Diagnosis and classification in spondyloarthritis: identifying a chameleon

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Abstract | Spondyloarthritis (SpA) defines a group of interrelated diseases, including ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic-related spondylitis and arthritis, and undifferentiated SpA. The clinical presentation of SpA is heterogeneous, and no single shared distinguishing feature exists for the conditions comprising SpA; in daily practice, diagnosis is usually made on the basis of a combination of symptoms, the findings of physical examination, imaging and laboratory investigations. Several classification criteria have been developed for AS and SpA, which are useful in a research setting but cannot be automatically applied to the diagnosis of individual patients. Currently, MRI is the most sensitive imaging modality available for detection of sacroiliitis, often enabling detection of axial inflammation long before structural lesions are observed radiographically, thus facilitating early diagnosis of axial SpA. However, MRI will never capture all facets of SpA and the expert opinion of a rheumatologist will remain the crucial step in recognition of this disease. In this Review, we discuss diagnosis and classification of AS and SpA, and highlight how MRI might facilitate both processes.

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Introduction

Almost 40 years ago, the concept of seronegative spondyloarthritis (SpA) was established;[1] SpA defines a group of closely related diseases, comprising ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, enteropathic-related spondylitis and arthritis, and undifferentiated SpA. These diseases have several clinical features in common, show familial clustering, and are associated with *HLA-B27* positivity. The clinical presentation of SpA is heterogeneous and can include back pain (usually of an inflammatory nature), oligoarthritis predominantly of the lower limbs, dactylitis ('sausage'-like digits), enthesitis at the heel or other sites, and extra-articular manifestations such as uveitis, inflammatory bowel disease and psoriasis. All these manifestations can occur in each of the SpA disease subgroups. Patients with SpA can also be classified, according to their clinical presentation: patients with axial SpA (axSpA) have predominantly axial involvement, reflecting inflammation of the sacroiliac joints (SIJ), the spine, or both; patients with peripheral SpA mainly demonstrate peripheral joint manifestations, consisting of peripheral arthritis, enthesitis and dactylitis.[2] Advantages of this approach to characterization of patients with SpA are a better description of the presenting disease and improved administration of treatment, as therapeutic strategies differ for axial versus peripheral SpA. No single shared distinguishing feature exists for the conditions comprising SpA, necessitating the combination of assessment of symptoms, physical examination, imaging and laboratory analyses for diagnosis in daily practice. This Review describes the diagnosis and classification of AS and SpA, and the role of MRI in these processes.

Competing interests
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Diagnosis and classification of SpA

Diagnostic versus classification criteria

In rheumatology, available criteria sets are usually designed for research purposes, but are also frequently used in clinical practice. The various types of criteria that have been developed serve different purposes, and a distinction between diagnostic and classification criteria should be made.[3] The purpose of diagnostic criteria is to help clinicians make a diagnosis. Diagnostic criteria are applied to individual patients, and should be sensitive to enable the identification of as many patients with the condition as possible and at early stages of disease. This requirement can lead to overdiagnosis on some occasions, and hence reduced specificity. The performance of diagnostic criteria depends on the prevalence of the disease. Diagnostic criteria allow some flexibility in diagnosis: a patient who fulfills the criteria set can be considered as a 'definite' case; however, patients might also demonstrate only some features of the disease, and can be considered as 'probable' or 'possible' cases.

By contrast, the purpose of classification criteria is to differentiate patients with a specific disease from patients with a different disease or from individuals in the general population.[3] Such criteria are used in research to create homogeneous groups of patients to facilitate comparisons

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Key points

- Classification criteria designed for high specificity are of limited utility when making a diagnosis in daily practice, as they lack sensitivity at early stages of disease
- The Assessment of SpondyloArthritis international Society (ASAS) axial spondyloarthritis (axSpA) criteria enable comparisons across trials in early nonradiographic disease, for which new disease-modifying treatment strategies are urgently needed
- Ongoing research will determine whether the ASAS axSpA classification criteria could contribute to a reduction in the delayed diagnosis of axSpA
- Although pelvic radiographs, MRI of the axial skeleton and *HLA-B27* testing are important for disease classification, negative findings for these assessments do not preclude a diagnosis of axSpA
- MRI enables detection of axial inflammation in early SpA long before structural lesions can be visualized on radiographs
- A data-driven definition of what constitutes a positive MRI finding in axSpA has top priority on the research agenda

among studies. Classification criteria demonstrate high specificity to avoid misclassification (that is, to prevent inclusion of a patient who does not have the disease), but have reduced sensitivity and, therefore, should not be applied for diagnosis in individuals. The performance of classification criteria is independent of the disease prevalence, because they are solely applied to patients in whom a diagnosis is already made; a patient can either fulfill or not fulfill the classification criteria. An important disadvantage of classification criteria is the potentially limited generalizability of study findings that are drawn from such a highly selected group of patients.

When developing new criteria sets, the study design, patient selection and reference standards are different for classification and diagnostic criteria.[4] Therefore, criteria sets developed for classification cannot automatically be applied for diagnostic use.

Modified New York criteria for AS

Currently, the modified New York (mNY) criteria are the most widely used for classification of AS.[5] According to the mNY criteria, a patient can be classified with definite AS when at least one clinical criterion and the radiological requirements are met (Table 1).[5] The clinical criteria include inflammatory back pain (IBP), limited spinal mobility and restricted chest expansion. To meet the radiological definition of AS, the patient must have at least grade 2 sacroiliitis bilaterally or grade 3 sacroiliitis unilaterally.[5]

An important restriction of the use of the mNY criteria in clinical practice is the exclusive focus on axial features, thereby omitting other clinically relevant features of the disease. Furthermore, the limitations in mobility of the spine and chest expansion usually occur late in the disease course and do not represent active inflammation, rather these symptoms are consequences of inflammation.

Sacroiliitis is considered the hallmark of AS, but is often difficult to identify; interpretation of radiographs, especially for grade 2 sacroiliitis, has limited sensitivity and specificity.[6] Pelvic radiographs can only detect structural changes such as erosions and sclerosis, and describing these findings as sacroiliitis is not appropriate as the result of inflammation is visualized rather than inflammation itself. Owing to slow progression of radiographic damage, a delay of up to 10 years between the onset of first symptoms and diagnosis of AS is common.[7,8] MRI studies have demonstrated severe inflammation of the SIJ early in the disease course in patients without evidence of damage on pelvic radiographs,[9] and MRI-detected active inflammation has been shown to predict subsequent occurrence of radiographic sacroiliitis.[10,11]

Overall, the mNY criteria are useful to apply to definite cases of AS for classification, but these criteria should not be used in daily practice for the recognition of patients with early axSpA: they are not sensitive enough in the early stage of the disease, they focus too much on structural damage, and other important features are not considered, such as extra-spinal symptoms, MRI findings, *HLA-B27* status, family history and response to NSAIDs.

Difficulties in diagnosis of early axial SpA

Early diagnosis and therapeutic intervention are important to modify disease progression, decrease the disease burden and avoid unnecessary diagnostic and therapeutic procedures.[12] Diagnosis of axSpA and AS is, however, a challenge, and several attempts have been made to facilitate and standardize the diagnosis early in the disease course.[13–15] One study reported a diagnostic algorithm,[14] whereas another calculated probability of axSpA using the likelihood ratios of various clinical features.[13,15,16] Both approaches required a combination of several clinical symptoms, laboratory parameters and imaging findings typical for axSpA to reach a diagnosis. A case ascertainment tool for undiagnosed AS has been developed that can be applied to population screening or surveys, and showed a sensitivity of 67.4% and a specificity of 94.6%.[17]

In many patients with axSpA onset of symptoms occurs in the third decade of life, starting with back pain that can be insidious at onset, and mild and nonspecific in the early stages of the disease.[18,19] Although chronic back pain is the primary symptom of axSpA, patients can be pain-free for long periods of time.[8] Similarly, other signs and symptoms of early axSpA are often subtle and can fluctuate over time, which can result in a delayed diagnosis not only in primary care but also in rheumatology practice.[20]

Moreover, the presenting symptoms need to be distinguished from those associated with other rheumatic conditions, nonspecific pain syndromes, or mechanical causes. Chronic back pain is common in the general population, and AS accounts for symptoms in no more than 5% of all patients presenting with chronic back pain.[21] Several criteria sets are available that define IBP, which all perform similarly and can be used in daily practice.[22–24] IBP is present in 70-80% of patients with axSpA, but also occurs in 20–25% of patients with mechanical back pain.[13] One study showed that investigating IBP using a single clinical characteristic is of limited value in primary care, but the combination of at least three criteria might be useful to facilitate a diagnosis of axSpA, but with moderate sensitivity and low specificity

Table 1 | Overview of features included in the different classification criteria sets for AS and SpA

Features of criteria	Modified New York criteria[5]	Amor criteria[31]	ESSG criteria[32]	ASAS axial SpA criteria[40]	ASAS peripheral SpA criteria[45]
Year of publication	1984	1990	1991	2009	2011
Inclusion or entry criteria	Sacroiliitis on radiograph* plus ≥1 clinical criterion	None, fulfillment of criteria requires a score of ≥6 points, assigned on the basis of clinical features that are considered from the list below. Weightings for each feature are shown in parentheses	Either IBP or synovitis (asymmetric or predominantly of the lower limbs) plus at least 1 other SpA feature	≥3 months back pain before age 45 years and either sacroiliitis on imaging (radiographs or MRI) plus ≥1 other SpA feature (imaging arm) or *HLA-B27* positive plus ≥2 other SpA features (clinical arm)	Arthritis, enthesitis or dactylitis plus ≥1 SpA feature marked with[a] or ≥2 other SpA features marked with[b]
SpA features to be considered					
IBP‡	✓	×	×	✓	✓ (ever)[b]
Alternating buttock pain	×	✓ or gluteal pain (1 point)	✓	×	×
Pain at night or morning stiffness	×	✓ (1 point)	×	×	×
Arthritis	×	✓ asymmetrical oligoarthritis (2 points)	×	✓	✓[b]
Dactylitis	×	✓ (2 points)	×	✓	✓[b]
Enthesitis (heel)	×	✓ (2 points)	✓	✓	✓[b]
Good response to NSAIDs	×	✓ (2 points)	×	✓	×
Psoriasis	×	✓ (2 points)§	✓	✓	✓[a]
Inflammatory bowel disease	×	✓ (2 points)§	✓	✓	✓[a]
Balanitis	×	✓ (2 points)§	×	×	
Uveitis	×	✓ (2 points)	×	✓	✓[a]
Diarrhea <1 month before onset arthritis	×	✓ (1 point)	✓#	×	×
Urethritis/cervicitis <1 month before onset arthritis	×	✓ (1 point)	✓#	×	×
Preceding infection	×	–	×	×	✓[a]
Positive family history for SpA‖	×	✓ (2 points)¶	✓	✓	✓[b]
HLA-B27	×	✓ (2 points)¶	×	✓	✓[a]
Elevated CRP	×	×	×	✓	×
Sacroiliitis	×	✓ (radiographic*; 3 points)	✓ (radiographic*)	×	✓[a] (radiographic* or MRI-detected)
Limitation in mobility of lumbar spine	✓	×	×	×	×
Limitation in chest expansion	✓	×	×	×	×

*Radiographic sacroiliitis is considered present when at least grade 2 bilaterally or grade 3–4 unilaterally. ‡Different definitions for IBP exist for the different criteria sets. §Presence of psoriasis, balanitis or inflammatory bowel disease is considered as 1 item, and 2 points are given in total if at least one is present. ‖Different definitions for a positive family history exist for the different criteria sets. ¶Presence of either *HLA-B27* positivity or a positive family history is sufficient to obtain the score of 2 points. #Presence of either urethritis/cervicitis or acute diarrhea within 1 month before onset of arthritis is sufficient to fulfill this SpA feature in the ESSG criteria. Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of Spondyloarthritis international Society; CRP, C-reactive protein; ESSG, European Spondyloarthropathy Study Group; IBP, Inflammatory back pain; SpA, spondyloarthritis.

(sensitivity 78.8%, specificity 46.4%).[25] However, owing to the moderate sensitivity and specificity observed in previous studies, IBP alone is not sufficient for diagnosis; the presence of IBP only increases the probability of axSpA from 5% to 14–16%.[13]

Radiographs can be normal in early axSpA and can remain so for many years after disease onset.[13,,26,27] However, in the early stage, sacroiliitis can be visible on MRI (‘nonradiographic stage’). Similarly, inflammation in the spine can also be visible on MRI before structural damage occurs. Importantly, patients with nonradiographic axSpA are not different from those with definite AS with respect to disease activity, pain, quality of life, and response to treatment.[26] Several trials in patients with nonradiographic axSpA have shown a good response to biologic agents, with a similar or increased proportion of responders observed in early axSpA compared with trials in established AS.[28–30]

ESSG and Amor criteria

In the early 1990s, two sets of classification criteria were developed that are also applicable to early-stage and mild SpA: the European Spondyloarthropathy Study Group (ESSG) criteria and Amor criteria.[31,32] Both criteria sets cover the whole spectrum of SpA conditions and do not specifically focus on axial or peripheral SpA.

The presence of sacroiliitis is considered in both criteria sets, but not mandatory for fulfillment. For fulfillment of the ESSG classification criteria, the patient should meet the entry criteria of either IBP or peripheral synovitis, plus have at least one SpA-associated feature from a list of seven (Table 1).[32] The Amor criteria consist of a list of 12 items, with the scores for each item weighted differently (ranging from 1–3);[31] a total of 6 points are required to meet the Amor criteria, but none of the items are mandatory (Table 1). Compared with the ESSG criteria,[32] the Amor criteria consider additional items such as response to NSAIDs and genetic predisposition (*HLA-B27* positivity).[31]

In terms of feasibility, the ESSG criteria are easy to apply, whereas the Amor criteria take more time to complete but are more comprehensive. Both criteria sets have been validated as classification criteria in different populations, and have comparable sensitivity (around 70–90%) and specificity (around 90–100%).[31–36] However, performance of both criteria sets was considerably lower when applied in early, mild or possible cases of SpA, indicating that they have limited value as diagnostic tools.[32,36–38] Furthermore, the ESSG and Amor criteria do not provide information regarding clinical manifestations, such as axial versus peripheral features, in individual patients. SpA should not be considered as a single disease entity, as its presentation is heterogeneous, and doing so could influence the results of studies evaluating treatment effects or disease outcomes. In addition, neither criteria set incorporates the findings of sacroiliitis on MRI. Specific issues influencing the performance of the ESSG criteria are that patients presenting with dactylitis or enthesitis might not be included owing to the specific entry criteria required, and the lack of consideration of *HLA-B27* status—although the diagnostic value of *HLA-B27* testing was acknowledged during the development of the ESSG criteria. A drawback of the Amor criteria is the definition of peripheral arthritis as an oligoarticular form of arthritis, thereby excluding patients presenting with monoarthritis or polyarthritis.

ASAS axial and peripheral SpA criteria

The recognition of a nonradiographic stage in early AS—a condition now covered by the concept of axSpA—and the limitations of the existing classification criteria highlighted the need to develop new criteria sets, which would identify patients at an early stage and differentiate axSpA from peripheral SpA. Such criteria would enable trials to be conducted in nonradiographic axSpA, for which treatments could not be assessed previously owing to the absence of specific classification criteria. Experts from the Assessment of SpondyloArthritis international Society (ASAS) developed classification criteria for axSpA and peripheral SpA. To cover the many aspects of axSpA as optimally as possible, the ASAS attempted to create criteria that combined a wide range of typical SpA features, such as clinical manifestations, family history, imaging and laboratory analyses.[39] The final ASAS axSpA criteria, published in 2009, cover the entire spectrum of axial disease, irrespective of the presence of radiographic sacroiliitis.[40] The axSpA criteria consist of two arms: the 'imaging arm' and the 'clinical arm'. Both arms require that the patient should have chronic back pain that onsets before the age of 45 years and persists for ≥3 months (Table 1).[40] To fulfill the imaging arm, a patient should have sacroiliitis, either on MRI images or on conventional radiographs, and have at least one feature of SpA.[40] To fulfill the clinical arm, the patients should be *HLA-B27* positive and have at least two other SpA-associated features;[40] sacroiliitis is not mandatory for fulfillment of the ASAS axSpA criteria, when the criteria for the clinical arm are met.

The ASAS axSpA criteria have been validated in a large international cohort of patients, in which 60.2% of the patients were diagnosed with axSpA, on the basis of expert opinion.[40] The ASAS axSpA criteria showed similar sensitivity (82.9%) and slightly better specificity (84.4%) compared with the Amor criteria (sensitivity 82.9% and specificity 77.5%, after adjustment for MRI), but much better specificity than the ESSG criteria (sensitivity 85.1%, specificity 65.1%, after adjustment for MRI).[40] With a pre-test probability of axSpA in this cohort of 60.2% and a positive likelihood ratio of 5.3, the post-test probability of axSpA is 89.0% when fulfilling the criteria and 97.5% when the imaging arm alone was considered.[40] Although the ASAS axSpA criteria have not been validated for diagnostic purposes prospectively in daily practice, these data suggest that the criteria could assist in making a diagnosis in a setting of high disease prevalence.

Inclusion of assessments of several SpA features, including MRI and *HLA-B27* testing, in the ASAS axSpA criteria is a major step forward in the identification of different axSpA phenotypes; however, the criteria also have some drawbacks. Owing to the MRI and *HLA-B27* entry criteria, use of the ASAS axSpA criteria is not feasible in field studies or population surveys, which are performed using easy-to-administer and inexpensive instruments—usually questionnaires, limited clinical examinations and occasionally basic imaging and laboratory tests. Furthermore, both MRI and *HLA-B27* testing are expensive and their availability can be limited. When MRI is unavailable, a substantial proportion of patients will remain unrecognized. This issue could particularly affect women, who seem to be at a lower risk of radiographic progression; male gender was found to be a risk factor for developing radiographic sacroiliitis and, therefore, for evolution from nonradiographic axSpA to AS.[26] By contrast, gender was more equally distributed in cohorts and trials including patients with undifferentiated and nonradiographic axSpA.[26,28–30,32,33,41–44] In comparison with other diagnostic tests for SpA, *HLA-B27* positivity has a high sensitivity and specificity, although the performance depends on the prevalence of *HLA-B27* in a particular population.[13] In AS, 75–95% of the patients are *HLA-B27* positive, whereas in undifferentiated and nonradiographic axSpA the prevalence is much lower (42–75%).[26,28–30,41–44] Absence of HLA-B27 does not preclude a diagnosis of SpA and is associated with a longer delay in diagnosis.[12,44]

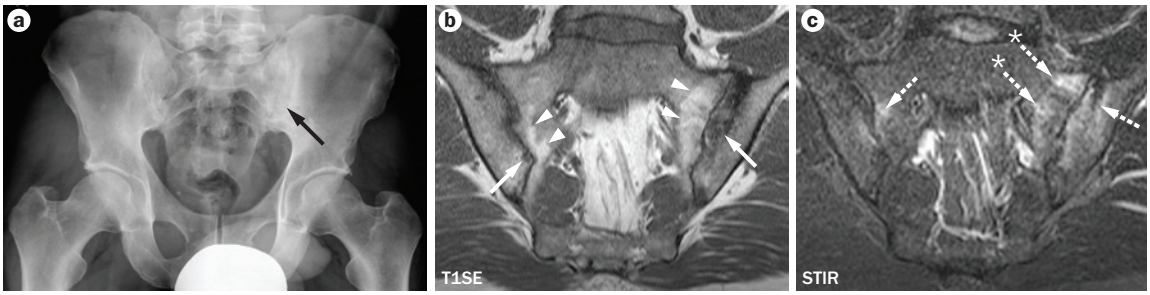

Figure 1 | Sacroiliitis in a patient with axSpA as observed on a pelvic radiograph and on SIJ MRI images. **a** | Pelvic radiograph of a 40 year old, *HLA-B27* positive male who meets the radiographic criteria of the modified New York criteria for AS. Both SIJ show blurred joint margins, sclerosis and erosion, more pronounced on the left side with pseudo-widening of the joint space (black arrow). **b** | Demonstration of two features that can be detected on T1SE sequence MRI images of the SIJ: joint erosion (arrows) and fat infiltration (arrowheads). Extended erosion in the left iliac bone corresponds to radiographic pseudo-widening of the left SIJ. **c** | STIR MRI sequences reveal bone marrow edema (broken arrows, with and without asterisks). The dotted arrows with asterisks point to ongoing active inflammation within the areas of fat infiltration detected by T1SE MRI. Abbreviations: AS, ankylosing spondylitis; SIJ, sacroiliac joint; axSpA, axial spondyloarthritis; STIR, short tau inversion recovery; T1SE, T1-weighted spin-echo.

In 2011, the ASAS peripheral SpA criteria were published.[45] These criteria were developed in patients with peripheral manifestations, but without back pain (Table 1). Sensitivity was much better for the ASAS peripheral SpA criteria (77.8%) than the Amor and ESSG criteria (55.1% and 35.2%, respectively).[45]

The emerging role for MRI in axSpA

MRI sequences and lesions in axSpA

Since the early 1990s, MRI of the SIJ and spine has been increasingly used to assess patients with clinically suspected early axSpA for whom pelvic radiographs are normal or demonstrate equivocal findings. The superior spatial and contrast resolution of MRI enables visualization of bone and soft tissue structures involved in the SpA disease process. This ability—together with the absence of ionizing radiation—makes MRI an ideal imaging modality to evaluate inflammation in the axial skeleton, which has limited accessibility to clinical examination.[46] Two MRI sequences widely used to assess axSpA are the fluid-sensitive short tau inversion recovery (STIR) and the fat-sensitive T1-weighted spin-echo (T1SE) sequences, which provide complementary information regarding inflammation.[47] So-called 'cartilage sequences' have been suggested to facilitate evaluation of structural lesions, but the utility of this method in the diagnosis of axSpA has not been validated in controlled studies.[48] Systematic studies in patients with axSpA failed to show advantages of costly contrast-enhanced MRI sequences over the commonly used STIR technique for assessment of inflammation in the SIJ and spine.[49,50] STIR and T1SE sequences can detect both active and structural lesions in early axSpA, in contrast with the postinflammatory structural changes associated with advanced disease that are the limit of radiographic detection (Figure 1).[51] Bone marrow edema—characterized by increased signal in STIR MRI (Figure 1c)—is considered the most important abnormality indicating active inflammation in axSpA, and is usually first detected in the cartilaginous SIJ compartment.[52,53] Among the structural lesions that are well visualized on T1SE sequence, erosion of the SIJ is highly specific for axSpA (Figure 1b). Erosions are identified on T1SE MRI image by a break in the cortical bone signal together with a change in the signal for adjacent bone marrow.[54–56] The diagnostic utility of fat infiltration in the SIJ remains a matter of debate, as this lesion is also frequently observed in healthy individuals and in patients with mechanical back pain.[57] New bone formation in the SIJ is often easily identified as bright areas on T1SE MRI images, representing bone marrow fat. Syndesmophytes in the spine, however, are often difficult to visualize using MRI if they lack bone marrow fat, appearing as black areas indicative of cortical bone, which are difficult to differentiate from the dark signal of peri-spinal ligaments.

How to use MRI for recognition of axSpA

What constitutes a 'positive MRI' for axSpA?

In a multicenter cross-sectional study of 649 unselected patients with back pain of ≥3 months duration, bone marrow edema on SIJ MRI images assessed by local SpA experts was observed in 64.7% and 2.6% of patients considered to have or not have axSpA, respectively;[40] the evaluation of the MRI images was performed with all clinical and laboratory data available.[40] On the basis of these findings, for the first time, not only radiographic sacroiliitis, but also active inflammatory lesions detected using MRI were included as major imaging-based disease determinant in classification criteria, developed by the ASAS.[40] The incorporation of MRI into such criteria raises the question of which SIJ lesions constitute MRI evidence of axSpA. A joint ASAS–OMERACT expert consensus statement suggested that two bone marrow edema lesions on the same SIJ slice or one lesion in the same SIJ quadrant on at least two consecutive slices are indicative of axSpA.[58] However, the interpretation of this definition of bone marrow edema lesions, with regard to morphological appearance and anatomical location, as being 'highly suggestive' of axSpA could be challenging for rheumatologists and even for radiologists not specialized in SpA.

A subsequent systematic data-driven approach proposed the inclusion of erosions, which are highly specific

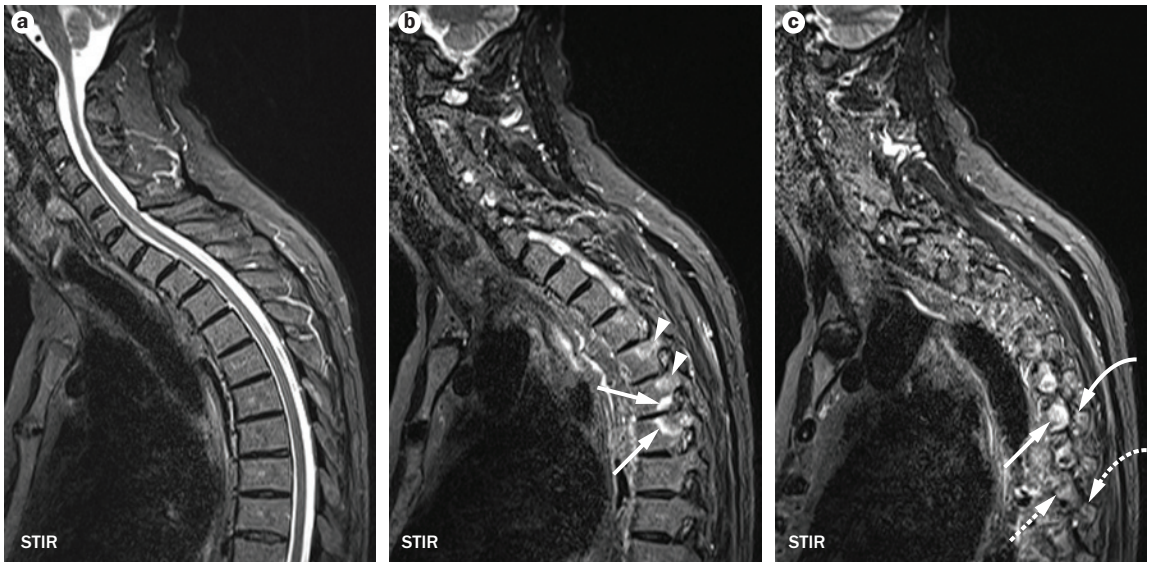

Figure 2 | Spinal MRI can identify SpA-associated inflammation. Three MRI images with STIR sequence applied of a 48 year old, *HLA-B27* negative male patient with AS who presented with interscapular pain on deep breathing and rotation of the trunk. **a** | A central MRI slice, showing the central spinal canal, without inflammation. **b** | A lateral MRI slice through the pedicles displays bone marrow edema in the fifth and sixth thoracic vertebra, representing costovertebral joint inflammation (arrows). In addition, bone marrow edema is visible in pedicles (arrowheads). **c** | A far lateral MRI slice shows bone marrow edema both in the rib (straight solid arrow) and transverse process (curved solid arrow), corresponding to costotransversal joint inflammation. Broken arrows indicate a normal rib (straight broken arrow) and transverse process (curved broken arrow) for comparison. Inflammatory lesions in the lateral spinal compartment (costovertebral, costotransverse, and facet joint) are highly specific for SpA and can be captured by dedicated spinal MRI protocols for SpA that include lateral slices.[62,65] Abbreviations: AS, ankylosing spondylitis; SpA, spondyloarthritis; STIR, short tau inversion recovery.

for axSpA, in a definition of a positive MRI.[55] This suggestion was based on the observation that bone marrow edema meeting the ASAS–OMERACT criteria was seen also in 23% of patients with mechanical back pain and in 7% of healthy volunteers, whereas erosion was recorded in only 4% and 2% of these individuals, respectively.[55] Moreover, MRI-detected erosions in at least two SIJ quadrants were detected in 59% of patients with early axSpA with no or only ambiguous structural changes on pelvic radiographs.[56] Trained rheumatologists were able to detect erosions on MRI images with a reliability comparable to identification of bone marrow edema.[59] Global evaluation of all active and structural lesions detected in the SIJ using MRI had better diagnostic performance than assessments based on bone marrow edema alone or in combination with erosions.[55,60]

An unresolved issue regarding which findings constitute a positive MRI in SpA is whether spinal MRI-detected lesions might increase diagnostic utility compared with using SIJ MRI alone (Figure 2). Spinal MRI protocols should obtain lateral slices beyond standard neurosurgery acquisition techniques, in which scans are restricted to the central spinal canal, as both lateral and posterior spinal inflammatory lesions are highly specific for axSpA.[61,62] Future approaches to define which MRI features are indicative of axSpA should ideally assess both active inflammation and structural lesions, evaluate the potential contribution of spinal lesions in addition to changes in the SIJ, and should be data-driven from longitudinal studies with follow-up imaging.

Case–control selection and MRI thresholds

Control subjects in studies of diagnostic efficiency should include healthy controls, to assess the 'background noise' of the test findings, as well as age-matched and gender-matched controls with a disorder that is challenging to differentiate from the disease that the test is designed to diagnose.[63] The latter disease control group for studies in axSpA should ideally consist of patients with non-specific back pain. The impact of different control groups is exemplified by two studies of the diagnostic utility of spinal corner bone marrow edema lesions in axSpA; both studies found the same positive likelihood ratio of 12, but with different cut-off values of 2 and 3 lesions.[64,65] As detection of vertebral corner bone marrow edema lesions on spinal MRI is reliable, the difference in the cut-off value is largely attributable to different control groups included. The controls in one study consisted of age-matched and gender-matched healthy volunteers with a median age of 31 years, an age group that represents the demographic that develops axSpA symptoms;[65] however, this study lacked disease controls with mechanical back pain. The second study, which had a retrospective design, enrolled older control individuals (mean age of 53 years) with a mixed disease spectrum, mainly comprising patients with specific causes of back pain such as spinal malignancy, spinal fracture or spinal tuberculosis, but only a limited number of healthy individuals.[64]

Comparison of the inclusion criteria for disease cases used for SpA across studies of the diagnostic potential of MRI is also important. Various classification criteria

proposed for SpA or IBP differ with regard to sensitivity and specificity, which can subsequently influence the diagnostic effectiveness observed for MRI. Selection bias is another concern if the indication for MRI is left to the clinician's discretion rather than applying the assessment to consecutive patients in a prospective manner.[66] A retrospective study design could miss false negative and false positive cases, as MRI is rarely performed in individuals considered completely normal, or definite SpA cases based on clinical or radiographic findings. Currently, the diagnostic performance of MRI in different clinical settings, such as axial versus peripheral SpA or idiopathic AS versus enteropathic-related or psoriasis-associated SpA, remains unclear.

MRI use in daily practice in suspected axSpA

Clinical examination remains the first step of the diagnostic process in patients with suspected axSpA. Once the findings on pelvic radiographs meet the radiographic criteria for AS,[5] additional assessment using SIJ MRI is usually not necessary in clinical practice. Furthermore, no evidence suggests that SIJ MRI should supplant pelvic radiographs in the clinical work-up of patients suspected to have axSpA. The optimal indication to order MRI is the presentation of patients with potential nonradiographic axSpA.[67] MRI-detected changes associated with axSpA have been attributed a major role in the ASAS axSpA criteria, but only in the presence of clinical symptoms suggestive for SpA.[40] Therefore, MRI can confirm a diagnosis of nonradiographic axSpA, suspected on clinical grounds, but will never be able to capture all phenotypes of the multi-faceted spectrum of SpA.[68]

Cross-sectional data from 27 patients with nonradiographic axSpA found a limited sensitivity of combined assessment of active and structural lesions using SIJ MRI of 51% (specificity 97%), compared to the gold standard method of diagnosis, the expert opinion of a rheumatologist.[55] This observation is supported by a longitudinal study in 109 patients with nonradiographic axSpA that reported a sensitivity of 38% and a specificity of 100% for evaluation of bone marrow edema, using histological analysis of CT-guided SIJ biopsies as the reference standard.[69] Despite these sensitivity limitations, MRI has a major role in recognition of nonradiographic axSpA suspected on clinical grounds. If undiagnosed over a prolonged period of time, this painful condition also represents a substantial psychological burden for the young patients, and early recognition of axSpA might affect vocational training and quality of life aspects. Axial MRI findings might also influence treatment decisions or improve evaluation of treatment response, for example, in patients with known axSpA who only partially respond to standard therapy or biologic agents.

Can MRI predict spinal ossification in axSpA?

Imaging of sacroiliitis is relevant for diagnostic assessment; however, SpA-associated disability mainly results from spinal ossification. Data suggest that MRI-detected spinal inflammatory lesions present at diagnosis have prognostic value. Three studies found an association between baseline bone marrow edema in the spine and the observation of new bone formation on spinal radiographs after 2 years, although with various degrees of association.[70–72] Moreover, an association between vertebral corner fat infiltration and future syndesmophyte formation has been demonstrated, particularly for vertebral corners that show a combination of bone marrow edema and fat infiltration.[73] Evidence suggests that the new spinal bone development in axSpA might be associated with fat metaplasia uncoupled from inflammation.[74] These associations have been found in patients treated with either biologic agents or with traditional SpA therapies. Nevertheless, the majority of new syndesmophytes observed in these studies developed at vertebral corners that did not have preceding MRI-detected abnormalities,[70–73] which might be the result of the limited sensitivity of MRI to detect inflammatory lesions or a sampling bias—spinal inflammation during the interval between baseline and follow-up MRI can be missed. Data from longitudinal studies in large cohorts are needed to evaluate a potential role of spinal MRI for prognostication of structural damage in axSpA.

Conclusions

SpA is a heterogeneous disorder for which no specific distinguishing feature is available. Several criteria sets have been developed to classify patients with signs and symptoms suggestive of one of the subgroups of SpA. With the application of new imaging techniques, such as MRI, a nonradiographic phenotype of AS has been recognized, leading to the concept of axSpA and, at a later stage, to the development of the ASAS axSpA classification criteria. The ASAS have also developed criteria sets for peripheral SpA, and both ASAS criteria sets are useful for disease classification in research settings; however, at present, further evaluation of the diagnostic performance of these criteria in inception cohorts comprising patients with possible SpA is necessary. Furthermore, a data-driven definition of which features constitute a positive MRI in axSpA is required. Nevertheless, MRI alone will never enable unequivocal diagnosis of the wide range of clinical phenotypes that constitute SpA, and the expert opinion of a rheumatologist will remain the crucial step in recognition of this disease. Metaphorically, the many faces of SpA are reminiscent of a chameleon's camouflage, which is hard to detect but appears obvious once the animal has been identified.

Review criteria

MEDLINE and PubMed databases were searched for original articles focusing on spondyloarthritis and ankylosing spondylitis published up to October 2011. The search terms used in combination with "spondyloarthritis" and "ankylosing spondylitis" were: "classification"; "diagnosis"; "criteria set"; "imaging"; "MRI"; and "radiographs". All papers identified were English-language full-text papers and abstracts from international rheumatology meetings. The reference lists of identified articles were searched for further papers.

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Author contributions

Both authors contributed equally to all stages of the preparation of this manuscript.