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Prevalence of cervical spine instability among Rheumatoid Arthritis patients in South Iraq

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ABSTRACT

Aim of the work: This study analysed the prevalence of cervical spine instability in Rheumatoid Arthritis (RA) patients following at a single centre in Basrah.

Patients and methods: Data were collected directly from patients through cervical spine examinations. Each patient was sent for dynamic (flexion and extension) lateral cervical radiographic imaging to assess the presence of atlantoaxial subluxation (AAS), superior migration of the odontoid (SMO) and sub-axial subluxation (SAS). Patients with positive radiographic findings were sent for MRI scans of the cervical spine to assess neurological compression.

Results: The prevalence rate of cervical spine instability in RA was 15/203 (7.4%) of the total sample, occurring primarily in patients of 37–65 years old (mean: 48 ± 8.9 years), were 3/15 (20%) aymptomatic. The majority (60%) being at the moderate stage of the disease activity (using a Clinical Disease Activity Index [CDAI). In terms of type of cervical spine involvement, isolated AAS was found to have the highest occurrence (73.3%), followed by combined SAS and SMO (13.3%), combined AAS and SMO (6.7%), and combined AAS and SAS (6.7%). A significant relationship was found between the type of cervical spine involvement in RA and a disease onset duration, disease activity, body mass index and peripheral erosion with P value < 0.05.

Conclusion: Cervical spine subluxation in RA patients may be asymptomatic It is therefore essential to obtain a dynamic radiographic image of the cervical spine in order to diagnose cervical spine involvement and protect the patient from severe outcomes.

The clinical trial **registration number** included in a the official document from Ministry of Higher Education and Science Research/Basrah University/Faculty of Medicine to Basrah Health Directorate/Research and Development Division is 72/3588 in 7 Jan 2017.

1. Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease of unknown aetiology that primarily targets synovial tissues, cartilage and bone. RA is also the most common form of immune-mediated arthritis.[1] Involvement of the cervical spine often follows the peripheral joints.[2] The cervical spine is composed of two distinct parts, the upper cervical spine (CI and C2, with the atlantoaxial, atlantoodontoid, and atlantooccipital joints) and the lower cervical spine (C3 to C7, with the uncovertebral and facet joints at each level). Rotation of the neck occurs mainly in the upper cervical spine and flexion-extension in the lower cervical spine.[3] Because they are extremely mobile, the various components of the cervical spine, particularly the occipitocervical junction, are subjected to considerable stress. The joints are stabilized by a large number of ligaments, including the transverse ligament, the alar ligaments, and the accessory atlantoaxial ligaments.[4–7] The cervical spine can severely affect RA, but findings on the proportion of its involvement vary between different studies conducted on different populations (e.g., 30%,[8] 30%–50%,[9] and 19%–88%[10]). RA is the most frequently-observed chronic inflammatory disease, affecting approximately 1% of the white population, with females affected 3 times more often than males.[11] The age at diagnosis is typically 30–50 years old, with

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the most serious and potentially lethal manifestation of RA being the instability of the upper cervical spine.[10] Involvement of the cervical spine in patients with RA is associated with higher morbidity and mortality than similar cervical spine involvement in patients without RA. Therefore, in order to achieve better disease management and save the lives of more patients, greater awareness of the various pathologic processes that can affect the cervical spine is required.[2]

Atlantoaxial subluxation (AAS) is diagnosed based on the distance between the anterior arch of the atlas and odontoid process of the axis, with a distance of 3 mm or above being indicative of AAS. In most cases, AAS presents within two years of onset. There is a significant risk of myelopathy when the diameter between the posterior arch of the atlas and odontoid process of the axis is 14 mm or less. Patients with AAS typically complain of occipital headaches (Arnold's neuralgia, caused by compression in the greater occipital nerve). Further symptoms include the loss of sensory and motor functions in the limbs, along with neck stiffness, earache (caused by compression of the greater auricular nerve), abnormal gait, loss of balance, tinnitus (cause by changes in the vertebral artery flow), and vertigo.[10] Lhermitte's sign, in which the patient feels a buzzing sensation similar to an electric shock shooting down the spine and often into the arms, legs, hands and feet, can present when bending the neck forwards.

Complications of AAS include chronic hydrocephalus, cerebral infarction, quadriparesis, and sudden death.[7] Basilar invagination complications typically appear in more severe RA cases, often presenting at a later stage. Symptoms have been found to occur in 4–34% of RA patients. Here, compression of the brainstem can occur as a result of the odontoid process moving upwards. AAS can appear in 7–29% of cases and may be found to exist in isolation or across multiple points (resulting in a staircase-like abnormality which is characteristic of sub-axial subluxation).[12]

In an earlier study on 102 RA patients with AAS appearing within two years of disease onset, a connection between erosion of peripheral joints and AAS was determined. The study showed that these patients were predicted to experience diminished functional capacity over time.[12] With this being said, RA progression has been delayed through early intervention in form of disease-modifying antirheumatic drugs (DMARDs) and anti-inflammation drugs. This can also impact the extent of cervical spine involvement in RA. It is anticipated that there could be a reduced prevalence of cervical involvement in RA through the adoption of such measures, since early administration of DMARDs may hinder pannus growth.[12]

The purpose of this study was to establish the prevalence of cervical spine involvement in RA patients following at a single centre in Basrah in order to detect factors for early diagnosis in asymptomatic RA patients with cervical spine involvement. It is hoped that by achieving early diagnosis, disastrous irreversible neurological deficits can be avoided.

2. Patients and methods

A descriptive analytical cross-sectional study was conducted at Basrah Teaching Hospital from January 2017 to November 2017. The study reviewed 203 RA patients who fulfilled the 2010 RA classification criteria.[13] RA patients who attended the rheumatology and biological therapy clinics at Basrah Teaching Hospital were included. Excluded from the study were patients with degenerative spondylosis, juvenile RA and traumatic cervical spine instabilities.

The clinical trial registration number included in a the official document from Ministry of Higher Education and Science Research/ Basrah University/Faculty of Medicine to Basrah Health Directorate/ Research and Development Division is 72/3588 in 7 Jan 2017.

Data were collected directly from patients by the same researcher, with the aid of clinical examinations and radiographic assessments. All patients were also asked to complete the research questionnaire. Patients were also divided by gender (male and female) for analysis. Five age groups were set for the sample: 20–30 years old (Group 1), 31–40 years old (Group 2), 41–50 years old (Group 3), 51–60 years old (Group 4), and over 60 years old (Group 5). Marital status was classified as unmarried, married, divorced, and widowed.

Body Mass Index (BMI) was categorised normal range BMI 18.50–24.99, Grade I overweight BMI 25.00–29.99, Grade II overweight BMI 30.00–39.99, Grade III overweight BMI≥40.00 [BMI = weight kg/height^2(m^2)].[14] Patients were further categorised by residency, classified as either Basrah residents (Group 1) or patients from other governorates (Group 2). Date of onset for disease symptoms and the date of diagnosis were determined to assess the duration of anti-rheumatic medication use along with the period that each patient spent untreated. Medications were divided into two categories: first-line treatment, such as steroids and nonsteroidal anti-inflammatory drugs (NSAIDs); and second-line treatment, such as conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) and biological disease modifying anti-rheumatic drugs (bDMARDs).

Symptoms of cervical spine involvement in each patient were determined as follows: neck pain, vertigo, tinnitus, loss of equilibrium, and upper and lower limb symptoms (e.g., pain, weakness or numbness). Urinary sphincter function was assessed as normal or abnormal. Faecal sphincter function was also assessed as normal or abnormal. Family history of RA in first- and second-degree relatives was also recorded. Patients were also categorised based on smoking habits, as active smokers or non-smokers.

A full physical examination of the cervical spine was conducted for every patient. Patients were examined for the existence of neck deformity and rheumatoid nodules. Passive and active neck movements were categorised according to range of movement and pain (normal, stiff, or stiff and tender). The Lhermitte's sign test was also performed along with spinal tapping. A general neurological examination was then performed for each patient, reviewing sensory and motor deficits, deep tendon reflexes, and signs of upper or lower motor neuron lesions.

Disease activity was assessed using the Clinical Disease Activity Index (CDAI) value for each patient, examining 28 joints for tenderness and swelling (4 middle interphalangeal joints, the interphalangeal joint of the thumb, 5 metacarpophalangeal joints, and the wrist, elbow, shoulder and knee joints). The Visual Analogue Scale (VAS) was used to measure pain. The CDAI value is calculated based on the tender joint count, swollen joint count, patient global assessment of disease activity and the evaluator assessment of disease activity (Remission CDAI $\leq$ 2.8, Low Disease Activity CDAI > 2.8 and $\leq$ 10, Moderate Disease Activity CDAI > 10 and $\leq$ 22, High Disease Activity CDAI > 22).[15] After obtaining the results, the data were processed using the RheumaHelper mobile application for Android, providing a final CDAI value.

All patients were sent for dynamic (flexion and extension) lateral cervical radiographic imaging to assess the presence of atlantoaxial subluxation (AAS), superior migration of the odontoid (SMO), and sub-axial subluxation (SAS). Patients with positive plain radiographic changes were sent for an MRI of the cervical spine. It is also important to mention that radiology technicians followed guidance on how to position the patient whilst performing the procedure, which was carried out with the patient in a sitting position, shoulders down, with maximum gradual active flexion and extension. Measurements were then taken directly from the monitor of the digital X-ray machine. An antero-posterior view of both hands was also generated for each patient to assess the existence of peripheral joint erosion.

AAS was determined by calculating the anterior atlantodens interval (AADI) and posterior atlantodens interval (PADI) (Fig. 1). SMO was determined using the Clark station method, the station of the atlas is determined by dividing the odontoid process into thirds in the sagittal plane. Normally, the anterior ring of C1 should be adjacent to the cephalad third of C2 (station I). If the ring of C1 is adjacent to the middle third of C2, mild cranial settling is indicated (station II). If the anterior ring of C1 is adjacent to the base of C2, it is considered evidence of severe cranial settling (station III) (Fig. 2).[11] And Ranawat criterion Diameter of the first cervical vertebra ring and distance from this diameter to the centre of the second cervical vertebra pedicle (Fig. 3).[16] Measurement of superior migration is unchanged in flexion or extension of spine. SAS was determined by measuring the vertebral body translation distance (Fig. 4). The MRI done for 15 patients, normal picture found in 11 (5.4%) patients, while 4 (2%) patients had positive findings (i.e. Static Neurologic compression).

3. Statistical analysis

All statistical calculations were done using the statistical package for the social science (SPSS 20). Data were described as mean ± standard deviation (±SD), and range, or frequencies (number of cases) and percentages when appropriate. For comparing quantitative variables of more than 2 groups ANOVA test was used and for parametric categorical data Chi Square test (X2) was performed. For non-parametric data Kruskal-wallis test was used.P-value <0.05 was considered significant.

4. Results

The prevalence of cervical spine instability with RA in Basrah was 15/203 (7.4% of the total sample), occurring primarily in the age group of 41–50 years old (33.3%). The mean age was 48 ± 8.9 years, with the majority (92.8%) of patients being female. Rheumatoid nodules were found in 12/15 (80%) patients with cervical subluxation in RA. (Table 1) Isolated atlantoaxial subluxation was found in 11/15 (73.3%) of RA patients, with combined SAS, SMO and AAS found in 2/15 (13.3%) of RA patients. Combined SMO and AAS was observed in 1/15 (6.7%) of RA patients, with combined SAS and AAS found in 1/15 (6.7%) of RA patients (Fig. 5). The mean age of RA patients with cervical spine involvement was 48 ± 8.9 years, with a range of 37–65 years. The highest frequency was found in the 41-50-year-old group. None of the patients were found to have less than 5 years of disease duration when presenting cervical subluxation in RA. AAS was found in 5 patients with disease duration of 5–10 years and 10 patients with disease duration of over 10 years. Combined SMO and SAS were found in patients with disease duration of over 10 years.

Among the 203 RA patients included in the study presented with single or multiple symptoms of cervical spine involvement were noted in 176 (86.7%) patients, (65%) reported neck pain. In other hand 12/15 (80%) of cervical instability RA patients are symptomatic were included neck pain in 12 (80%) patients, neurological upper limb symptoms in 12 (80%) patients, neurological lower limb symptoms in 12 (80%) patients, tinnitus in 11 (73.3%) patients, vertigo in 9 (60%) patients, loss of equilibrium in 8 (53.3%) patients, abnormal urinary sphincter function in 3 (20%) patients, and abnormal faecal sphincter function in 1 (6.7%) patient.

In terms of disease activity, 3 (20%) patients had low activity, 6 (40%) had moderate activity, and 2 (13.3%) had high activity. In the case of combined SAS, SMO and AAS, 1 (6.7%) patient showed low activity, with the other patient showing moderate activity. In combined SMO and AAS, 1 (6.7%) patient showed moderate activity. The final patient, with combined SAS and AAS, also showed moderate activity.

Peripheral joint erosion was found in 7 (46.7%) of RA patients with cervical subluxation and isolated AAS, 1 (6.7%) patient with combined AAS + SMO + SAS, 1 (6.7%) patient with combined AAS + SMO, and 1 (6.7%) patient with combined AAS + SAS.

5. Discussion

This study analysed cervical spine involvement in RA by examining 203 outpatients (diagnosed using 2010 ACR/EULAR classification criteria) attending Basrah Teaching Hospital. The study was conducted from January 2017 to November 2017. The majority (89.2%) of patients were Basrah residents, with the remaining patients coming from other governorates. Clinical and radiographic assessments showed cervical spine involvement in RA

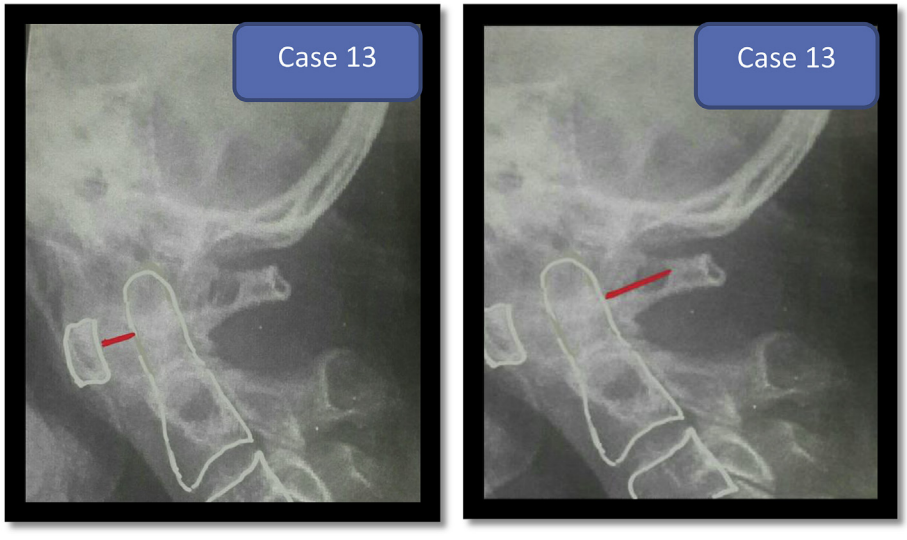

Fig. 1. Lateral dynamic cervical radiograph of sub-axial subluxation (a)) was measured anterior atlantodens interval (AADI). (b) was measured posterior atlantodens interval (PADI).

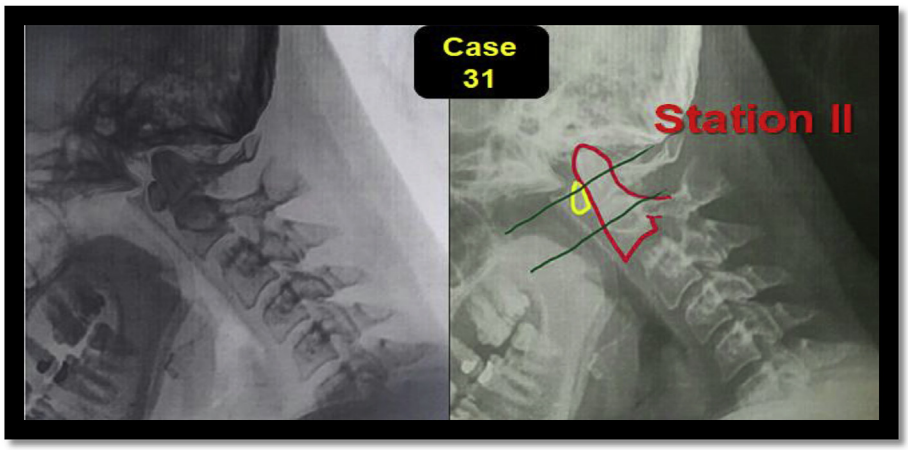

Fig. 2. Superior migration of the odontoid (SMO) measured by Clark station method, the station of the atlas is determined by dividing the odontoid process into thirds in the sagittal plane.

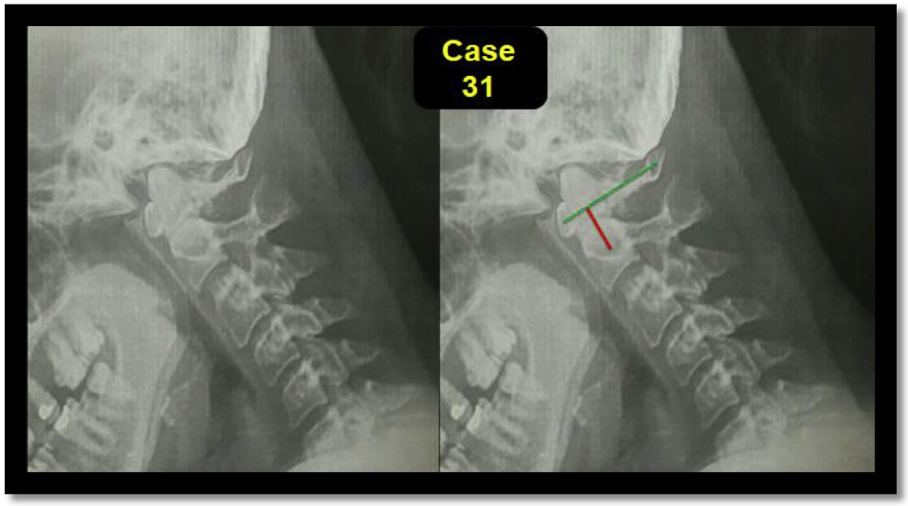

Fig. 3. Superior migration of the odontoid (SMO) measured by Ranawat criterion Diameter of the first cervical vertebra ring and distance from this diameter to the centre of the second cervical vertebra pedicle.

with subluxation in 15 (7.4%) patients. The mean age of the 15 patients with cervical spine involvement in RA was 48 ± 8.9 years old (range: 37–65 years old). These results are somewhat similar to that of Yurube et al.,[2] who described the mean age at the time of outcome assessment as 58 years old (range: 33–69 years old). The results on gender are also shared in the majority of other studies, where women have been found to be 2–3 times more likely than men to develop cervical spine involvement in RA. In the present study, 13 (86.7%) females were affected, which is around 4–5 times higher than our male participants. Suggest that the higher prevalence of RA in women is possibly may be an early "preclinical" effect of hormones in the pathogenesis of RA and several potential mechanisms of immunologic activity that may be related to hormones including glycosylation of autoantibodies and alterations of T and B cell function, and these may be important in early development of RA and in established classified disease.[17]

Babić-Naglić et al. report that RA tends to invade small joints more often than medium and large joints. The researchers suggest that RA involves the upper (rather than the lower) cervical spine due to its multiple synovial-lined articulations, complex ligamentous system, and its rich vascular folds (periodontal venous plexus and pharyngovertebral veins) in the atlantoaxial and lateral atlantoaxial joints.[9–12] Numerous investigators have attempted to elucidate the natural history of RA and its effects on the cervical spine, with wide variation in their findings.[12,18–20] The average disease duration from the onset of RA for our patients was 15 years (range: 6–34 years) which is relatively close to that of Yurube et al.,[2] who documented the mean disease duration as 12 years with a range of 2–30 years. However, Boden et al.[21] found shorter average disease duration of 7.1 years with a range of 4–12 years. This may be because biological therapies such as TNFα-inhibitors decrease inflammation and joint erosion, and it should be noted that cervical spine involvement will occur sooner in the case of rapid-progression peripheral joint disease.

Suggest that the wide variation in the prevalence of cervical spine involvement in RA is related to the geographic hypothesis was explained previously in an interesting study conducted by Méndez-Bryan et al.,[22] which concluded that there may be a zone of maximal prevalence of more aggressive forms of RA between latitude 50° and 60° north (i.e., North Europe, North America and Canada), and that severity decreases as we move towards the equator and influenced by many factors, including differences in

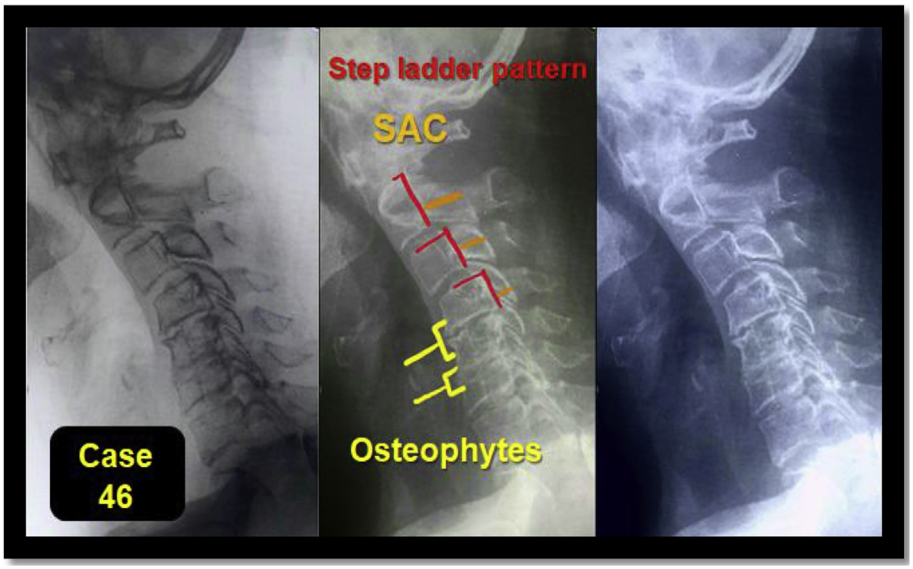

Fig. 4. Sub-axial subluxation (SAS) was determined by measuring the vertebral body translation distance.

Table 1
Comparison of the demographic, clinical, and serological profiles of patients with and without cervical spine instability.

	With cervical instability n = 15/203(7.4%)	Without cervical instability n = 188/203(92.6%)	P value
Age (years)	37-65 mean 48 ± 8.9	21–75 years 49.3 ± 8.67	0.43
Disease duration (years)	2–29	1–27	0.02
Age at disease onset (years)	20–40	21–60	0.20
Gender			0.01
Male	2	21	
Female	13	167	
Rheumatoid factor	8	140	0.19
Presence of erosive arthritis	10	137	0.04
Subcutaneous nodule	12	160	0.03
CDI			
Remission	0	45	0.02
Low Disease Activity	4	111	
Moderate Disease Activity	9	17	
High Disease Activity	2	15	
BMI			
Underweight	9	31	0.04
Normal	6	118	
Grade I overweight		32	
Grade II overweight		6	
Grade III overweight			
Smoking	1	8	0.86
Family history of RA	6	33	0.03

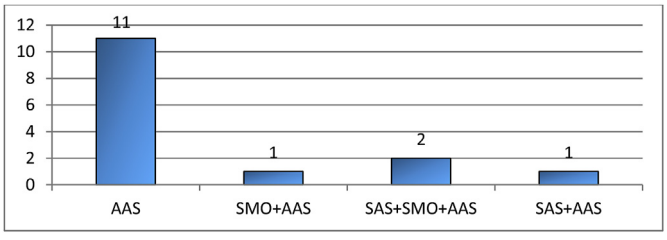

Fig. 5. Frequency of radiographic changes in the cervical spine of 203 individuals with RA (atlanto-axial subluxation(AAS) in 11/203, combined superior migration of the odontoid (SMO)and atlantoaxial subluxation (AAS) in 1/203, combined sub-axial subluxation (SAS)and SMO and AAS in 2/203, combined SAS and AAS in1/203).

follow-up period, disease duration (i.e., patients with long-term RA would have a higher rate of cervical involvement), type of clinical treatment performed (i.e., the use of DMARDs, whether singular or combined), the criteria used for diagnosis, and the radiological method used (i.e., plain radiograph vs MRI). For the same reasons, the total prevalence of cervical spine subluxation in RA reported in the present study was 7.4%. This result differs from other studies, such as that of Aggarwal et al.,[23] who reported a percentage of 20–90% in Denmark; Nguyen, Ludwig, Silber, et al.,[24] who reported a percentage of 43–86% in the USA; and Wasserman et al.,[25] who reported a percentage of 30–50% in New York, USA. These findings are in accordance with Al-Ghamdi and Attar,[26] who reported a percentage of 6.2–16% in Jeddah, KSA. Regarding cervical spine involvement, Na et al.'s[27] Korean study reported that AAS begins as an isolated lesion before SMO appears, with SMO always present in combination with AAS. The authors also stated that SAS will present after the fusion of C1–C2 or in combination with AAS. In the current study, we found isolated AAS in 11 (73.3%) patients; combined AAS, SMO and SAS in 2 (13.3%) patients; combined AAS and SMO in 1 (6.7%) patient; and combined AAS and SAS in 1 (6.7%)

patient. Yurube et al.'s[28] study presented similar results.

In the present study, the most common type of upper cervical subluxation is isolated AAS (73.3%), followed by SMO (20%) and SAS (20%). These results are close to that of Oda et al.'s[19] Japanese study, which found occurrence rates of 77.6%, 36.4% and 22.4% for AAS, SMO and SAS, respectively. Similarly, Resnick et al.[29] found AAS, SMO and SAS to occur at a rate of 86%, 33% and 20.8%, respectively, which is closer to our findings. The reason for the high occurrence of AAS in cervical spine subluxation in RA is that the atlantodens joint has greater mobility than other joints, with a greater synovial tissue surface area, and a single ligament (i.e., the transverse ligament) can cause subluxation if it is involved in RA. In the present study, the earliest evidence of cervical spine involvement in RA patients was found to be 5 years after disease onset. The results indicated that 5 (33.3%) patients experienced the development of AAS within 5–10 years, whilst all cases of SMO and SAS developed over a period of more than 10 years. These findings are in agreement with the results of Joaquim et al.[30] However, research conducted in the early 1980s by Winfield et al.[25] indicated an earlier onset range of 2–10 years. Many factors can affect the pattern of cervical spine subluxation with RA, including disease activity status, the use of anti-rheumatic agents, smoking tobacco, and BMI. Ranawat et al.[31] found that the frequency of atlantoaxial instability increased in line with disease severity. The present study finds a link between cervical instability and disease activity status, with 0% of affected patients in remission, 26.7% with mild RA, 60.0% with moderate RA, and 13.3% with severe RA. However, our findings contradict those of Oda et al.,[19] who reported that cervical instability in RA was not present amongst patients with mild RA, but that it was present in 52% and 88% of patients with moderate and severe RA, respectively. Zhang et al.[32] also reported that over the past 50 years, there has been a significant decrease in the prevalence of AAS, possibly due to improved disease control with modern DMARDs and biological agents. This argument supports the present study, as all our patients were on csDMARDs, with 66.7% on biological agents.

In our study, only 1 (6.7%) RA patient with cervical spine instability was an active smoker, whilst the other 14 (93.3%) patients were non-smokers. Giles et al.[33] explained that many patients with active RA experience weight loss, with RA being a well-recognised contributor to malnutrition. This is reflected in our findings, where 64% of patients were underweight, whilst the remaining 36% of patients had a normal BMI. An interesting epidemiological finding indicated that RA patients with a BMI in the obese range tend to experience a less aggressive version of the disease, and the experimental data indicated that adiponectin and other adipocytokines could be responsible for an inverse association of adiposity and radiographic damage in RA.[34]

Regarding the presentation of our patients with cervical spine instability, the most common presentation was neck pain and neurological symptoms in the upper and lower limbs, which were all reported in 80% of 15 patients with cervical spine instability. This finding is in agreement with the results of Rajangam et al.,[35] who found that the most common presentation was neck pain (40–88% of patients). The cohort study of Neva et al.[36] also reported that 65% of RA patients reported neck pain, with no evidence of radiographic subluxation. This finding is identical to our results, where 65.5% of the total sample of 203 patients was found to experience neck pain with no evidence of radiological subluxation. On the other hand, 20% of our patients were asymptomatic despite radiographic findings indicating instability. These 20% of patients represent the group most at risk of permanent disability or sudden death if early diagnosis is not reached. This argument is supported by numerous researchers, including Neva et al.,[36] Kankaanpää and Santavirta,[37] and Cunningham.[38] The presence of rheumatoid nodules has been noted as a risk factor for the progression of instability,[12,39] and 80% of our RA patients with cervical spine involvement were found to have rheumatoid nodules. Furthermore, numerous researchers[31,40,41] have found a correlation between higher rates of cervical spine involvement in RA and peripheral joint erosion, younger age at disease onset, and a high disease activity score. In conclusion, this study analysed the prevalence of cervical spine instability in Rheumatoid Arthritis patients at a single centre in Basrah which is 7.4%. There were geographic difference in the cervical spine instability in RA and it was more in female, between 30 and 50 years, the duration of the onset of disease is more than 5 years, there was high or moderate disease activity status, presence rheumatoid nodules, peripheral joint erosion and low BMI.

Conflicts of interest

None.

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