overlap syndrome, systemic lupus erythematosus, or ankylosing spondylitis) or having diabetes mellitus and metabolic diseases. All patients signed the consent form for joining the study, and the study was approved by the Ethics Committee for Sohag University.

Methods

We did the following for all patients:

1. The routine investigations for RA including rheumatoid factor (RF), C-reactive protein (CRP), ESR, complete blood picture, renal serum creatinine, and liver enzymes were performed.
2. *X-ray of the cervical spine*. Lateral views were taken in the following neck positions (flexion, extension, neutral) and anteroposterior open mouth view, using a 5-ft tube-to-plate distance and centered on the second vertebra. The parameters assessed were AAS, basilar invagination, erosion of the odontoid process of the axis, and subaxial instability. A diagnosis of AAS was made if the distance between the anterior aspect of the dens and the posterior aspect of the anterior arch of atlas are more than 3 mm during flexion.[12] Atlantoaxial impaction (basilar invagination) was measured using the Redlund-Johnell and Pettersson method (the McGregor line). This line is contracted from the base of the hard palate to the outer cortical table of the occiput. The tip of the odontoid was measured perpendicular to this line Superior migration was considered present if the tip of the odontoid is 4.5 mm above this line.[13] Subaxial subluxation was diagnosed if a vertebra has moved 3 mm or more in relation to the next vertebra when measured from the posterior line of the vertebral bodies. In addition, the posterior atlanto-dental interval was measured from lateral view radiographs.[14] Reading of cervical X-ray was done by a radiologist.
3. *X-ray hands and feet for measuring the Larsen score*.[15] Larsen has introduced the following guidelines for scoring: 0 = Intact bony outlines and normal joint space; 1 = Erosion less than 1 mm in diameter or joint space narrowing; 2 = One or several small erosions, diameter more than 1 mm; 3 = Marked erosions; 4 = Severe erosions, where there is usually no joint space left, and the original bony outlines are partly preserved; and 5 = Mutilating changes, where the original bony outlines have been destroyed.

Kaarela and Kautiainen suggested including 10 metacarpophalangeal joints and wrists and the second to the fifth metatarsophalangeal joints in the scoring, with a range of 0 to 100.[16] Scoring of Larsen was done by 2 rheumatologists; the inter-observer variability was insignificant so the mean of the 2 scoring results was entered in the statistical sheet.

4. *Disease activity score (DAS28 score)*. The score is calculated by a complex mathematical formula, which includes the number of tender and swollen joints (of a total of 28—shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and the knees), the ESR, and the patient's "assessment of global health" or visual analog scale.[17]
5. *Neck Disability Index (NDI)*. It includes 10 items, each item was scored out of 5 (with the no disability response given a score of 0) giving a total score for the questionnaire out of 50. Higher scores represented greater disability. The result has been expressed as a percentage (score out of 100) by doubling the total score.[18]

Statistics

A statistical package for social sciences (IBM-SPSS), version 22 IBM, Chicago, USA, was used for statistical data analysis.

Data are expressed as mean, standard deviation, number, and percentage. Mean ± SD was used as a descriptive value for quantitative data.

Student *t* test was used to compare the means between 2 groups, and Mann-Whitney test was used to compare median of nonnormally distributed data.

Pearson χ^2 test was used to compare percentages of qualitative data.

Table 1. The laboratory, clinical, and radiographic findings in the 50 patients with rheumatoid arthritis.

VARIABLE	RESULT
CRP positive, No. (%)	26 (52)
Hb, mean ± SD	12.23 ± 1.44
RF positive, No. (%)	41 (82)
ACPA positive, No. (%)	48 (96)
Neck pain, No. (%)	41 (82)
Numbness, No. (%)	32 (64)
Vertigo, No. (%)	19 (38)
Tinnitus, No. (%)	25 (50)
DAS28, mean ± SD	4.86 ± 1.33
NDI, mean ± SD	25.8 ± 13.6
AAS, No. (%)	14 (28)
BI, No. (%)	6 (12)
SAS, No. (%)	4 (8)
Cervical X-ray findings	
Normal, No. (%)	30 (60)
Single X-ray findings, No. (%)	16 (32)
Combined X-ray findings, No. (%)	4 (8)

Abbreviations: AAS, atlantoaxial subluxation; ACPA, anticitrullinated protein antibody; BI, basilar invagination; CRP, C-reactive protein; Hb, hemoglobin; NDI, Neck Disability Index; RF, rheumatoid factor; SAS, subaxial subluxation.

Pearson correlation test was used to compare 2 quantitative variables.

Univariate binary regression analysis was used to determine the possible risk factors for the cervical involvement of patients with RA. Receiver operating characteristic (ROC) curve analysis was used to determine the possible risk factors for the cervical involvement of patients with RA and to determine the possible cutoff points.

Results

The study included 50 patients with RA, 4 men and 46 women, with mean and standard deviation of age 44.2 ± 11.7 years with a range from 25 to 70 years, disease duration of 9.7 ± 5.2 years with a wide range from 1 to 26 years, and age at disease onset of 34.5 ± 11.5 years with a range from 19 to 58 years. Cervical X-ray showed AAS in 28%, SAS in 8%, and basilar invagination in 12% (Table 1).

The Larsen score showed a very high variation from patient to patient. This was reflected the very high difference between mean (14.2) and median (6), the very high standard deviation (26.2), and the very wide range (0-160). This means that the median here may be more accurate and useful than the mean.

The extra-articular manifestations were seen only in 12 cases (24%). The most common extra-articular manifestation was rheumatoid nodules, seen in 5 cases, followed by Raynaud's phenomenon (4 cases). Sjogen's syndrome, dry eye, and vasculitis were all seen in only 1 patient each. None of our cases showed combined extra-articular manifestations.

The mean DAS28 score (4.17 ± 1.33) fell in the moderate disease activity range but this score shows high range, from complete remission (DAS28 = 1.8) to very high disease activity (DAS28 = 7.06). Nearly half of our patients (21 cases, 42%) fell in the moderate disease activity, with another quarter (13 cases, 26%) having high disease activity. Low disease activity and remission were found in only 8 cases each.

A total of 36 cases (72%) were on current combined disease-modifying antirheumatic drug (DMARD) therapy and 13 cases were on DMARD monotherapy but with a history of another mono or combined DMARD therapy. Only 1 case was treated with monotherapy with no history of other DMARD therapy.

The most commonly used DMARD was methotrexate (MTX), which was used in nearly all cases, either in the present (62%) or in the past (34%) history. This was followed by hydroxychloroquine (HCQ), used in 88% of cases, then Salazopyrine (SSZ), used in 56% of cases, and finally, Leflunomide (LEF), which was used in only 30% of cases. No patients were under biologics.

By doing *t* test comparison between age at disease onset and cervical symptoms, we found that age at disease onset affects only the incidence of numbness with a significant difference of $P = .035$, whereas other cervical symptoms did not show any significance.

Pearson correlation showed very weak, positive, and nonsignificant correlation between age at disease onset and NDI with $r = .112$ and $P = .437$.

Table 2 shows that the patients with cervical involvement tend to be younger at their disease onset than those with no cervical involvement as detected by cervical X-ray. The relation was significant regarding all cervical involvements except for basilar invagination.

Table 3 shows that radiological severity measured by Larsen methods affects only the incidence of tinnitus with a significant difference, whereas other cervical symptoms did not show any relation to it.

There is a positive, weak but significant correlation between Larsen score and NDI. Here, we used Spearman correlation instead of Pearson correlation test because Larsen is not normally distributed among our cases $r = .389$ and $P = .005$. Mann-Whitney showed that radiological severity significantly increases the risk for SAS, $P = .040$. All other cervical complications of RA tend to have nonsignificant relation with disease severity.

Pearson correlation showed a positive, weak but significant correlation between DAS28 and NDI with $r = .379$ and $P = .007$, and *t* test showed that disease activity was not

Table 2. Comparison between age at disease onset and cervical X-ray findings in 50 patients with rheumatoid arthritis.

CERVICAL X-RAY	MEAN AGE AT DISEASE ONSET, Y		*T* TEST	*P* VALUE
	POSITIVE	NEGATIVE		
Atlantoaxial subluxation	30.29 ± 7.14	36.14 ± 12.57	2.065	.045 (S)
Basilar invagination	31.33 ± 11.20	34.93 ± 11.66	0.712	.480
Subaxial subluxation	24.25 ± 4.92	35.91 ± 11.56	3.721	.009 (S)
Overall cervical X-ray findings	30.10 ± 8.02	37.43 ± 12.69	2.293	.026 (S)

Positive and negative in this table refers to presence or absence of cervical X-ray findings, respectively; S refers to significant.

Table 3. Comparison between Larsen score and neck symptoms among the study population.

		LARSEN SCORE		MANN-WHITNEY	*P* VALUE
		POSITIVE	NEGATIVE		
Neck pain	Mean ± SD	15.68 ± 28.7	7.22 ± 4.49	176.000	.830
	Median, range	6 (0-160)	6 (2-14)		
Numbness	Mean ± SD	11.88 ± 17.1	18.22 ± 37.62	280.500	.879
	Median, range	7.5 (0-77)	6 (0-160)		
Vertigo	Mean ± SD	10.47 ± 15.8	16.42 ± 30.95	244.000	.311
	Median, range	6 (0-68)	8 (0-160)		
Tinnitus	Mean ± SD	19.56 ± 33.9	8.76 ± 13.68	209.000	.044 (S)
	Median, range	9 (0-160)	4 (0-68)		

Positive and negative in this table refers to presence or absence of neck symptoms. Here, we used Mann-Whitney instead of *t* test because Larsen score is not normally distributed among our cases.

associated with any of the cervical involvements of RA as detected by plain X-ray.

Table 4 shows that the only probable risk factor for cervical involvement (detected by X-ray) in patients with RA is the age at disease onset. Taking into consideration that odds ratio of age at disease onset is <1, this means that cervical involvement in RA is more in earlier age at disease onset.

The ROC analysis shows that age at disease onset can predict cervical involvement in RA, with a significant difference (Figure 1).

Using coordinate points of the above ROC curve, the most relevant age at disease onset is 26.5 years, below which cervical involvement can be predicted, with a sensitivity of 70% but with a low specificity of 26.7%.

We also did ROC analysis with the disease duration, DAS28, and Larsen score which could not predict cervical involvement in any of them.

Discussion

Our study included 50 cases; most of our cases were women (92%), with only 4 cases (8%) being men, and the mean age of our study group was 44.2 ± 11.7 years.

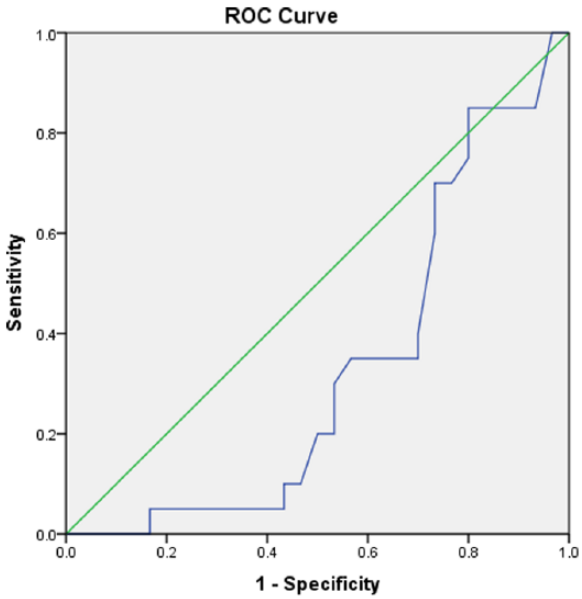
The NDI has been used effectively in both clinical and research settings as the most widely used and most strongly validated instrument for assessing self-rated disability in patients with neck pain.[19] By applying it in our study, it showed very wide variation, ranging from 8% to 57.1%. The most common cervical symptom among our cases was neck pain, seen in 82% of cases, followed by numbness (64%), then tinnitus (50%), and finally, vertigo, seen in only 38% of cases. Previous studies by Chellapandian et al[20] and Aggarwal et al,[21] respectively, showed that neck pain was seen in 68% and 70% of cases. These were higher than those reported by Souza et al[22] who reported an incidence of neck pain in only 54.3% of their 81 cases; it looks that most studies reported neck pain in more than 50% patients with RA.

The results of cervical X-ray in our study showed that AAS was found in 28% of cases, basilar invagination was found in 12% of cases, and SAS was found in 8% of cases. The overall cervical X-ray was abnormal in 40% of cases, of whom single cervical finding was found in 32% and 2 or more findings were found in 8% of cases. Our results were more or less similar to that seen by Alcala et al[23] who found that the overall prevalence of cervical X-ray involvement was around 33% of their cases.

Table 4. Univariate binary regression analysis for risk factors for cervical involvement in patients with rheumatoid arthritis.

	B	SE	WALD	*P* VALUE	OR (95% CI)
Age at disease onset	−0.063	0.030	4.532	.033	0.939 (0.886-0.995)
Disease duration	0.090	0.059	2.321	.128	1.095 (0.974-1.229)
Sex	−0.747	1.193	0.392	.531	0.474 (0.046-4.908)
DAS28	0.034	0.218	0.025	.875	1.035 (0.675-1.586)
CRP	0.539	0.585	0.849	.357	1.714 (0.545-5.396
RF	−0.348	0.775	0.202	.653	0.706 (0.155-3.224)
Larsen score	0.055	0.031	3.199	.074	1.057 (0.995-1.123)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; RF, rheumatoid factor.



Area Under the Curve

Area	Std. Error	P value	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.328	0.076	0.040	0.178	0.477

Figure 1. ROC curve for age at disease onset as a predicting factor for cervical involvement in rheumatoid arthritis. ROC indicates receiver operating characteristic.

However, they reported that odontoid erosion was the most common X-ray finding (20%), followed by subaxial instability (16%), AAS (15.5%), and finally, basilar invagination (8%). The study done by Neva et al[24] showed similar data to our results, with an overall prevalence of cervical involvement of around 44% among patients with RA and also with AAS being the most common finding, seen in 34% of cases.

The study done by Chellapandian et al[20] in India showed that cervical involvement was seen in 42.7% of their cases, which is very similar to our results. Also, the prevalence of individual cervical X-ray findings was somewhat different from our study, as they found that odontoid erosions were the commonest finding (25.3%), followed by AAS (21.3%), and finally, osteoporosis in 2.6% of their patients.

Other Indian studies by Aggarwal et al[21] and Rajangam et al,[25] respectively, showed much higher prevalence of cervical involvement in RA (65% and 69.9%). And the study done by Souza et al[22] showed even more prevalence of radiographic cervical involvement, seen in 84% of their cases.

In research studies, the most common used scores are the Sharp/Van der Heijde[26] and the Larsen score, and many studies showed significant positive correlation between both scores[27–29] so we preferred to use the Larsen one in this study, as it is easier and less time-consuming and showed a very high variation from patient to patient. This reflected the high difference between mean (14.2) and median (6), the high standard deviation (26.2), and the wide range (0-160). This means that the median here may be more accurate and useful than the mean.

Comparison between age at disease onset and cervical symptoms revealed that age at disease onset affected only the incidence of numbness with a significant difference, whereas other cervical symptoms did not show any correlation with disease onset age.

Our results revealed that patients with cervical involvement tend to be younger at their disease onset than those with no cervical involvement as detected by cervical X-ray. The relation was significant regarding all cervical involvements except for basilar invagination.

Comparison between disease activity (measured by DAS28) and neck symptoms among our study cases showed that disease activity affects only the incidence of neck pain with a significant difference, whereas other cervical symptoms did not show any correlation with disease activity.

Comparison between disease radiological severity (measured by Larsen score) and neck symptoms among our study population showed that disease severity affected only the incidence of tinnitus with a significant difference, whereas other cervical symptoms did not show any correlation with disease severity.

In our study, disease radiological severity significantly increases the risk for SAS. All other cervical X-ray findings of RA tend to have nonsignificant relation with disease severity. Here, we used Mann-Whitney test instead of Student *t* test because Larsen score is not normally distributed.

Using univariate binary regression analysis for risk factors for cervical involvement in patients with RA, we found that the only probable risk factor for cervical involvement (detected by X-ray) in patients with RA is the age at disease onset.

Taking into consideration that odds ratio of age at disease onset is <1, this means that cervical involvement in RA is more in earlier age at disease onset.

Using ROC curve for age at disease onset as a predicting factor for cervical involvement in RA showed that age at disease onset can predict cervical involvement in RA, with a significant difference.

Using coordinate points of the above ROC curve, the most relevant age at disease onset is 26.5 years, below which cervical involvement can be predicted, with a sensitivity of 70% but with a low specificity of 26.7%.

However, ROC analysis shows that each of disease duration, DAS28 or Larsen score cannot predict cervical involvement in RA, with a nonsignificant difference.

Our study was similar to that seen by Alcala et al[23] who found that only patients with longer disease duration and earlier age at disease onset showed a significant rise of cervical involvement of RA. However, they did not test the role of disease activity or severity in the development of cervical RA complications.

On the contrary, the study done by Souza et al[22] concluded that cervical involvement is significantly associated with the disease severity measured by the functional capacity classification according to Steinbroker et al[30] and the classification of RA according to ACR, formerly known as the ARA (American Rheumatism Association).[31] They found that cervical involvement was not significantly associated with neck pain as it may occur in asymptomatic patients.

A study done by Paimela et al[32] found that the annual progression of Larsen score of patients with RA was significantly faster among patients with involvement of cervical spine than in those without, indicating a significant correlation between cervical involvement and severity of RA.

The study done by Neva et al[24] showed a positive and significant relation between cervical involvement and each of disease duration, RF positivity, health assessment questionnaire, and disease activity (measured by DAS28, ESR, CRP).

It should be noted that their study involved patients with RA of long duration, and furthermore, all patients were on the waiting list for orthopedic surgery, which might be considered as representing a failure of conservative treatment.

However, the study done by Chellapandian et al[20] stated that there was a statistically significant correlation of cervical spine involvement with duration of the disease, disease activity measured by tender and swollen joint counts, rheumatoid nodules and disease severity measured by joint deformities, and erosions in X-rays of hands and feet. They also found a statistically significant relation with extra-articular manifestations and RF positivity. This was similar to the observations published by Aggarwal et al[21] who reported all these positive correlations except for the extra-articular features.

Study Limitations

This study involved 50 patients with RA, which is considered a small sample size, and further studies are needed to assess the relationship between age at RA onset and cervical spines involvement.

Conclusions From Our Study

- Cervical spine misalignment is a common radiographic finding in patients with RA. Disease radiological severity significantly increases the risk for SAS, whereas all other cervical X-ray findings of RA tend to have nonsignificant relation with the disease severity.
- The age at disease onset affects cervical spine involvement in patients with RA more than the disease radiological severity measured by Larsen score.
- Radiography remains the mainstay for imaging in RA (spines, hands, and feet); it is inexpensive, readily available, easily reproducible, and it allows easy serial comparison for assessment of disease progression, whereas the major role for computed tomography and magnetic resonance imaging is in preoperative assessment.

Author Contributions

HSA designed the protocol, read the larsen score, wrote the manuscript. RA collected the patients and did the rheumatological assessment. WEM did the radiological assessment and read the X-ray cervical. All other co-authors worked in and edited the statistical analysis and the final manuscript.

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