Sensitivity and Specificity of Magnetic Resonance Imaging for Axial Spondyloarthritis

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Abstract: Diagnosing spondyloarthritis (SpA) early in young patients with inflammatory back pain and normal findings on radiographs of the sacroiliac joints (SIJ) remains a challenge in routine practice. Magnetic resonance imaging (MRI) is regarded as the most sensitive imaging modality for detecting early SpA before the radiographic appearance of structural lesions. The recently published Assessment of SpondyloArthritis International Society classification criteria for axial SpA include for the first time a positive MRI demonstrating sacroiliitis as an imaging criterion indicative of SpA together with at least 1 clinical feature of SpA. A systematic and standardized evaluation of the SIJ in patients with SpA showed that MRI has much greater diagnostic utility than documented previously and allowed a data-driven definition of a positive MRI for SpA. Single MRI lesions suggestive of inflammation can be found in the SIJ and the spine in up to one quarter of healthy controls and young patients with mechanical back pain.

Key Indexing Terms: Spondyloarthritis; Ankylosing spondylitis; Inflammatory back pain; Mechanical back pain; Magnetic resonance imaging; Diagnostic utility. **[Am J Med Sci 2011;341(4):272–277.]**

Diagnosing early spondyloarthritis (SpA) in young patients presenting with symptoms of inflammatory back pain (IBP) and normal findings on plain radiographs of the sacroiliac joints (SIJ) remains a challenge in routine practice. This is reflected by a substantial diagnostic delay of 5 to 7 years.[1] Radiography displays postinflammatory structural changes in the subchondral bone of the SIJ that are often visible only after a symptom duration of several years.[2,3] Sensitivity and specificity of radiographic signs of sacroiliitis[4] are only moderate and could not be improved on training of rheumatologists and radiologists.[5] Magnetic resonance imaging (MRI) shows early inflammatory changes in bone marrow and soft tissues and is regarded as the most sensitive imaging modality for detecting early SpA. It may therefore display early inflammatory abnormalities in the SIJ and the spine before the appearance of structural lesions on radiography. MRI may allow a confirmation of a diagnosis of early SpA suspected on clinical grounds as early as 4 months after symptom onset.[6]

The recently published Assessment of SpondyloArthritis (ASAS) International Society classification criteria for axial SpA[7] include for the first time a positive MRI demonstrating sacroiliitis as an imaging criterion indicative of SpA, but require additionally the presence of at least 1 clinical feature of SpA. An ASAS working group has also proposed a definition of a positive MRI for sacroiliitis according to consensus opinion that is entirely based on the presence of bone marrow edema (BME) on the short tau inversion recovery (STIR) sequence or osteitis on the T1-weighted gadolinium-enhanced sequence.[8] Structural abnormalities that may be observed on T1-weighted sequences are not included in this definition.

An ASAS International Society initiative has recently been started to define a positive MRI of spinal inflammation in SpA based on expert opinion evaluation of data from 4 studies assessing the diagnostic utility of inflammation in the spine.[9–12]

Diagnostic Utility of MRI for Spinal Inflammation in SpA

The thoracic spine is the second most frequent region affected by inflammation after the SIJ.[13,14] Inflammatory involvement of the spine is highly relevant for patients with SpA. Spinal inflammation causes substantial morbidity and may result in disability due to progressive axial ossification. Three recent studies concluded that inflammatory spinal lesions detected by MRI are predictive of new syndesmophytes as shown on follow-up x-rays 24 months later, although the association with progression varied between studies.[15–17] New syndesmophytes developed significantly more frequently in vertebral corners (VCs) with inflammation than in those without inflammation seen on baseline MRI.

Assessment of the sensitivity and specificity of active spinal inflammation is based on the classification of different inflammatory abnormalities seen on MRI. The definitions of active spinal lesions proposed by the Canada/Denmark International MRI Working Group include VC inflammatory lesions (CIL) and noncorner inflammatory lesions in central sagittal slices of spinal MRI scans, vertebral lateral inflammatory lesions (LIL) seen on lateral MRI slices and facet joint or other posterior element inflammatory lesions.[18,19] One recent study concluded that the presence of at least 2 CIL was of diagnostic utility,[9] whereas a second study concluded that at least 3 CIL were necessary.[11] This difference in cutoff level is largely attributable to different characteristics of the patient and control groups in the 2 studies. The study that indicated an optimal cutoff level of $\geq$3 CIL[11] had a retrospective design, the patients were relatively older (mean age 52.5 years, range 19–91 years, only 48% of the patients aged 50 years or younger) and had a long mean symptom duration of 15.2 years. The control group was heterogeneous consisting of patients with degenerative spine disease, spinal malignancy, various disorders such as spinal tuberculosis, spinal fracture or osteonecrosis, and mul-

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tiple spinal hemangiomas and few were healthy. The study that concluded that diagnostic utility was optimal with a cutoff level of ≥2 CIL[9] had a prospective design evaluating whole body (WB) MRI in the assessment of the spine in 2 groups of patients with confirmed ankylosing spondylitis (AS) and with recent-onset IBP. The patients were younger (median age 30.8 years, range 18–45 years) and showed a relatively short symptom duration both for patients with confirmed AS (8 years) and with IBP (10 months). The control group consisted of age- and sex-matched healthy volunteers (according to the Nordic questionnaire[20]) aged 45 years or younger, from the staff of the same hospital that was recruiting the patients. In this latter study, only lesions detected concordantly between 2 readers who scored independently were used to calculate sensitivity and specificity. This approach attempted to avoid taking into account equivocal MRI signal alterations such as low intensity or small lesions, and it may be translated into clinical practice where only clear-cut inflammatory lesions are likely to be taken into consideration. The limitation of this study was a lack of an age-matched control group with mechanical back pain. However, this study showed a finding of clinical relevance in that a single CIL was observed in up to 26% of healthy controls. It is essential for routine practice to avoid misclassification of healthy individuals as having SpA on the basis of an isolated or doubtful CIL.

Definitions for structural spinal lesions detected by MRI have recently been published by the Canada/Denmark International MRI Working Group.[21,22] There are a few data on the diagnostic utility of structural lesions of the spine in SpA. An analysis of VC fat lesions by Bennett et al[12] in the retrospective study cited above indicated a positive likelihood ratio (LR) of 5 for the presence of at least 1 VC fat lesion and a positive LR of 13 for more than 5 VC fat lesions. The same study limitations apply as cited above, particularly the relatively high median age of the study population, because such lesions are often observed in clinical practice in elderly individuals with mechanical back disorders. There is a need for more data from systematic studies in a younger population with SpA and age- and sex-matched controls before conclusions on the diagnostic utility of structural spinal lesions can be drawn.

WB MRI: A Promising Imaging Modality for Assessing Inflammation of the Entire Spine in SpA

Scanning the entire spine by conventional MRI with images of the upper and lower half of the spine is less convenient for the patient and more time consuming than WB MRI, which also scans the SIJ, the anterior chest wall and the shoulder and hip girdle.[23] WB MRI was first introduced in oncology and angiology because of its comprehensive scanning of all body regions. However, it may also prove useful in systemic musculoskeletal disorders such as SpA. WB MRI is based on multichannel technology with a multicoil system and parallel imaging. Fusion of the images is performed by dedicated software resulting in the same spatial resolution as in conventional MRI. A moving table platform allows seamless scanning without the need to reposition the patient or the coils. The examination time is 25 to 30 minutes, which includes positioning of the patient. The costs of WB MRI are about 1.5 times the cost of conventional MRI of a limited body region. The option of also imaging the lower extremities as a measure for enthesitis has to be weighed against an additional examination time of 20 minutes, which may be relevant for patients with active SpA. The WB MRI technique may also detect clinically asymptomatic, yet potentially relevant incidental findings in the axial skeleton or soft tissues such as disc hernia, goiter or tumorous lesions.

WB MRI and conventional MRI showed a good correlation for active SIJ and spinal inflammation scored using the Spondyloarthritis Research Consortium of Canada (SPARCC)[24] method in patients with confirmed SpA with an intrareader correlation for the SIJ of 0.87 to 0.94 and for the spine of 0.79 to 0.89, respectively.[14,25] The inter-reader reliability for spinal inflammation was higher for WB MRI than for conventional MRI, possibly attributable to an easier interpretation of a single WB MRI film representing the entire spine than the evaluation of 2 conventional MRI films covering the upper and lower halves of the spine separately. Therefore, WB MRI may prove to be preferable for the assessment of inflammatory lesions in the entire spine.

Diagnostic Utility of MRI for Sacroiliitis

A systematic literature review in 2004[26] addressed those studies that focused on the diagnostic utility of MRI in patients with either established AS or IBP and concluded that the overall sensitivity and specificity of MRI for sacroiliitis was 0.90 with a positive LR of 9.0. This estimate of diagnostic utility has since been incorporated into diagnostic algorithms for diagnosing SpA in clinical practice that rely on estimates of the degree to which a positive MRI increases the pretest probability of SpA.

There are several reasons, however, why this estimate of diagnostic utility requires reappraisal. Most studies included in the systematic review lacked age- and sex-matched controls and used dynamic (not standard) contrast-enhanced MRI, which is costly, unreliable and not used in routine practice.[27–31] Moreover, there is increasing acceptance of the necessity for including certain methodological aspects of study design such as standardization of technique for acquiring and reading magnetic resonance (MR) images, consensus definitions of abnormalities visible on MRI and standardized calibration/training of readers from different sites.

The ASAS/OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) definition of a positive MRI of the SIJ has been developed by expert consensus opinion and is based solely on active inflammatory lesions.[8] It requires subchondral or periarticular BME highly suggestive of sacroiliitis, as shown by the presence of at least 2 lesions on a single SIJ slice or by at least 1 lesion on 2 consecutive coronal slices. Structural SIJ lesions were not incorporated in this proposal because of a lack of data on structural SIJ changes at the time of the consensus.

The aim of the MORPHO study (named after the morphologic appearance of bright BME on STIR images showing in both SIJ, which resembles the pattern of light reflection on opened wings of Morpho butterflies found in South American rainforests) was to assess the diagnostic utility of both acute and structural MRI lesions of the SIJ in patients with SpA. It was an international multicenter evaluation of 187 subjects, including age- and sex-matched controls, in a young population representing the demographic that develops SpA.[32,33] The study goals were to develop a standardized methodology for the diagnostic evaluation of the SIJ by MRI based on: (1) standardized definitions of active inflammatory and structural MRI lesions of the SIJ by the Canada-Denmark MRI Working Group[18,21]; (2) a reference image set developed by consensus among study investigators (www.arthritisdoctor.ca); (3) an online training module of SIJ abnormalities; (4) calibration of readers according to a standardized methodology developed by SPARCC[24]; and (5) assessment using MRI sequences widely

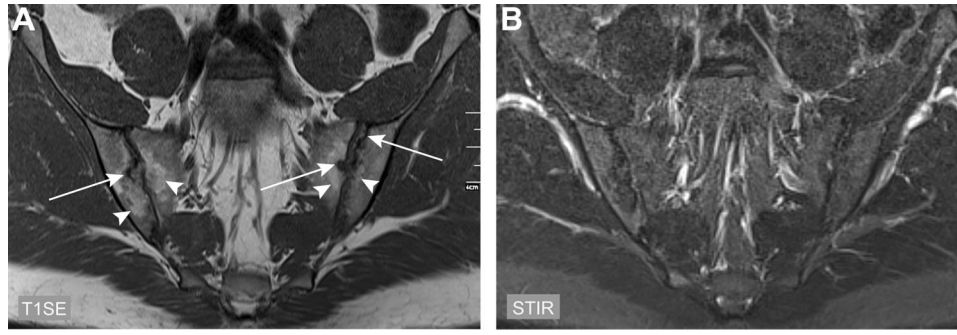

FIGURE 1. (A) T1SE sequence. (B) STIR sequence. MRI of the SIJ of a 34-year-old HLA B27-positive male patient with ankylosing spondylitis, symptom duration 9 years, BASDAI 7.5. The T1SE sequence (T1-weighted Turbo spin-echo; Figure 1A) is clearly pathological and shows erosions on the iliac side of both SIJ and on the sacral side of the left SIJ (white arrows). Fat infiltration is visible on both sides of the SIJ (arrowheads). The STIR sequence (B) displays no bone marrow edema; therefore, one cannot make a diagnosis of SpA based on this image alone. This MRI example illustrates how the T1SE sequence alone can be diagnostically useful, particularly when the STIR sequence shows no bone marrow edema.

used in routine practice. The goals of the study were to assess the relative importance of acute and structural lesions for diagnostic utility and to define a positive MRI for SpA using a data-driven approach.

One hundred two patients with SpA and age 45 years or younger were recruited in the rheumatology outpatient clinics of 2 university hospitals. Treatment with biologics before the SIJ scan was an exclusion criterion. Seventy-five of the patients met the modified New York classification criteria for AS[4] and had a disease duration of ≤10 years. The mean age of the 75 patients with AS was 31.1 years and the mean disease duration 6.1 years; 72% were men and 83% were HLA B27 positive; the mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[34] was 4.4. Twenty-seven patients with IBP not fulfilling the radiographic modified New York criteria were also enrolled. They either met the Berlin criteria for IBP[35] with the addition of at least 1 clinical or laboratory feature of SpA or met the Calin criteria for IBP.[36] The 27 patients with IBP had a mean age of 29 years and a mean symptom duration of 29 months; 67% were men, 92% were HLA B27 positive and their mean BASDAI was 4.2.

The first control group consisted of 26 patients with nonspecific back pain (NSBP) aged 45 years or younger (mean age 33.8 years, 58% men), who were defined on clinical grounds and according to radiographs of the SIJ. A second control group consisted of 59 healthy volunteers aged 45 years or younger (mean age 31.0 years, 63% men) from the staff of both university hospitals that were recruiting patients with SpA. The status of healthy controls was defined by the Nordic questionnaire.[20]

Scans included coronal T1-weighted Turbo spin-echo (T1SE) and STIR sequences angled parallel to the SIJ (see examples in Figures 1A and 1B). These are the usual sequences and scan parameters for routine MRI evaluation of patients with SpA in the involved institutions. Two recent studies showed that additional expensive and time-consuming contrast-enhanced MRI sequences do not improve diagnostic utility in this clinical setting over T1-weighted and STIR sequences alone for the evaluation of the SIJ[37] and the spine.[38] The MR scans were read in random order and scored independently by 5 readers (2 radiologists and 3 rheumatologists) blinded to patient demographics and diagnosis. The primary outcome was a diagnosis of SpA made by at least 2 readers according to global assessment of the MRI scans compared with the gold standard of the clinical classification of the 187 participants.

Standardized definitions of active inflammatory and structural lesions of the SIJ on MRI developed by the Canada/Denmark MRI Working Group were adopted,[18,21] focusing on 4 types of MRI lesions: BME on STIR images and joint erosion, marrow fat infiltration and ankylosis on T1-weighted images. Bone sclerosis and abnormalities of the synovial cavity were not addressed because of poor reproducibility in preread-out exercises. BME was defined as an increase in bone marrow signal in the SIJ on STIR images; the center of the sacrum at the same craniocaudal level was used as the primary reference for normal bone marrow signal. An erosion was defined as a full-thickness loss of dark appearance of either iliac or sacral cortical bone of the SIJ and change in normal bright appearance of adjacent bone marrow on T1-weighted images; adjacent bone marrow demonstrates altered signal intensity on T1-weighted images compared with normal iliac or sacral marrow on the same slice at the same craniocaudal level. Fat infiltration was defined as a focal increased signal in bone marrow on T1-weighted images. Ankylosis was defined as a bright signal on T1-weighted images extending across the SIJ.

A reference SIJ MR image set was developed by consensus among study investigators and video teleconference sessions that focused on the application of the standardized definitions of MRI lesions served to calibrate the reader team. The MR images of the SIJ were assessed according to the presence of lesions in individual SIJ quadrants in consecutive coronal slices as developed for the assessment of SIJ inflammation using the SPARCC method. The online training module has been validated by demonstrating that inexperienced rheumatology fellows can achieve reliability of detection of BME comparable to that recorded by experienced SPARCC readers after reviewing the training module.[24]

A customized online data entry module with 2 sections was used to record the MRI findings. The first section contained 3 questions addressing global assessment of each scan: (1) "This MRI scan confirms the presence of SpA (agree/disagree)"; (2) "Your conclusion is based on which MRI sequence (STIR, T1SE, both sequences)"; and (3) "What is the primary MRI feature on which your diagnosis of SpA is based (BME, fat infiltration, bone erosion, ankylosis, not applicable as SpA is not present)." The second section of the web-based data entry

module consisted of a detailed recording section where the SIJ is represented as a schematic with 4 quadrants. Each lesion was recorded as being present/absent on a dichotomous basis in each quadrant. Ankylosis was recorded in each half of the joint.

Diagnostic utility of MRI for SpA according to global evaluation of both T1-weighted and STIR MR scans was determined by calculating sensitivity, specificity, positive and negative LR for individual reader data, concordant data according to at least 2 readers, and for data recorded concordantly by all 3 rheumatologists and both radiologists.

In patients with preradiographic IBP, the percentage with at least 1 MRI lesion of the SIJ compatible with BME, erosion and fat infiltration, that were recorded concordantly by any 2 readers was 78%, 59% and 44%, respectively. In contrast, erosion and fat infiltration (both lesions found in 93% of the patients) were observed with about the same frequency as BME (91%) in the AS patient group. Erosions were detected in half of the patients with IBP reporting a mean symptom duration of 29 months and therefore demonstrates that structural damage of the SIJ starts early in the disease course, long before it can be captured by radiography. However, participants of both control groups also showed MRI lesions meeting these definitions with a frequency between 8% and 27% (BME, erosion and fat infiltration in 27%, 8% and 19% in the NSBP patient group, respectively, and in 22%, 8% and 24% among healthy volunteers, respectively). The clinical implication from these observations is that low-grade acute lesions of the SIJ visible on MRI should be interpreted with caution to avoid misclassification of young subjects with back pain as patients with SpA. Compared with BME-like lesions and fat infiltration, erosions were observed much less frequently in both control groups, and they may therefore be the most specific feature of SpA.

The mean sensitivity, specificity and positive and negative LR for the diagnosis of SpA in patients with AS for all 5 readers were 0.90 (0.83–0.97), 0.97 (0.94–0.99), 45 (16–73) and 0.10 (0.01–0.18), respectively. The corresponding values for the diagnosis of SpA in patients with IBP were 0.51 (0.48–0.52), 0.97 (0.94–0.99), 26 (9–43) and 0.50 (0.49–0.53), respectively. The number (percentage) of patients diagnosed concordantly as SpA by at least 2 readers according to the global evaluation of both MRI sequences was 74/75 (99%) for the AS group and 14/27 (52%) for the patients with IBP.

We postulated that global assessment captured additional diagnostic information beyond that provided by BME and that this information would largely be due to the presence of erosions. We therefore proposed an alternate definition of a positive MRI, termed the MORPHO proposal, which defines SpA as being present on MRI if any of the following 3 criteria are met: (1) BME in at least 2 SIJ quadrants in the same slice or a single SIJ quadrant in 2 consecutive slices (according to the ASAS definition); (2) erosion in at least 2 SIJ quadrants in the same slice or a single SIJ quadrant on 2 consecutive slices; (3) BME and erosion in any SIJ quadrant though not necessarily in the same quadrant.

Applying the ASAS definition to the MRI assessment of patients with IBP, sensitivity, specificity, positive and negative LR for any 2 readers for the diagnosis of SpA were 0.67, 0.88, 5.7 and 0.4, respectively. The inclusion of erosions according to the MORPHO proposal improved sensitivity to 0.81 compared with the ASAS definition (sensitivity 0.67), with no change in specificity of 0.88 in both proposals, so that the overall diagnostic utility was better (positive and negative LR 6.9 and 0.2, respectively). Although the positive LR of 6.9 was still not as good as by global assessment of MRI (positive LR 9.8), the negative LR was better (0.2 versus 0.5). The lower negative LR of the MORPHO proposal compared with the other 2 approaches may prove useful in daily routine where ruling out a diagnosis of SpA may be as important as confirming the disorder.

T1w images alone or together with STIR images were indicated as most important for the conclusion that the MRI was indicative of SpA in 97% of patients with AS by the radiologists and in 74% by the rheumatologists, respectively, and for the patients with IBP in 67% by the radiologists and in 30% by the rheumatologists, respectively. The greater sensitivity and hence better diagnostic utility of the radiologists for the combined SpA group was mainly attributable to their more frequent recognition of structural lesions, suggesting that rheumatologists may require greater awareness and more intensive training to recognize structural lesions.

A second reading exercise was performed 6 months later on a random selection of 30 patients with AS with a symptom duration of ≤5 years and 34 controls from the original study population. The goal of this reading exercise was to determine whether additional training by video teleconference sessions directed at recognition of structural abnormalities on T1w sequences would improve diagnostic utility, particularly for the 2 least experienced readers. In 1 of the 2 readers with limited experience, sensitivity substantially increased from 77% to 97% at the cost of a slight decrease in specificity (94% versus 100%), whereas the second less experienced reader improved both sensitivity (100% versus 93%) and specificity (97% versus 79%). The T1w sequence alone or in combination with the STIR sequence was considered most important by the radiologists in 95% of the patients with AS both in the pre- and postcalibration readout, whereas the rheumatologists increased their preference regarding the T1w sequence alone or in combination with STIR from 69% in the precalibration to 85% in the postcalibration reading exercise.

Several conclusions can be drawn from the MORPHO study. A systematic and standardized approach to assess acute and structural lesions of the SIJ shows that MRI has much greater diagnostic utility in SpA than has been documented previously. Low-grade acute and structural lesions may be present in patients with NSBP and healthy volunteers with a frequency of up to 27%. Structural lesions occur frequently and early in the disease course of SpA, and they contribute substantially to diagnostic utility. Rheumatologists rely primarily on the STIR sequence, whereas radiologists also focus on structural abnormalities on T1SE sequences. Training rheumatologists to recognize structural lesions on T1SE MRI sequences improves diagnostic utility of MRI.

Considering these advances in imaging axial SpA, it is important to emphasize for clinical practice that the place of MRI in the diagnostic work-up of SpA suspected on clinical grounds is particularly useful where plain x-rays of the pelvis are normal or show equivocal findings.[39]

Future Directions

The need for training rheumatologists to interpret MRI in inflammatory disorders of the axial skeleton and for recognizing structural lesions on SIJ scans will be addressed by specific training courses. A rheumatology imaging workshop in SpA where participants will receive direct hands-on training in using MRI will be held in Canada in August 2010.

An OMERACT initiative on assessing structural SIJ lesions started in May 2010 and will contain a reading exercise comparing 4 published methodologies for scoring lesions in the SIJ. The diagnostic utility of more cartilage-specific MRI

sequences such as nonenhanced T1FS or gradient echo sequences for assessing structural MRI lesions of the SIJ and the spine is a further research topic.

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