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Inflammation in ankylosing spondylitis – a systematic description of the extension and frequency of acute spinal changes using magnetic resonance imaging (MRI)

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Key words: ankylosing spondylitis – inflammation – T1/Gd-DTPA-MRI – STIR-MRI – ASspiMRI Score
Background. Magnetic resonance imaging (MRI) is increasingly used to detect inflammation in the spine of patients with ankylosing spondylitis (AS).

Objectives. To differentially detect the presence and extension of inflammation in the 3 spinal segments of AS patients by using MRI.

Methods. In 38 patients with active AS, acute spinal lesions were assessed by T1-weighted gadolinium-enhanced spin-echo MRI (T1/Gd-DTPA) and short-tau inversion recovery (STIR) sequences. MRI was quantified by using the validated scoring system ASspiMRI-a. Acute spinal lesions were detected in the whole spine and in each spinal segment. One vertebral unit (VU) was defined as the region between two virtual lines drawn through the middle of each vertebral body.

Results. A higher number of inflammatory spinal lesions was found by STIR sequence as compared to Gd-DTPA: inflammation was present in 30.6% of the VUs as assessed by STIR, compared to 26.8% of the same VUs assessed by T1/Gd-DTPA. Inflammation was found more frequently in the thoracic spine (TS) than in the cervical (CS) or the lumbar spine (LS) with both techniques. Using STIR, spinal inflammation was detected in 27%, 73% and 24% of the patients for the CS, the TS and the LS, respectively. The VU T7/8 was found to be most often affected VU by both techniques (27.8% by T1/Gd-DTPA and 34.5% by STIR).

Conclusions. Spinal inflammation is a frequent manifestation in AS patients, and it appears more frequently in the TS. The scoring system ASspiMRI-a is a useable tool for evaluation of acute spinal changes in AS.
Introduction

Ankylosing spondylitis (AS), the prototype of the spondyloarthritides [1], starts in the sacroiliac joints and may extend to the spine in the majority of patients having inflammatory back pain as its leading symptom [2]. Sacroiliitis, spondylitis, spondylodiscitis and spondyloarthritis are the main inflammatory manifestations [3]. There is increasing evidence that new imaging tools such as MRI are a major advance in the assessment of spinal inflammation in AS and other diseases [3], while conventional x-ray examinations are still the gold standard for imaging of the chronic spinal changes in AS; this is especially true for long-term studies [4]. Anti-TNF- agents have dramatically changed the therapeutic strategies in AS, since both infliximab and etanercept have shown strong clinical efficacy on a short- and intermediate-term basis [5-9]. Importantly, the improvement in clinical disease activity was shown to correlate with the amelioration of acute spinal changes, as documented by T1-weighted post-Gd-DTPA and STIR follow up MRI examinations [10].

The thoracic spine is difficult to visualize by conventional radiography, so scoring of acute and chronic spinal lesions in this region is not part of established radiological scoring systems, which assess only the lumbar and the cervical spine. Therefore, to our knowledge about the presence of acute and chronic spinal lesions in the thoracic spine has been rather limited to date. The differential involvement of spinal segments by inflammation has not been systematically analysed until now.

The main aim of this study was to assess the presence and the extent of inflammation in all three spinal segments in patients with AS by using T1-weighted fat saturated post-Gd-DTPA and STIR MRI sequences, and to compare the differential involvement of the three spinal segments.
**Patients and Methods**

**Patient’s characteristics**

The 38 AS patients examined had been referred to the University outpatient clinic because of back pain due to AS. Some patients were candidates for inclusion in the large RCT on the efficacy of infliximab in AS performed in Germany [5]. All had been conventionally treated with NSAIDs before the inclusion in this study. None of them had ever been treated with biologics. Out of 38 patients, there were 24 (63.2%) male. The mean age of the patients was 40.9 years (range 32-54 years); 92% were HLA-B27 positive. The mean (SD) ESR was 31.2 ± 23.0/1 hour and the mean CRP was 22.2 ± 21.9 mg/dl. The patients had active disease with a mean BASDAI of 6.4 ± 1.4 and a BASFI of 5.5 ± 2.1 (Tab. 1). Prior to the study, the diagnosis AS was confirmed by radiological examinations of the sacroiliac joints in all patients.

**Magnetic resonance imaging (MRI)**

MRI investigations were executed with a 1.5 Tesla unit Magnetom Vision (Siemens AG Medical Solutions, Erlangen, Germany), using a spine-array coil and/or a body-array coil. The MRI techniques applied to assess sacroiliac and spinal inflammation in AS patients were performed as described [3]. The sagittal section orientation was chosen and the following sequences were used:

1. T1-weighted spin-echo (SE) sequences (repetition time (TR)/echo time (TE) 500/14-20 ms, slice thickness 3-4 mm, 2 acquisitions) before, and
2. using the same sequence with fat saturation after application of gadolinium-diethylenetriamine-pentaacetic acid (Gd-DTPA; Schering AG, Berlin, Germany, at 0.1 mmol/kg body weight).

No dynamic imaging was performed. Taking C2 and L5 as orientation points the spine was examined in 2 parts, always starting with the upper part. After rapid adjustment of the table into the appropriate position the lower part of the spine was examined.

3. Similarly, short tau inversion recovery (STIR) sequences (TR/inversion time (TI)/TE 4,000/150/60 ms, slice thickness 3-4 mm, 1 acquisition) with intrinsic fat saturation were performed.
4. T2-weighted images were also available and were taken into account in doubtful cases of differentiation between chronic and acute lesions.

**Scoring of spinal inflammation in MRI**

The MR images were blinded for patient identity and were then chosen by an independent person. Evaluation was performed by two readers (JB, WG), by evaluating each time first the T1/Gd-DTPA and then the STIR MR images of one patient in each reading session. Each evaluation was performed twice by each reader (different timepoints). Thus, each image was evaluated four times in total. The analysis of acute spinal changes in MRI was performed by evaluating the T1/Gd-DTPA and STIR MRI sequences with the new MRI scoring system ASspiMRI-a (Fig. 1, 2) [10, 12]), which is a part of the ASspiMRI score [10]. This scoring system was developed by our group in order to assess acute spinal lesions by evaluating the enhancement in T1-weighted MRI sequences after application of Gd-DTPA, as also by evaluating bone and bone marrow edema in STIR MRI sequences (ASspiMRI-a [10, 13]). Chronic spinal lesions can also be evaluated by using T1-weighted MRI sequences (ASspiMRI-c, [10, 14]). These data are reported in detail elsewhere [14]. Spinal involvement due to AS was assessed by using the lateral view of the spine and evaluating spinal changes on the basis of vertebral units (VU). One VU is defined...
as the region between two virtual lines drawn through the middle of a vertebral body (Fig. 3, [10]).
Overall, 23 VUs from C2 to S1 were assessed by using the ASspiMRI-a (6 VUs in the CS from C2/3 to C7/T1; 12 VUs in the TS from T1/2 to T12/L1 and 5 VUs in the LS from L1/2 to L5/S1).

Acute spinal changes are evaluated by the ASspiMRI-a by grading in a range between 0 and 6 (Fig. 1). In detail, enhancement and bone marrow edema are graded as mild if covering ≤ 25% of a VU [grade 1], moderate if covering ≤ 50% of a VU [grade 2] and severe if covering > 50% of a VU [grade 3]. If, in addition to the signs of acute inflammation, erosions are visible, these are graded as minor if eroding ≤ 25% of a VU [= grade 4], intermediate if eroding ≤ 50% [= grade 5] and major if destructing > 50% of a VU [= grade 6] (Fig. 3).

Definite involvement of a VU in the evaluation of both MRI sequences indicates inflammation/edema with and without erosion and it is defined as a VU score > 0 in the ASspiMRI-a.

Evaluation of the scorings
Inflammatory spinal involvement by AS was analysed by comparing the same VU in each of the two MRI sequences and by calculating these results on the basis of four different aspects: i) the mean score of the four readings for each single VU, ii) the inflammation seen in each VU (affection by the disease or not), iii) the involvement of each spinal segment and iv) the analysis of each individual patient.

Statistical analysis
The reliability of the scoring system with an inter- and intrarater variance and also the correlation coefficients between the scorings are presented elsewhere [15]. Spinal activity was analysed on the level of a single VU, on the level of a spinal segment, on the level of the spine and on the level of a single patient, per MRI sequence.
Comparisons between the T1/GdDTPA and STIR sequence scores were performed by first calculating the means of the four readings for each VU per sequence and then by comparing similar VUs per sequence. The statistical comparisons of the scorings in the two MRI sequences was performed by using the Wilcoxon test. For the assessment of inflammation on the patient-level, both readers had to score positive findings in the same patient for confirmation of inflammation. VUs with scorings ‘1’ to ‘6’ were considered positive for inflammation, while VUs with a scoring ‘0’ were considered negative for inflammation. Proportions of affected VUs per sequence (STIR, Post-GD) in the same patients were compared using McNemar test.
Results

Comparison between the T1/Gd-DTPA and the STIR sequence using the MRI activity score ASspiMRI-a

Spinal inflammation was most frequently found in the TS (mean score 0.69 and 0.74 per VU for T1/Gd-DTPA and STIR sequence. The other two segments were less frequently affected (mean score 0.24 and 0.28 in the CS and 0.41 and 0.34 in the LS for T1/Gd-DTPA and STIR, respectively). All means and standard deviations (SD) are shown in Table 2.

The VUs which were found to be most frequently affected by inflammation were the same by both MRI techniques. As assessed by STIR, it was the VU C7/T1 in the CS (26.2%), in the TS it was the VU T7/8 (53.7%, Fig. 6) - this was also the VU most frequently affected in the whole spine - and in the LS it was the VU L1/2 (27.1%). The numbers and proportions of all VUs, as assessed by both MRI techniques, are shown in Figures 4 and 5.

Definite inflammatory involvement of each spinal segment was found in 16% of the VUs of the CS by using T1/Gd-DTPA sequences and in 20.7% by STIR sequences, respectively (p < 0.05). In the TS, 34.5% and 38.7% of the VUs (p < 0.001) and in the LS 20.3% and 23% (p < 0.05) of the VUs showed definite inflammation in the T1/Gd-DTPA and the STIR sequences, respectively.

Looking at the whole spine, definite inflammation was found in 26.8% of the VUs in the evaluation of the T1/Gd-DTPA sequence and in 30.6% in the evaluation of the STIR sequence (p = 0.001).

When analyzing each patient individually, evaluation of the T1/Gd-DTPA sequences showed that 23.7% of the AS patients had definite spinal inflammation in the CS, 73.7% in the TS and 18.4% in the LS. Evaluation by STIR sequence showed definite inflammatory involvement in 27%, 73% and 24.3% of the patients for the CS, the TS and the LS, respectively.
Discussion

This study shows that inflammation is a prevalent feature in ankylosing spondylitis, which can be assessed by MRI techniques such as T1/GdDTPA and STIR. The scores of both magnetic resonance sequences confirm that the TS is more frequently affected by inflammation in AS than the other two spinal segments. This important finding is substantiated by the results of the analyses of the different levels assessed: a single VU, a spinal segment and an individual patient. The subanalysis of definite involvement provides conservative but solid data on active spinal inflammation in AS.

The analyses indicate that the preference of AS to affect the thoracic spine is not solely explained by the greater number of VUs or vertebral bodies in the TS. Apparently, AS affects the thoracic spine and especially its lower part more frequently, to a greater extent, and with a greater inflammatory intensity. Other spinal disorders may also preferentially occur in the lower parts of the thoracic and the upper parts of the lumbar spine: osteoporotic fractures, intervertebral disc problems and vertebral injuries. The lower thoracic and upper lumbar part of the spine may reflect an area of higher vulnerability for reasons of statics [16-18].

Indeed, as the more detailed analyses revealed, the spinal region showing the most frequent inflammatory involvement in AS was the region between the middle part of the TS (T7/8) and the middle part of the LS (L2/3). This information is important for the question of which spinal region should be the main site of imaging in AS patients in daily practice or in clinical studies. On the basis of the provided evidence, we suggest that at least the lower part of the TS and the LS should be included in MRI examinations in AS patients with active disease.

There is increasing interest in the assessment of disease activity and spinal inflammation by MRI because of the successful use of biologics in AS, especially infliximab [5, 9] and etanercept [7, 8]. Furthermore, T1-weighted post-contrast agent and STIR MRI techniques are being increasingly used to detect active spinal lesions in AS, especially in clinical trials, in order to evaluate whether inflammation “visibly” improves after treatment with anti-TNF.

Taken together, the ability of MRI to detect acute spinal changes may be a major step forward in the area of imaging inflammation in AS. The thoracic spine is most frequently involved in AS. Such states can be assessed both by STIR and by T1-weighted contrast agent enhanced MRI.
References:
Analysing chronic spinal changes in ankylosing spondylitis - a systematic comparison of conventional x-rays with magnetic resonance imaging (MRI) using established and new scoring systems. Ann Rheum Dis, 2004.


Table 1: Demographic data of the 38 AS patients (BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, BASFI= Bath Ankylosing Spondylitis Functional Index, BASMI= Bath Ankylosing Spondylitis Metrology Index, CRP=C-Reactive Protein, ESR=Erythrocyte Sedimentation Rate)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
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<td>32</td>
<td>54.0</td>
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<td><strong>Disease duration (years)</strong></td>
<td>14.9</td>
<td>2.0</td>
<td>34.0</td>
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<td><strong>BASDAI Score</strong></td>
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<td><strong>BASFI Score</strong></td>
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<td>0.9</td>
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<td><strong>BASMI Score</strong></td>
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<td><strong>CRP (mg/l)</strong></td>
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<td>1.0</td>
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<tr>
<td><strong>ESR (mm/h)</strong></td>
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<td>3.0</td>
<td>78.0</td>
<td>22.9</td>
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<td></td>
<td>Mean Score / VU</td>
<td>SD</td>
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<tr>
<td><strong>CS</strong></td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.24 ±0.63</td>
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<td>Gd-DTPA</td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.28 ±0.65</td>
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<td>STIR</td>
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<tr>
<td><strong>TS</strong></td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.69 ±1.24</td>
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<td></td>
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<tr>
<td>Gd-DTPA</td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.74 ±1.22</td>
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<tr>
<td>STIR</td>
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<tr>
<td><strong>LS</strong></td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.41 ±1.04</td>
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<tr>
<td>Gd-DTPA</td>
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</tr>
<tr>
<td>ASspiMRI-a</td>
<td>0.34 ±0.79</td>
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<tr>
<td>STIR</td>
<td></td>
<td></td>
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<tr>
<td><strong>Spine (all 3 segments)</strong></td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.51 ±1.09</td>
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<tr>
<td>Gd-DTPA</td>
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<tr>
<td>ASspiMRI-a</td>
<td>0.54 ±1.04</td>
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<td></td>
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<tr>
<td>STIR</td>
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</table>

**Table 2**: Descriptive data in the evaluation of acute spinal changes with mean scores for each spinal segment (CS=Cervical Spine, TS=Thoracic Spine, LS=Lumbar Spine) and for the whole spine as evaluated by using the ASspiMRI-a for Gd-DTPA and STIR sequences.
Figure legends

Fig. 1. The new scoring system ASspiMRI-a for evaluation of acute spinal lesions in patients with ankylosing spondylitis as assessed by Gd-DTPA and STIR MRI

Fig. 2. The ASspiMRI-a scoring system in detail. Grading with 1-3 indicates only erosion with differentiation of the range of inflammation (in the Gd-DTPA sequence) or edema (in the STIR sequence). Grading with 4-6 indicates inflammation with erosion, in relation to the extension of the erosion in the assessed VU.

Fig. 3. Definition of the Vertebral Unit (VU) for using the ASspiMRI score in the evaluation of MR images in the spine of AS patients.

Fig. 4. Relative involvement of each single VU in the assessment of inflammation by using the Gd-DTPA MRI sequence and evaluating with the ASspiMRI-a scoring system. Values are in % of VU affected, ** = VU most frequently affected in each spinal segment, “CS” = Cervical Spine, “TS” = Thoracic Spine, “LS” = Lumbar Spine

Fig. 5. Relative involvement of each single VU in the assessment of inflammation by using the STIR MRI sequence and evaluating with the ASspiMRI-a scoring system. Values are in % of VU affected, ** = VU most frequently affected in each spinal segment, “CS” = Cervical Spine, “TS” = Thoracic Spine, “LS” = Lumbar Spine

Fig. 6. Spondylitis anterior in T6/7 and T7/8 and spondylitis posterior in T8/9 as seen in the STIR MRI sequence. Inflammation is seen as a spot in the vertebra (arrows).
Figure 1

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>normal, no lesions</td>
</tr>
<tr>
<td>1</td>
<td>mild enhancement and bone marrow edema, covering ≤ 25% of a VU</td>
</tr>
<tr>
<td>2</td>
<td>moderate bone marrow edema, covering ≤ 50% of a VU</td>
</tr>
<tr>
<td>3</td>
<td>severe bone marrow edema, covering &gt; 50% of a VU</td>
</tr>
<tr>
<td>4</td>
<td>bone marrow edema and erosion covering ≤ 25% of a VU</td>
</tr>
<tr>
<td>5</td>
<td>bone marrow edema and erosion covering ≤ 50% of a VU</td>
</tr>
<tr>
<td>6</td>
<td>bone marrow edema and erosion covering &gt; 50% of a VU</td>
</tr>
</tbody>
</table>
Figure 3

1 vertebral unit
Figure 4

The figure shows the affection (%) for different group combinations. The affection values range from 10.96% to 52.41%. The specific group combinations are labeled with their affection percentages. For example, group combinations 3/4, 4/5, and 5/6 have affection values of 14.38%, 17.73%, and 17.78% respectively. The highest affection is observed in the group combinations 12/L1 and 11/12, with values of 46.21% and 48.97% respectively. The y-axis represents the group combinations, while the x-axis represents the affection percentage.
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Ann Rheum Dis published online September 30, 2004

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