Cervical spine involvement in rheumatoid arthritis: correlation between neurological manifestations and magnetic resonance imaging findings

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Objective. To evaluate the correlation between neurological deficits indicative of compressive myelopathy and MRI findings in a series of patients with RA and symptomatic involvement of the cervical spine.

Methods. Forty-one consecutive patients with RA were studied using cervical spine MRI. Unconditional logistic regression analysis was used to identify MRI parameters of cervical spine involvement associated with the development of neurological dysfunction.

Results. The mean age of the 41 patients (33 women and 8 men) was 59 yrs (range 23–82 yrs), while the median disease duration was 18 ± 9 yrs (range 4–40 yrs). According to Ranawat’s classification, 17 (42%) patients were in Class I, 21 (51%) in Class II and 3 (7%) in Class III. Thus, patients with clinical manifestations of compressive myelopathy (Ranawat’s Class II + III) represented 58% (24/41) of all cases. Among the different MRI parameters of cervical spine involvement analysed, only the presence of atlantoaxial spinal canal stenosis [odds ratio (OR) 4.55; 95% CI 1.14–18.15], atlantoaxial cervical cord compression (OR 9.6; 95% CI 1.08–85.16) and subaxial myelopathy changes (OR 11.43; 95% CI 1.3–100.81) were associated with a significantly increased risk for neurological dysfunction (Ranawat’s Class II or III).

Conclusion. In RA patients with symptomatic cervical spine involvement, there is a strong correlation between the development of neurological dysfunction and MRI identification of atlantoaxial spinal canal stenosis, especially in those cases with evidence of upper cervical cord or brainstem compression and subaxial myelopathy changes.

Key words: Rheumatoid arthritis, Cervical spine, Compressive myelopathy, Magnetic resonance imaging.

Introduction

The cervical spine, particularly the craniovertebral junction, is one of the most common sites of RA. According to the literature, the prevalence of cervical spine lesions of any kind among RA patients ranges between 25% and 86%, although only a small percentage (between 7% and 34%) will develop severe neurological symptoms requiring surgery [1, 2]. The inflammatory process usually leads to progressive joint destruction and ligamentous laxity, with resultant instability and subluxation in the cervical spine. Both the upper cervical spine (C1 and C2, with the atlantoaxial, atlanto-odontoid and atlanto-occipital joints) and the subaxial cervical spine may be involved (Fig. 1).

The most important complication of cervical spine involvement in RA is the compression of the spinal cord or brainstem. This can result from static or dynamic subluxation of the spine or from direct compression by a synovial pannus. Although the development of compressive myelopathy is rare [3, 4], its presence is associated with poor prognosis [5]. Any neurological deterioration progresses if untreated, and in one series, almost 50% of these patients die within a year [6]. In this phase, there is little chance of recovery to normal levels after surgery [7]. This poor prognosis has led to an emphasis on prompt diagnosis and treatment to prevent the development of irreversible neurological deficits. However, the diagnosis of rheumatoid cervical myelopathy is usually difficult to establish early in the disease process. Neurological examination in rheumatoid patients is frequently hampered by the presence of arthritis and deformations, with associated muscle weakness and atrophy. In addition, neurological signs correlate poorly with the severity of radiographic abnormalities.

For these reasons, MRI has become the imaging modality of choice in assessing cervical spine involvement in RA [8–11].

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Severity of the neurological compromise was categorized according to the Ranawat classification of rheumatoid myelopathy [16]: Class I—neck pain without neurological deficit; Class II—subjective weakness with hyperreflexia and dysesthesia; Class IIIA—moderate objective weakness and signs of long tract involvement permitting some degree of self-sufficiency (ambulatory); Class IIIB—severe objective weakness and long tract signs with complete loss of self-sufficiency (bed- or chair-bound).

**MRI protocol**

MR studies were performed at 1.5 T units (Gyroscan ACS NT or Gyroscan Intera; Philips Medical Systems, Best, the Netherlands). Each series was obtained with a quadrature transmit/receive neck coil, with the patient supine and the neck in neutral position. The following sequences were used: (i) a sagittal T₁-weighted spin-echo series with 423–450/17 (repetition time ms/echo time ms), section thickness of 4 mm, section gap of 0.4 mm, field of view of 250 × 250 mm², rectangular field of view of 100 or 80%, two signals acquired, and an acquisition matrix of 256 × 256; (ii) a sagittal T₂-weighted fast spin-echo series with 3216–3230/120, echo train length of 17 mm, section thickness of 4 mm, section gap of 0.4 mm, field of view of 260 × 260 mm, rectangular field of view of 100 or 80%, six signals acquired and an acquisition matrix of 256 × 256 or 251 × 512; and (iii) two transverse, 3D T₂ fast field-echo series: one of the series was located at the atlantoaxial joint and the other in the subaxial cervical spine, depending on findings of stenosis on the sagittal images; the imaging parameters of this sequence were as follows: 31–34/14, section thickness of 4 mm, 32–36 sections, field of view of 230 × 230 mm, rectangular field of view of 60–65%, four signals acquired, flip angle of 5° and an acquisition matrix of 256 × 256.

In three patients, we used flexion neck sagittal T₁-weighted fast spin-echo series with 3216–3230/120, echo train length of 17, section thickness of 4 mm, section gap of 0.4 mm, field of view of 260 × 260 mm, rectangular field of view of 100 or 80%, six signals acquired and an acquisition matrix of 256 × 256 or 251 × 512.

If more than one MR examination was recorded per patient, images from the first examination were used for analysis.

**Analysis of MR images**

Images were independently reviewed by two of the authors (J.A.N.G. and M.S.; 11 yrs experience in musculoskeletal radiology and 9 yrs experience in neuroradiology, respectively) who were unaware of clinical information or other patient data. In cases of interobserver difference, a consensus was achieved for each score.

At the atlantoaxial joint, MR images were reviewed with particular attention to the presence of periodontoid synovitis, odontoid erosions, stenosis of the spinal canal, anterior, posterior or superior vertebral subluxation, upper cervical cord or brainstem compression, alteration in signal intensity of the spinal cord [high signal intensity on T₂-weighted and/or short time inversion recovery (STIR) MR images] and alterations of the cervicomedullary angle. Synovitis was defined as an area in the synovial compartment showing intermediate to low signal intensity on T₁-weighted images and intermediate to high signal intensity on T₂-weighted and STIR MR images of a thickness greater than the width of the joint capsule. Erosion of the odontoid process was defined as a bone defect with sharp margins, visible in two planes.

Stenosis of the atlantoaxial canal was considered to be present when the posterior atlantodental interval (PADI), measured from the posterior aspect of the dens to the anterior aspect of the C1 lamina, was ≤14 mm (Fig. 2).

Anterior atlantoaxial subluxation was considered to be present when the anterior atlantodental interval (AADI), measured from the posterior aspect of the anterior ring of C1 to the anterior aspect of the dens, was >3 mm [17]. Posterior atlantoaxial subluxation was considered to be present when the anterior arch of the atlas moved over the odontoid process. Vertical subluxation at C1-C2 was defined as migration of the odontoid tip by >4.5 mm above McGregor’s line [17].

Upper cervical cord or brainstem compression was considered to be present in cases with obstruction of the subarachnoid space (disappearance of the cerebrospinal fluid in both the anterior and posterior subarachnoid spaces on T₂-weighted images) and deformity of the spinal cord or brainstem (decreased cord diameter at the level of subarachnoid space obstruction compared with the cord diameter superior or inferior to the stenotic level).

The cervicomedullary angle was measured by drawing lines along the anterior aspects of the cervical cord and along the medulla. Normal angles range between 135° and 175° [17].

At the subaxial spinal level, MR images were evaluated for the presence of stenosis of the subaxial spinal canal (defined as a sagittal diameter <14 mm) [2], spinal cord compression (considered to be present in cases with obstruction of the subarachnoid space and deformity of the medulla) and modified signal intensity within the spinal cord (high signal intensity on T₂-weighted and/or STIR MR images) (Fig. 3).

MR images of the same patients presented in a randomized fashion to the reviewers were interpreted twice, with an interval of 4–24 months (mean 12 months) between the two interpretations to determine the intraobserver reliability.

**Statistical analysis**

Continuous data were described as mean ± s.d. and categorical variables were presented as percentages. We grouped the sample into two clinical subsets according to the presence or absence of signs of compressive myelopathy (Ranawat’s Class II or III) [10]. Comparisons between groups were made using the Student’s t-test for independent continuous variables or the Mann–Whitney U-test when the assumption of normality was not achieved. The chi-square test was applied for analysis of categorical data.

Unconditional logistic regression analysis was used to identify MRI parameters of cervical spine involvement associated with the development of neurological dysfunction (Ranawat’s Class II
or III). Statistical significance was defined as $P \leq 0.05$. For assessment of intraobserver reliability, $\kappa$-statistics were employed on all variables.

### Results

The main characteristics and MRI findings of the study cohort are summarized in Table 1. The mean age of the 41 patients (33 women and 8 men) at the time of the study was 59 ± 12 yrs (range 23–82), and the median disease duration was 18 ± 9 yrs (range 4–40). According to Ranawat’s classification, 17 (42%) patients were in Class I, 21 (51%) in Class II, and 3 (7%) in Class III (two IIIA and one III B). Thus, patients with clinical manifestations of compressive myelopathy (Ranawat’s Class II + III) represented 58% (24/41) of all cases.

Table 2 compares patients with and without myelopathic symptoms. While there were no differences in the demographic characteristics and clinical data, comparison of the MRI parameters of cervical spine involvement did reveal significant differences, there being a higher frequency of atlantoaxial spinal canal stenosis (58 vs 23%; $P = 0.02$), atlantoaxial cervical cord compression (37 vs 6%; $P = 0.02$) and subaxial myelopathy changes (42 vs 6%; $P = 0.01$) among patients in Ranawat’s Class II or III. None of the other variables tested reached statistical significance, although the differences in prevalence of vertical subluxation (29 vs 6%; $P = 0.06$), pathological cervicomedullary angle (17 vs 0%; $P = 0.07$) and subaxial spinal cord compression (46 vs 18%; $P = 0.06$) did approach significance.

The odds ratios (ORs) of the association between the occurrence of neurological dysfunction (Ranawat’s Class II + III) and the MRI parameters of cervical spine involvement are given in Table 3. Similar to that observed in the comparative study, the presence of atlantoaxial spinal canal stenosis, atlantoaxial cervical cord compression and subaxial myelopathy changes on MR images were associated with a significantly increased risk of neurological dysfunction. The OR for atlantoaxial spinal canal stenosis and atlantoaxial cervical cord compression was, respectively, 4.5 and 9.6, equivalent to an 8-fold and 10-fold increased risk of neurological dysfunction. Subaxial myelopathy changes showed an OR of 11.4, indicating that its presence was associated with an 11-fold greater risk for neurological dysfunction. The other parameters showed no significant increase in risk.

Intraobserver agreement was very good for both radiologists ($\kappa = 0.92$ and 0.88, respectively).

### Discussion

Cervical spine involvement is a relatively common feature in RA, with many patients developing radiographic instability. However, only a small percentage of this subset of patients eventually develop neurological complications [3], including myelopathic symptoms [2, 5], vertebrobasilar insufficiency or even sudden death from acute respiratory failure due to brainstem compression [6, 18]. There is therefore ongoing interest in understanding why this subset develops a neurological deficit and in finding ways to identify them early on.

Several potential risk factors for progression of cervical disease have been identified. These can be divided into non-radiographic and radiographic risk factors. The non-radiographic factors...
AADI corticosteroids [19–21]. The radiographic factors include an inflammatory response as assessed by analytical parameters development of bone erosion, intensity of the initial systemic matoid nodules, severe peripheral disease with early and extensive include male gender, RF seropositive status, presence of rheumatoid nodules, severe peripheral disease with early and extensive development of bone erosion, intensity of the initial systemic inflammatory response as assessed by analytical parameters (mainly CRP), long-standing disease and prolonged use of corticosteroids [19–21]. The radiographic factors include an AADI >8–10 mm [22, 23], a PADI <14 mm [2], the presence of vertical subluxation [22, 24] and a subaxial sagittal canal diameter of ≤14 mm [17]. However, the reliability of these radiographic criteria in identifying patients at risk of developing a neurological deficit is highly controversial. The presence of periodontoid soft tissue pannus of varying thickness is frequently observed at the atlantoaxial level, and subaxial spinal canal stenosis caused by soft tissues, mainly intervertebral disc disease and ligamentum flavum hypertrophy, is not uncommon. Hence, the true space available for the spinal cord in these cases is less than that measured on plain radiographs. Early diagnosis of rheumatoid cervical myelopathy represents a diagnostic challenge. Neurological examination is often demanding because subtle changes may be masked by the presence of severe peripheral articular disease. Muscle atrophy, joint subluxation, tendon rupture and peripheral nerve entrapment can make findings difficult to interpret. In addition, there is general agreement that the clinical manifestations of compressive myelopathy correlate poorly with the severity of radiographic abnormalities [22]. Thus, plain radiographic findings have relatively little prognostic value. Nevertheless, once neurological deficits occur, progression is inevitable and almost 50% of these patients die within a year if untreated [6]. In this phase, surgery can improve the pain and halt the neurological deterioration, but it only slightly improves the pre-existent neurological deficit [6, 25, 26]. Thus, more emphasis is now placed on the importance of treatment before irreversible neurological damage has occurred, and the goal is to identify patients at risk prior to the development of neurological symptoms.

In this clinical context, the advent of MRI has enabled better visualization of spinal cord compression caused by both bone and

### Table 2. Comparison between patients with and without clinical manifestations of compressive myelopathy

<table>
<thead>
<tr>
<th>MRI parameters</th>
<th>Ranawat Class I (n = 17)</th>
<th>Ranawat Class II + III (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, ± s.d., yrs</td>
<td>57 ± 14</td>
<td>60 ± 11</td>
<td>0.45</td>
</tr>
<tr>
<td>Women/men</td>
<td>14/3</td>
<td>19/5</td>
<td>0.80</td>
</tr>
<tr>
<td>Mean disease duration, ± s.d., yrs</td>
<td>16.7 ± 9.5</td>
<td>20.5 ± 9</td>
<td>0.20</td>
</tr>
<tr>
<td>Positive RF</td>
<td>15 (88)</td>
<td>20 (83)</td>
<td>0.66</td>
</tr>
<tr>
<td>Rheumatoid nodules, n (%)</td>
<td>2 (12)</td>
<td>4 (17)</td>
<td>0.66</td>
</tr>
<tr>
<td>Erosions in the peripheral joints, n (%)</td>
<td>0.35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinbrocker stage, n (%)</td>
<td>15 (88)</td>
<td>23 (96)</td>
<td>0.23</td>
</tr>
<tr>
<td>I + II</td>
<td>11 (65)</td>
<td>11 (46)</td>
<td></td>
</tr>
<tr>
<td>III + IV</td>
<td>6 (35)</td>
<td>13 (54)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3. Risk estimates of developing neurological dysfunction (Ranawat Class II or III) adjusted to different MRI parameters of cervical spine involvement

<table>
<thead>
<tr>
<th>MRI parameters</th>
<th>P*</th>
<th>OR crudeb</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atlantoaxial level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis of the spinal canal without cord compression</td>
<td>0.027</td>
<td>4.55</td>
<td>1.14, 18.15</td>
</tr>
<tr>
<td>Stenosis of the spinal canal with cord compression</td>
<td>0.02</td>
<td>9.6</td>
<td>(1.08, 85.16)</td>
</tr>
<tr>
<td>Stenosis of the spinal canal with cord compression and evidence of alteration in signal intensity of the medulla</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synovitis</td>
<td>0.182</td>
<td>0.24</td>
<td>(0.03, 2.25)</td>
</tr>
<tr>
<td>Odontoid erosions</td>
<td>0.662</td>
<td>0.67</td>
<td>(0.11, 4.13)</td>
</tr>
<tr>
<td>Anterior subluxation</td>
<td>0.424</td>
<td>1.7</td>
<td>(0.46, 6.28)</td>
</tr>
<tr>
<td>Vertical subluxation</td>
<td>0.064</td>
<td>1.41</td>
<td>(0.44, 14.26)</td>
</tr>
<tr>
<td>Pathological cervicomedullary angle (&lt;135°)</td>
<td>0.076</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subaxial level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stenosis of the spinal canal without cord compression</td>
<td>0.175</td>
<td>3.95</td>
<td>(0.9, 17.4)</td>
</tr>
<tr>
<td>Stenosis of the spinal canal with cord compression</td>
<td>0.061</td>
<td>3.95</td>
<td>(0.9, 17.4)</td>
</tr>
<tr>
<td>Stenosis of the spinal canal with cord compression and evidence of alteration in signal intensity of the medulla</td>
<td>0.011</td>
<td>11.43</td>
<td>(1.3, 100.81)</td>
</tr>
</tbody>
</table>

*Chi-square association test. bOR determined by logistic regression analysis. The presence of atlantoaxial myelopathy and pathological cervicomedullary angle (<135°) were excluded from the model because none of the patients in Ranawat Class I have these morphological abnormalities. Bold values signify p < 0.05.*
soft tissue pannus, and has become the imaging modality of choice for establishing the diagnosis, location and extent of compressive myelopathy. Moreover, our study shows that some of the different morphological abnormalities detected by MRI are associated with an increased risk of developing neurological dysfunction (Ranawat’s Class II or III). These imaging parameters are the presence of atlantoaxial spinal canal stenosis, atlantoaxial cervical cord compression and subaxial myelopathy changes.

In the presence of atlantoaxial spinal canal stenosis, defined as a PADI <14 mm, an approximately 5-fold increased risk for neurological dysfunction was seen. This risk increases up to 10-fold in those cases with concomitant evidence of upper cervical cord or brainstem compression. Our findings are consistent with a previous study conducted by Boden et al. [2] that evaluated the reliability of various radiographic criteria used to identify patients at risk of developing neurological dysfunction. In this study of 73 RA patients with a mean follow-up of 7 yrs, the authors found that the PADI showed a far stronger correlation with the risk of neurological compromise than did the AADI. According to their results, a PADI of <14 mm yielded 97% sensitivity for detecting patients with neurological deficits.

Other imaging parameters evaluated at the atlantoaxial level, such as the presence of anterior atlantoaxial subluxation (considered to be present when the AADI was >3 mm), vertical subluxation and a pathological cervico-medullary angle (<135°), were more frequent in our subset of patients with myelopathy symptoms, although in the logistic regression analysis they were not associated with a significant increase in risk. Some earlier studies have reported an increased risk of compressive myelopathy in patients with vertical subluxation or anterior atlantoaxial subluxation of >9 mm [22, 27], and in patients with a cervico-medullary angle of <135° [28]. In contrast, the study by Reijnierse et al. [14] found that none of the MR features at the atlantoaxial level correlated significantly with neurological classification. These discrepancies may, in part, be attributed to methodological differences, including different study designs (prospective vs retrospective) and selection bias (inclusion of symptomatic patients only, patients without neurological signs only or both).

In this regard, we are confident that with a larger sample of patients, some of the parameters in our study, particularly the presence of a pathological cervico-medullary angle (P = 0.07) and vertical subluxation (P = 0.06), could achieve statistical significance. The lack of significance for anterior atlantoaxial subluxation could be due to the fact that only a small percentage of our patients with this subluxation had an AADI >9 mm. In addition, we cannot rule out that some cases of dynamic anterior atlantoaxial subluxation may have been overlooked, because only a small percentage of our patients had MR images obtained with the neck flexed. However, MR flexion views seem unable to detect lesions missed in the neutral position [29].

In our study, stenosis of the spinal canal occurred more frequently subaxially than at the atlantoaxial level, being observed in 85 and 44% of patients, respectively. However, despite its frequency, the presence of subaxial spinal canal stenosis was not related to the occurrence of myelopathy symptoms, not even in those cases with evidence of spinal cord compression on MRI. Although our results, only evidence of subaxial myelopathy changes was associated with a significantly increased risk of neurological dysfunction. In its absence, an 11-fold increase in risk for neurological dysfunction was seen. These data seem to indicate greater behavioural adaptation of the subaxial segment compared with the atlantoaxial segment.

Our study has several limitations. First, we included only symptomatic patients, and consequently our findings are only applicable to patients with established RA and symptomatic cervical spine involvement. However, in the absence of symptoms, the indication for a cervical spine MRI study in patients with advanced disease seems difficult to justify. The second limitation of our study involves the small size of the patient sample.

In summary, in our series we found a strong correlation between neurological deficits indicative of compressive myelopathy and some MRI parameters of cervical spine involvement. In RA patients with symptomatic cervical spine involvement, the development of neurological dysfunction correlates with MRI identification of atlantoaxial spinal canal stenosis, especially in those cases with evidence of upper cervical cord or brainstem compression and subaxial myelopathy changes. This information should be borne in mind when assessing these patients and may help optimize the timing of surgical intervention.

**Rheumatology key messages**

- Cervical spine MRI appears to be a valuable method to identify RA patients at risk of developing neurological dysfunction.
- MRI information should be borne in mind when assessing these patients and may help optimize the timing of surgical intervention.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**

Cervical spine involvement in RA


