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Investigating the prevalence of cervical spine instability in patients with rheumatoid arthritis

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Abstract

Introduction Rheumatoid arthritis (RA) is a chronic, progressive, and systemic disease that broadly affects connective tissues, especially synovial joints. The aim of this study was to investigate the prevalence of cervical spine instability in patients diagnosed with RA.

Material and methods Fifty patients with rheumatoid arthritis referred to Imam Khomeini Hospital in Urmia were selected by the census. After taking a history, the neck X-ray was taken from the lateral view in static, flexion, and extension.

Results Among 50 patients, 11 were male (22%) and 39 were female (78%). The average disease duration period was 5.63 ± 5.21 years. 43 patients (86%) had normal AADI, 5 patients (10%) had abnormal dynamic AADI, and 2 patients (4%) had abnormal AADI static. Basilar invagination instability was not found in the studied patients. There was no significant difference in terms of gender between normal and abnormal cases of AADI. Among normal AADI cases, 40 cases (93%) were taking drugs and among abnormal AADI cases, 4 cases (57.1%) were taking drugs and 3 patients (42.9%) were not receiving drug treatment. There is a significant difference between normal and abnormal cases of AADI in terms of drug use.

Conclusions In our study, 7 cases of abnormal AADI were found among 50 patients, of which 2 had abnormal static AADI, which indicates the worsening of cervical spine instability. The study also found that those not treated with DMARDS were more likely to have cervical spine instability.

Keywords Rheumatoid arthritis, Cervical spine, Instability, Neurological symptoms

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease with systemic clinical presentations. RA has mainly affected the musculoskeletal system like ligaments, joints, and bones, but it can also be present in some other organs [1, 2]. The pathological mechanism of RA in the musculoskeletal system includes bone erosion and damage of articular cartilage, mainly in small joints. The metatarsophalangeal joints are the most frequent joints involved in patients with RA. However, some other joints are also involved in the pathology of RA [3, 4]. The cervical spine is another joint influenced by RA and stands as the second most commonly involved joint. Cervical spine involvement in patients with RA is associated with spinal instability and in severe cases, even with neurological complications. Spinal instability of patients with RA showed that it resulted from chronic inflammation of the synovium, bone erosion, and ligament laxity. Epidemiological analysis showed that approximately 16–74% of patients with RA suffered from cervical joint involvement [5].

The variety in the prevalence of cervical spine involvement in patients with RA is attributed to the disease control and the study population. Therefore, several risk factors have been recognized for the development of cervical spine instability in patients with RA, including uncontrolled RA as the main risk factor, age younger than 45 years [6], corticosteroid use [7], discontinuation of disease-modifying anti-rheumatoid drugs (DMARDs) [8], early onset cervical instability [9], and erosive changes [8]. During the last decades, improvement in the clinical management of patients with RA by introducing DMARDs and biological therapies is associated with reducing morbidity and severity and subsequently resulted in a lower rate of cervical spine instability and better outcomes for patients [10]. It was shown that conventional X-ray is the most frequently radiological approach for diagnosis of cervical instability [5] and atlantoaxial subluxation (AAS) and subaxial subluxation (SAS) are, respectively, the most common radiological findings in patients with RA. Moreover, cranial settling or also called basilar invagination is the most severe form of spinal instability [10].

The prevalence of RA is estimated 1% in the worldwide population and higher in the American and European populations in comparison with the Iranian population which is 0.37% [11, 12]. Due to the heterogeneity of the prevalence of cervical spine instability and the role of epidemiological studies population and also because there is no study specifically conducted on Iranian nationality patients, here in this study, we investigate the prevalence of cervical spine instability in patients diagnosed with RA. Moreover, we tried to determine the risk factor responsible for the development of cervical instability in RA patients to highlight the importance of risk factors for the establishment of cervical instability and provide an appropriate guideline for clinicians, governments, and health institutes.

Materials and methods

Study design

This is a retrospective study on patients with RA who were referred to the Imam Khomeini Hospital, Uremia, Iran, from March 2020 to March 2021. The present study was accomplished to determine the prevalence of cervical spine instability in patients diagnosed with RA and identify the risk factor for RA-induced cervical spine instability. This study was approved by the Ethics Committee of Urmia University of Medical Sciences, West Azerbaijan, Iran. Written informed consent was obtained from all the patients. X-rays were obtained at the beginning of the study from all patients enrolled; no further imaging, including MRI and CT scan, was requested. No additional costs were charged to patients. This observational study was outlined based on the STROBE guideline for epidemiological observational studies [11].

Inclusion and exclusion criteria

The inclusion criteria were a definitive diagnosis of RA who was referred to Imam Khomeini Hospital between March 2020 and March 2021, the written informed consent was received, and after that patient enrolled in the study. However, the first presentation of disease before 18, history of cervical trauma, history of surgery on the cervical spine, Lhermitte sign on extension/flexion of the neck, without written informed consent.

Study methods

Patients referred to our tertiary center were considered to include in our study based on the eligibility criteria. The demographic, radiological, and medical information of patients including sex, age, duration of disease, drug history, neurological manifestations, clinical symptoms of other joints rather than the cervical spine, and radiological imaging of the neck at the lateral view were obtained. The cervical imaging of lateral view was taken at static and flexion–extension positions by AADI more than 4mm to investigate the atlantoaxial subluxation which is presented in the early stages of the disease and basilar invagination.

Ethical approval

The methodology of the present study was accepted by the ethics committee of the Uremia University of Medical Science. All of the study processes were explained to the patients who fulfilled the eligibility criteria before

enrollment and all included patients' written informed consent. This study is conducted with considering the ethical consideration of the Uremia University of Medical Science and we adhered to the Helsinki statement in all stages of the study.

Statistical analysis

The identified data of demographic and medical information of patients were analyzed. The patients' information was analyzed by descriptive statistics tests, and the results were presented as mean ± standard deviation (SD) and frequency (percentage). An Independent *t* test was used to compare quantitative variables, and the Chi-square test was used for qualitative variables. Appropriate statistical tables and graphs have been used to describe the data. For the variables of gender, age, AADI, duration of involvement with the disease, drugs, and joint symptoms in other parts of the patient's body, frequency tables and frequency percentages were used. The mean ± SD was reported for the variables of age and duration of the disease. All statistical analysis was carried out by IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA). A *P* value of less than 0.05 is considered significant.

Results

Patients

Fifty patients met the eligibility criteria and enrolled in the study. Of 50 patients, 11 patients (22%) were male and 39 (78%) were female with a 3.54:1 female-to-male ratio. The mean age of patients was 51.52 ± 13.4 years with a minimum and maximum of 21 and 82 years, respectively. The mean disease duration of patients was 5.63 ± 5.21 years. The minimum and maximum disease duration were 3 months and 20 years, respectively. The average duration of disease in cases without instability was 4.55 ± 4.22 and in those with instability was 12.28 ± 6.12 (Table 1). There is a significant difference between the two groups based on disease duration, and patients with cervical instability had a longer disease duration (*P* value = 0.001).

Abnormal AADI and basilar invagination

About 43 patients (86%) had a normal AADI, 5 patients (10%) had an abnormal dynamic AADI, and 2 patients (4%) had an abnormal static AADI. Moreover, there is no instability reported regarding basilar invagination. Of the 43 patients with normal AADI, 10 patients were male (23.3%) and 33 patients were female (76.7%). Regarding abnormal cases, 1 case (14.3%) was male and 6 cases were female (85.7%). There was no significant difference regarding sex distribution between patients with normal and abnormal AADI (*P* value = 0.59). The mean age of patients with normal and abnormal AADI was 51 ± 12.88 and 54.71 ± 17.07, respectively. No significant difference in mean age was observed between the two groups (*P* value = 0.5) (Table 2).

Table 1 The demographic data of patients enrolled in the study

Variable	Number (%)		Range	Mean ± SD
Sex	Male = 11			
	Female = 39			
Age			21–82	51.52 ± 13.40
Disease duration	Normal AADI	4.55 ± 3.47	Total = 3 months–20 years	5.63 ± 5.21
	Abnormal AADI	12.28 ± 7.1		
AADI static (< 3)	Normal	48 (96)		
	Abnormal	2 (4)		
Dynamic AADI	Normal	43 (86)		
	Abnormal	7 (14)		

Abnormal AADI and systemic clinical symptoms

The rate of finger and toe joint involvement was 68%, knee 40%, wrist 48%, shoulder 22%, elbow 22%, back pain 6%, and neck pain 70% across the entire RA population. None of the studied patients had neurological symptoms. In the examination of patients with abnormal AADI with systemic joint involvement, 6 cases (85.7%) had systemic joint involvement and 1 patient (14.35%) had no systemic joint involvement. Moreover, 41 patients (95.3%) with normal AADI had joint involvement rather than cervical spine joint and 2 patients (4.7%) had no systemic joint involvement. There is no significant difference between patients with normal and abnormal AADI regarding systemic joint involvement (*P* value = 0.32). Finger joint involvement, toe joint involvement, knee joint involvement, wrist joints involvement, ankle joint involvement, shoulder joint involvement, elbow joints involvement, and neck pain were reported in 71.4%, 57.1%, 42.9%, 57.1%, 42.8%, 42.9%, 14.3%, and 85.73% of patients with abnormal AADI and there is no significant difference between patients with normal AADI and abnormal AADI (Table 3).

Abnormal AADI and pharmacotherapy

In the investigation of patients with normal AADI who underwent medical treatment, 40 (93%) used medications, and 3 (7%) had no pharmacotherapy. Regarding patients with abnormal AADI, 4 patients (57.1%) used therapeutic agents, and 3 patients (42.9%) without use drugs. There was a significant difference between abnormal and normal patients in the course of using medication and the risk of cervical instability was significantly

Table 2 The relationship between normal and abnormal AADI and sex distribution, systemic joint involvement, and medication use

Variable	Male (%)		Female (%)		*P* value
AADI and sex distribution	Normal	10 (23.3)	Normal	33 (76.7)	0.59
	Abnormal	1 (14.3)	Abnormal	6 (85.7)	
	Total = 11		Total = 39		Total = 50
AADI and systemic joint involvement	Positive		Negative		0.32
	Normal	41 (95.3)	Normal	2 (4.7)	
	Abnormal	6 (85.7)	Abnormal	1 (14.3)	
	Total = 47		Total = 3		Total = 50
AADI and medication use	Positive		Negative		0.007
	Normal	40 (93)	Normal	3 (7)	
	Abnormal	4 (57.1)	Abnormal	3 (42.9)	
	Total = 44		Total = 6		
AADI and age	Normal		Abnormal		0.5
	51 ± 12.88		54.71 ± 17.07		

Table 3 The distribution of positive and negative signs in patients with RA and the relationship with AADI

Variables	AADI	Patients with positive signs (%)	Patients with a negative sign	*P* value
Hand finger joints	Normal	29 (67.4)	16	0.83
	Abnormal	5 (71.4)		
Foot finger joints	Normal	30 (69.7)	16	0.45
	Abnormal	4 (57.1)		
knee	Normal	17 (40.5)	30	0.9
	Abnormal	3 (42.9)		
Wrist	Normal	20 (46.5)	26	0.6
	Abnormal	4 (57.1)		
Ankle	Normal	16 (37.2)	31	0.81
	Abnormal	3 (42.8)		
Shoulder	Normal	8 (18.6)	39	0.15
	Abnormal	3 (42.9)		
Elbow	Normal	10 (23.3)	39	0.59
	Abnormal	1 (14.3)		
Lumbar pain	Normal	3 (7)	47	0.47
	Abnormal	0 (0)		
Neck pain	Normal	24 (55.8)	20	0.06
	Abnormal	6 (85.7)		

higher in patients without using drugs than in patients using drugs (*P* value = 0.007) (Table 2).

Discussion

Rheumatoid arthritis (RA) is a chronic, progressive, and systemic disease that specifically manifests in its tissues. It affects especially the synovial joints [13]. Rheumatoid arthritis is the most common type of immune-mediated arthritis. The involvement of the cervical spine occurs several times after the involvement of the peripheral joints. The cervical spine consists of two separate parts including the upper cervical spine (C1–C2) and lower cervical (C3-C7) spine. Neck rotation occurs in the upper part of the cervical spine and FLEX-EXT occurs in the lower parts. The most serious and potentially fatal complication of rheumatoid arthritis is the instability of the upper spine. Upper spine involvement in patients with rheumatoid arthritis is associated with higher morbidity and mortality than those with lower cervical spine involvement and without rheumatoid arthritis [14]. Involvement of the upper spine occurs in the first stages of the disease, and then, rarely, the lower spine is also involved [15].

Most rheumatoid arthritis patients with abnormal imaging of the cervical vertebrae remain asymptomatic for years, and a small portion of patients eventually require surgery, which is primarily due to neurological problems. In people who were candidates for surgical intervention, surgery in the early stages is in priority. If the surgery is delayed, the outcome will be poor and the possible death will be increased [16]. Cervical radiography is the most effective tool in examining patients suspected of instability of the cervical spine, and a lateral view in static and flexion–extension mode is very effective in measuring dynamic and static instability of the cervical spine. AADI, which is the distance between the anterior surface of the DENS and the posterior surface of the anterior ring of C1, is between 0 and 3 mm normally for adults, while between 3 and 6 mm indicates atlantoaxial instability and above 9 mm is an indication of surgery [17]. AADI diameter is diagnostic in terms of persistent neurological disorders. MRI and X-ray are used for follow-up [15]. Additional patient

comorbidities must be taken into account as they may impact ADI measurement as well.

In this study, 43 people (86%) were normal in terms of cervical spine instability and 7 people (14%) had cervical spine instability. In the study conducted by Al-daoseri et al., 7.4% of the studied patients had instability of the cervical spine, of which 73.3% was AAS [14]. In the study conducted by André Luiz et al., atlantoaxial subluxation was present in 42.9% of the studied patients [18]. In the study conducted by Baek et al., among 1114 rheumatoid arthritis patients examined, 306 cases (27.5%) had cervical spine instability, and the most common type is atlantoaxial subluxation with 17.9% [19].

In the present study, 11 patients were male and 39 patients were female and it is shown that there was no significant relation between sex and AADI which were consistent with previous studies [3, 6, 17, 20–23]. Baek et al. concluded that the male sex has a significant relation with cervical spinal stability in patients with RA which was in contrast with the present study [19]. However, Al Dsoseri et al. showed that the female sex has a significant relationship with cervical instability in the Iraqi population investigated [14].

In the present study, it is shown that there was no significant relationship between age at the time of diagnosis and instability of the cervical spine which was strictly consistent with previous studies [8, 14, 19–21, 23, 24]. On the other hand, in the study of Ahn et al., it is demonstrated that younger age (less than 45 years) at the time of diagnosis in the Korean population with RA has a significant relationship with cervical instability [6].

In the study conducted by Joaquim et al., which is a systematic review, the most common radiological manifestation of cervical spine involvement was atlantoaxial subluxation, cranial settling, and subaxial subluxation in up to 80% of cases with RA [5]. They also concluded that MRI is the best imaging method for diagnosis of cervical involvement and the primary cause of cervical instability is systemic uncontrolled RA [5]. For following up they proposed that a CT scan and dynamic plain radiography could be advisable. In addition, they recommended long-term follow-up is needed for patients with late cervical spine instabilities [5]. The present study was conducted during the COVID-19 pandemic and investigated on C1-C2 cervical spine and confirmed by flexion–extension X-ray, and other imaging modalities including CT and MRI were not requested to minimize the confrontation with the virus.

RA as a chronic inflammatory disease leads to destruction in peripheral joints by erosion and the sustained inflammation increases the subluxation of the cervical spine up to 42% over 20 years of the beginning of the disease [25, 26]. It is shown that tight control or treatment of RA in the early stage diminishes, retard, and may prevent the possibility of subluxation induced in these patients [26]. In the present study, there was a significant difference between the two groups based on disease duration, and patients with cervical instability have a longer disease duration that was consistent with previous studies [3, 6, 14].

The positive effect of DMARDs in the treatment of RA is shown in the literature previously [25] and suggested to be used in the early stage of the disease. A study by Neva et al. demonstrated that early treatment of RA by DMARDs diminished or stopped the progression of cervical disorders in patients with RA [26]. The results of the present study showed that there was a significant relationship between the use of DMARDs and cervical spinal instability which was in line with the previous studies [6]. Conversely, there was no significant relationship between biologic DMARD use and cervical instability in patients with RA in Baek et al. [19] study. On the other hand, other conventional therapies in patients with RA include corticosteroids which lead to osteoporosis, cervical movement reduction, and subaxial subluxation worsening cervical spine instability [27–30]. We did not investigate the effects of corticosteroids on cervical spine instability in patients with RA and the study was only limited to patients who received DMARDs for treatment.

Babic-Naglic et al. reported that RA often involves small joints instead of medium and large joints [31]. Our results showed no significant relationship between the distribution of different joint involvement in patients with RA and the relationship with AADI. Moreover, in the present study, there was no significant relationship between AADI and systemic joint involvement. The other important point that should be considered is that the bone-on-bone injury or inflammation that leads to it will form a pannus which may reduce movement but not necessarily destabilize. Inflammation at the Dens may increase ADI by mass effect, but may not necessarily cause instability [32].

Many other factors have been reported in different studies which may have a positive effect on cervical spine instability in patients with RA including, ESR, CRP, erosions of peripheral joints, RF, and active disease, BMI [17]. Besides these factors, Al-daoseri et al. demonstrated that positive history of RA has a significant relationship with cervical instability in Iraqi patients [12]. The results of this study were in line with the present study.

The results of the studies are heterogeneous and various in different parts of the world and it seems that many factors may have positive effects on the instability of the cervical spine in patients with RA including ethnicity, different follow-up period, initial treatment method, radiological methods of diagnosis of the cervical instability,

previous treatments, coexisting conditions, other concurrent diseases, corticosteroid use, work-related disorder, and disease status. It is recommended that future studies focus on a larger number of patients and the above-mentioned factors. The results of the present study emphasized the importance of treatment in the early stage in RA patients. On the other hand, some risk factors responsible for the development of cervical instability in these patients were highlighted which will be a clue for clinicians, governments, and health institutes. Some studies proposed early and aggressive surgical intervention before neurological deficit and myelopathy manifestation to preserve cervical spine function, minimize long-term mortality, and increase neurological recovery in patients with RA [33]. However, early diagnosis, treatment, and repeated follow-up could reach more favorable in patients with RA [5].

Limitation

This study faced some limitations. First, the number of patients recruited in this study was limited due to the COVID-19 pandemic and the lack of cooperation of patients with the authors of the study. Second, due to the observational nature of the study adjusting baseline characteristics are not achievable to remove the confounder factors. Third, some related factors such as BMI, weight, job history, concurrent diseases, smoking, corticosteroid use, and laboratory findings such as ESR, CRP, and RF were not obtained due to a lack of patient collaboration during the pandemic for additional data gathering.

Conclusions

The results of our study showed that there was a significant relationship between disease duration and treatment with DMARDs with cervical spine instability. On the other hand, there was no significant relation between sex distribution, systemic joint involvement, age, distribution of joint involvement, and AADI. In the future, practitioners should follow up with patients with RA routinely by requesting laboratory and imaging to diminish and retard chronic inflammation that leads to additional side effects to protect from developing spine instability in the future.

Abbreviations

RA	Rheumatoid arthritis
DMARDs	Disease-modifying anti-rheumatoid drugs

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None.

Author contributions

AR was involved in supervision of the research, idea procurement, final approval of the manuscript. AJK helped in final approval of the manuscript. FES contributed to idea procurement, final approval of the manuscript. MAH was involved in supervision of the research, idea procurement final approval of the manuscript. RD helped in data collection, supervision of the research, idea procurement, final approval of the manuscript. NJR contributed to final approval of the manuscript. SANA was involved in data collection, corresponding author, supervision of the research, idea procurement, writing, drafting, analysis of the article, final approval of the manuscript.

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Availability of data and materials

Available on request.

Declarations

Ethics approval and consent to participate

Yes.

Competing interests

None.

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