



## Review

## Cervical spine involvement in rheumatoid arthritis – A systematic review ☆☆☆

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## ABSTRACT

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disorder that can compromise the cervical spine in up to 80% of the cases. The most common radiological presentations of cervical involvement are atlantoaxial subluxation (AAS), cranial settling and subaxial subluxation (SAS). We performed a systematic review in the PubMed Database of articles published later 2005 to evaluate the prevalence, progression and risk factors for cervical spine involvement in RA patients. Articles were classified according to their level of evidence. Our literature review reported a wide range in the prevalence of cervical spine disease, probably explained by the different studied populations and disease characteristics. Uncontrolled RA is probably the main risk factor for developing a spinal instability. Adequate treatment with DMARD and BA can prevent development of cervical instabilities but did not avoid progression of a pre-existing injury. MRI is the best radiological method for diagnosis cervical spine involvement. AAS is the most common form of RA. Long term radiological follow-up is necessary to diagnosis patients with late instabilities and monitoring progression of diagnosed injuries.

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**Abbreviations:** AA, atlantoaxial; AAI, atlantoaxial impaction; AAS, atlantoaxial subluxation; BAs, biological agents; DMARDs, disease-modifying antirheumatoid drugs; RA, rheumatoid arthritis; SAS, subaxial subluxation; SMO, superior migration of the odontoid; RL, rotational subluxation; VS, vertical subluxation.

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☆☆ Note: AAI, VS and SMO are used interchangeably in this manuscript.

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## 1. Introduction

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disorder that predominantly affects bone, joints and ligaments. However, as a systemic disease, RA can also involve other organ systems, such as the eye, lungs and vessels (vasculitis) [1,2]. Its clinical course is quite variable, ranging from a chronic and insidious presentation to acute severe outbreaks, sometimes altered with long periods of quiescence. The proliferative and erosive synovitis progresses to destruction of the articular

cartilage, especially in the metatarsophalangeal joints, the most commonly involved joints. The cervical spine is also commonly compromised, being the second most involved region in some series, resulting in spinal instability and neurological impairment in severe cases [1–4]. Up to 80% of the patients with RA can have some degree of cervical involvement [1,5,6]. The chronic inflammatory synovitis in the cervical spine results in severity that progresses to bone erosion and ligamentous laxity, leading to late spinal instability. The most common radiological presentations of spinal involvement in RA are: atlantoaxial subluxation (AAS) (the most common form of cervical compromise), cranial settling (also known as basilar impression, atlantoaxial impaction or superior migration of the odontoid [SMO]), the most severe form of spinal instability in RA), subaxial subluxation (SAS) or a combination of them [1,5].

The erosive pannus formation at the C1–2 joints antecedes bone destruction, leading to posterior laxity of the ligamentous complex that restrains the atlas in the axis, especially the transverse ligament but also the articular capsular joint of C1–2. The loss of ligamentous support results in AA instability, most commonly the anterior. In AAS, the anterior atlantodental interval (AADI) increases from its normal range of less than 3 mm, and the posterior atlantodental interval decreases (PADI), compressing the upper spinal cord [5]. Posterior atlantoaxial subluxation is rare, generally secondary to fracture of the dens and carry a higher risk of cord injury than AAS. Lateral subluxation can also occur sporadically, resulting in a rotational deformity. In patients with a high degree of atlantoaxial joints destruction, cranial settling can result in apparent cranial migration of the odontoid (actually is the cranium that settles caudally), most of the times with concomitant pannus development, and brainstem compression by the dens and/or the pannus itself. Cardiac arrest, stroke and obstructive hydrocephalus are potential causes of sudden death in these patients, justifying surgical treatment in the setting of cranial settling [6].

SAS, the second more common form of cervical instability in RA, is due to destruction of the facet joints and the intervertebral disc, appearing in isolation or associated with AAS and SMO. It can also be found in just one level or within multilevel involvement, resulting in a “staircase” deformity. Subluxation is characterized radiologically by 3.5 mm or more of translation at a given motion segment or more than 11° of angular instability, although other threshold are also found, such as 2 mm [1]. Anterior soft tissue masses, posterior ligamentous thickening as well as bony subluxation may cause osteophyte formation, ankylosis, bone collapse and kyphosis [5].

In the last decades, advances in clinical treatment with disease-modifying antirheumatoid drugs (DMARDs) and biological agents (BAs) are changing the natural history of RA and its consequent morbidity, decrease its severity and consequently improving patient's outcome, also decreasing the involvement and destruction of the cervical spine [1,5].

Considering the importance of cervical involvement in RA, we performed a systematic literature review of the prevalence, progression and risk factors for cervical spine involvement in RA patients.

## 2. Material and methods

A systematic literature review was performed in the Pubmed Database. The following search mechanism was used: (“arthritis, rheumatoid” [MeSH Terms] OR (“arthritis” [All Fields] AND “rheumatoid” [All Fields]) OR “rheumatoid arthritis” [All Fields] OR (“rheumatoid” [All Fields] AND “arthritis” [All Fields])) AND (“cervical vertebrae” [MeSH Terms] OR (“cervical” [All Fields] AND “vertebrae” [All Fields]) OR “cervical vertebrae” [All Fields] OR (“cervical” [All Fields] AND “spine” [All Fields]) OR “cervical spine” [All Fields]) AND atlantoaxial [All Fields]. A total of 272 results was obtained and the title and abstract were reviewed by one of the authors (AFJ). The Inclusion Criteria was clinical papers related to the prevalence and the clinical course of cervical spine disease in RA. We excluded literature reviews, case reports and

surgical techniques articles. We also excluded papers published before 2005. In addition, a manual search of all referenced articles not found in the main search was performed. A total of 23 full papers were full reviewed but we also excluded seven additional papers because they are related to surgical techniques, with a total of 16 studies included according to the purpose of our review. The articles selected were then classified according to an evidence-based medicine criteria proposed by Wright et al. [7].

- I High quality randomized controlled trial.
- II Lesser quality randomized controlled trial; prospective comparative study.
- III Case–control study; retrospective comparative study.
- IV Case series.
- V Expert opinion.

The results were then grouped according to the main theme of the papers evaluated, as it follows:

- Prevalence of cervical disease in patients with RA and risk factors for cervical instability progression
- Relationship between radiological modalities and the prevalence of cervical spine disease in RA
- Clinical effects of DMARD in the cervical spine
- Progression of cervical spine instabilities after surgical treatment
- Clinical outcome after surgical treatment of cervical RA
- Biological agents and cervical spine involvement

## 3. Results

### 3.1. Prevalence of cervical disease in patients with RA and risk factors for cervical instability progression

We identified 5 studies (3 prospectives and 2 retrospectives) that analyzed the prevalence of cervical involvement in a total of 1612 patients [8–11] (Table 1). The follow-up reported varied from 2 months to 46 years. The prevalence of cervical spine involvement ranged from 16% to 70.4% and AAS was the most common abnormality reported (Table 1). Conventional X-ray was the most frequent method applied for diagnosis [8–11], however some studies also analyzed CT or MRI [12]. AAS was the most frequent radiological abnormality found in all series [8–12]. Risk factors for cervical spine involvement or progression of diagnosed instabilities identified were: peripheral erosion [8,9,11], destructive changes [9,10], corticosteroid use [9], DMARD failure [8], age < 45 years [11] and cervical spine involvement at study entry [10].

Blom et al. evaluated the prevalence and the potential risk factors of cervical involvement in a cohort study of 134 RA patients with 6 to 12 years of follow-up [8]. Conventional X-rays were obtained at baseline, 3, 6, 9 and 12 years of disease and erosions of C1 and C2, AAS and AAI were evaluated. Independent variables assessed were disease activity, patients' functionality, peripheral joint damage at baseline, 3, 6, 9 and 12 years of follow-up. Twenty-two (16%) had cervical spine involvement at 9 years. The most common finding was AAS and C2 erosions, whereas the less common findings were AAI and C1 erosions. Patients with cervical involvement had a higher frequency of peripheral joint erosions and failed more DMARDs when compared to RA patients without cervical spine erosion. Finally, the authors concluded that patients without peripheral erosive disease at 3 years were unlikely to have cervical involvement after 9 years (Level II of Evidence).

Yurube et al., 2012, performed a prospective cohort study including 140 RA patients without cervical involvement followed for a minimum of 5 years [9]. Cervical findings were classified as: 1) AAS (when the atlantodental interval was >3 mm), 2) vertical subluxation (when the Ranawat value was <13 mm) and 3) SAS, when there was an irreducible translation > 2 mm. They attributed a diagnosis of “severe” for cases classified as it follows: 1) severe AAS: atlantodental interval > 10 mm, 2) severe VS: when the Ranawat value was <10 mm or 3) severe SAS:

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