How to investigate: Early axial spondyloarthritis

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Abstract

Axial spondyloarthritis (axSpA) is a chronic inflammatory condition of the axial skeleton that encompasses radiographic and non-radiographic axSpA and that can lead to chronic pain, structural damage, disability and loss of quality of life. Scientific advances, including the role of MRI assessment, have led to new diagnostic insights and the creation of a new set of classification criteria for axial and peripheral SpA. New criteria allow the identification of SpA patients with early disease and their enrolment in clinical studies. In this chapter we discuss the difference between diagnostic and classification criteria, the diagnostic approach to patients with suspected axSpA, the limitations of MRI assessment, and the importance of early identification of this condition. A practical algorithm to investigate axSpA, based on the current evidence, is also proposed. Clinical judgement should always be kept as the mainstay in the diagnosis of axSpA.

Key words

Axial spondyloarthritis; diagnosis; classification; MRI; radiographic progression

A. Introduction

The concept of spondyloarthritis (SpA) encompasses a group of potentially disabling immune-mediated inflammatory conditions that historically included ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, arthritis associated with inflammatory bowel disease/anterior uveitis, juvenile idiopathic arthritis (enthesitis-related arthritis) and undifferentiated SpA. All of these conditions share some similarities, and, currently, they are seen as manifestations of a common pathophysiologic pathway. Some patients have predominantly peripheral manifestations (peripheral SpA [pSpA]) while other have axial involvement (axial SpA [axSpA]), with or without peripheral manifestations.[1, 2]

For several decades, the absence of reliable biomarkers for the so-called seronegative spondyloarthropathies, and of an adequate imaging technique to identify and study those patients at earlier disease stages, delayed the development of this topic in Rheumatology, hampering the development of more robust classification criteria, the identification of prognostic factors, and the development of wider treatment options.

The emergence of the MRI as a tool to investigate patients suspected of having axSpA was a major breakthrough, as it allowed the identification of patients with early disease, before the establishment of structural damage. It contributed to the dissemination of the axSpA concept, encompassing patients with radiographic axSpA (r-axSpA, or AS), with definite structural damage on radiographic assessment, and non-radiographic axSpA (nr-axSpA), typically patients with symptoms of chronic (often inflammatory) back pain with evidence of (active/acute) sacroiliitis on MRI (bone marrow oedema [BMO]/osteitis) in the absence of definite X-ray changes; alternatively, patients with nr-axSpA may also be diagnosed based on the presence of a constellation of suggestive features (even in the absence of inflammation on MRI). Some patients with nr-axSpA may progress to r-axSpA while others will never experience such progression.

Despite recent advances, delay in diagnosis of SpA still persists. In a recent systematic literature review, an average diagnostic delay of 8.8 years was described in women and 6.5 years in men (the review excluded patients with psoriatic arthritis).[3] Early diagnosis and appropriate treatment of axSpA is of utmost importance because: 1) it can provide reassurance and knowledge to patients about their disease, avoiding unnecessary investigations and treatments, 2) it is associated with better treatment responses, namely to biologic treatments, 3) could hypothetically prevent the development/progression of structural damage, and 4) since axSpA

usually affects young active adults, early diagnosis and intervention will have an impact in work productivity, leading to direct and indirect healthcare cost savings.[4-12] In summary, early diagnosis carries many benefits, including the possibility of early interventions and, as such, the promise of better long-term outcomes, including better physical function and health related quality of life.

The objective of this chapter is to discuss the differences between classification and diagnosis of axSpA, the diagnostic approach to patients with suspected axSpA, and the importance of early identification of these patients.

B. Classification criteria are not diagnostic criteria

The importance of the distinction between diagnostic and classification criteria is relevant to all rheumatic diseases. In order to avoid their misuse in clinical practice, it is of major importance to fully understand the differences between them. Physicians must keep in mind that the gold standard for a clinical diagnosis should always be the clinical judgement comprising the full range of signs and symptoms, laboratory and imaging results. This kind of approach gives a subjective probability for a diagnosis according to the physician's experience, which is of additional value compared to a simple "yes or no" answer achieved by applying a certain set of criteria.

Diagnostic criteria have been created for some diseases. They are meant to be used in clinical practice and they aim to reflect the heterogeneity of a disease, as it tends to be broad, and to reflect all the main different features of that disease. Thus, the validation process is quite demanding, taking into account the complexity of such definition. On the other hand, classification criteria intend to create homogenous groups of patients with a certain condition applying a standardized definition, mainly for research purposes.[13]

The diagnosis of axSpA should therefore be a clinical exercise (and not a box ticking exercise), based on the recognition of a pattern of clinical, laboratory and imaging features that taken together are suggestive of axSpA. This exercise includes the exclusion of other diagnoses, namely clinical and imaging mimickers of axSpA such as diffuse idiopathic skeletal hyperostosis(DISH), osteitis condensans ilii, erosive osteochondrosis, Schmorl´s nodes, degenerative changes of SIJ, accessory sacroiliac joints/facets, sacral stress fractures, infectious sacroiliitis, alkaptonuria/ochronosis, Paget disease, sarcoidosis, familial Mediterranean fever, spinal calcium

pyrophosphate disease and disorders of mineral metabolism (hypoparathyroidism, hyperparathyroidism and hypophosphatemic osteomalacia).[14, 15]

The various classification criteria for SpA/axSpA that have been published are presented in Table 1. The mNY criteria for AS were published in 1984.[16] In the following years, other sets of classification criteria for SpA emerged, namely Amor (1990) and European Spondyloarthropathy Study Group (ESSG) criteria (1991).[17, 18] These new criteria were the first to take into account the non-radiographic disease sate, therefore allowing participation of this subgroup of patients in research studies, as the mNY criteria were very restrictive, requiring the presence of established radiographic abnormalities. More recently, the Assessment of SpondyloArthritis international Society (ASAS) proposed classification criteria for axSpA (2009) which were pioneering in several aspects. These criteria were the first to account for the relevance of sacroiliac joint (SIJ) MRI inflammation and the presence of HLA-B27 as major criteria.[1] The ASAS group also created a new set of criteria for pSpA.[2] Applying the ASAS criteria, it became possible to stratify SpA patients for research purposes, namely by sub diving the SpA population into r-axSpA, nr-axSpA and pSpA.

Concerns have been raised regarding the possibility of lack of specificity of the ASAS criteria for axSpA, namely in patients with a diagnosis of fibromyalgia (FM). In order to address this issue, Baraliakos et al studied 100 patients with FM and 200 with axSpA (half of them having nr-axSpA). Only 2% of FM patients fulfilled ASAS criteria for axSpA, with this percentage rising to 5% when only HLA-B27 positive FM patients were considered. On the other hand, 24% of axSpA patients also fulfilled the 2010 diagnostic criteria for FM (this percentage was 13.5% when the 1990 ACR classification for FM were considered). This overlap was higher if only patients with AS were considered (29% and 19%, for the two FM classification criteria, respectively).[19] These results clearly argue against a major flaw of the ASAS classification criteria in relation to misclassification of patients with FM as having axSpA.

A literature review and meta-analysis to assess the performance of ASAS criteria against physicians' diagnosis was recently performed, analysing data from 5739 patients. The ASAS axSpA criteria yielded a good pooled sensitivity (82%) and specificity (88%).[20] In this study, all the patients were first diagnosed by the physician, and only afterwards evaluated against the classification criteria. This means that, if the criteria are adequately applied - that is, after the clinical diagnosis has been made - they perform well in the identification of patients who could be considered for research studies. Classification criteria should therefore not be misused, and they

should only be applied after a clinical diagnosis has been made, when considering patients for research studies.[21]

C. Clinical evaluation and awareness is critical for early diagnosis of axSpA

Clinical evaluation and identification of features suggestive of axial SpA is the key to early diagnosis. Attention should be paid to the characteristics of the back pain, with the presence of inflammatory back pain (IBP) increasing the likelihood of axSpA; however, not all patients with IBP have axSpA and patients without IBP can also have axSpA. Various set of criteria for IBP have been proposed.[22-25] All of them are a combination of several of the following features suggestive of IBP: age at onset <40 years, back pain duration >3 months, insidious onset, improvement with exercise, no improvement with rest, pain at night (with improvement upon getting up), awakening at second half of the night because of back pain, association with morning stiffness (particularly if >30 minutes), and alternating buttock pain. Importantly, patients with other conditions that also cause back pain can have IBP in about 20% of cases, and up to 40% of IBP patients will experience spontaneous resolution of symptoms.[26] Moreover, as highlighted above, a significant proportion of axSpA patients will not describe IBP.[27] Therefore, the presence (or not) of IBP should not be used in isolation to make (or exclude) a diagnosis of axSpA, and this information should be used in combination with other axSpA features. These features include the presence of arthritis, dactylitis, enthesitis, tenosynovitis, typical postural changes and restriction of spinal mobility; extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease; family history of SpA; and response to previous treatments, such as non-steroidal anti-inflammatory drugs (NSAIDs). It is also important to inquire about other clinical features that may suggest an alternative diagnosis, such as history of trauma, surgery, radiculopathy, chronic widespread pain, osteoporosis, fractures, infection, and connective tissue disease symptoms.

From a laboratory perspective, testing for Human leukocyte antigen B27 (HLA-B27) is important; however, the presence of HLA-B27 in patients with chronic back pain does not suffice to make a diagnosis and the absence of HLA-B27 does not exclude the diagnosis. HLA-B27 is present in about 8% in populations of European descent and the prevalence of axSpA mirrors the prevalence of HLA-B27 in a given population, ranging between 0.3% and 1.4%.[28] HLA-B27 is positive in 85-95% of axSpA patients and in 75-85% of nr-axSpA patients.[29-31] Recently, it was shown in three independent cohorts with different ethnic backgrounds that a positive family history of SpA was

not associated independently of HLA-B27 with a diagnosis of axSpA, suggesting that in the majority of patients presenting with chronic back pain, a positive family history of SpA does not contribute to the likelihood of a diagnosis of axSpA if HLA-B27 status is known.[32] This study reinforced the importance of HLA-B27 testing.

Testing for acute phase reactants [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] can also be useful, with elevated CRP levels being observed in up to 40% of patients (which means that CRP is in fact negative in the majority of patients with axSpA). Interestingly, CRP positivity may change over time, and a recent report using clinical trial data suggested that in axSpA patients with normal CRP, the test should be repeated after ≥4 weeks as there is a substantial chance of finding a positive result at subsequent testing, which may have diagnostic and therapeutic implications.[33]

One factor contributing to the delay in diagnosis of axSpA is the delay in the referral of patients to specialist care. An important explanation for the referral delay in axSpA is that the cardinal symptom of axSpA, chronic back pain, is very common, especially in the primary care setting.[34] Several referral strategies to aid in the referral of patients with chronic back pain with possible axSpA to the rheumatologist have been proposed. Recently, 13 referral models were evaluated in the Leiden SPondyloArthritis Caught Early (SPACE) cohort.[4] Most referral strategies performed well but with different balances between sensitivity and specificity. If no patient is to be missed, the ASAS strategy (refer if ≥1/7 positive: IBP [ASAS definition], HLA-B27, good response to NSAIDs, family history of SpA, peripheral manifestations, extra-articular manifestations, and elevated acute phase reactants) would be preferable. If the number of referrals needs to be limited, the MASTER strategy (refer if ≥2/4 positive: IBP [≥1/3 pre-defined criteria], HLA-B27, good response to NSAIDs, and family history of AS) seemed to perform best. The authors therefore concluded that the "ideal" referral strategy may differ between countries, due to differences in healthcare structure and prevalence of referral parameters such as HLA-B27. In a population-based nationwide study, the EpiReumaPt referral strategy (refer if ≥1/5 positive: previous SpA/psoriatic arthritis diagnosis by a physician, IBP (≥3/8 pre-defined features), low back pain ≥ 3 months starting <45 years and ≥1/6 pre-defined SpA features, dactylitis or heel enthesitis) performed the best as a screening tool for SpA in patients from the general population when laboratory and imaging data were not available.[35] The ASAS, MASTER and EpiReumaPt strategies are compared in Table 2.

D. Role of imaging in the early diagnosis of axSpA

The presence of definite sacroiliitis on plain radiographs strongly supports the diagnosis of r-axSpA. This assessment is based on the presence of several radiographic features, such as erosions, sclerosis, joint space narrowing, pseudo-widening and ankylosis. A standard anterior-posterior (AP) view of the pelvis is recommended as it also allows visualisation of the hips (which may also be affected in axSpA) and other views that have historically been suggested (Ferguson, oblique, prone and cone-down views) do not seem to offer advantages over the pelvic AP view.[36, 37] However, definite radiographic sacroiliitis is a relatively late finding in the majority of patients with axSpA.[38-40] Furthermore, defining reliable morphologic criteria that distinguish in particular grade 1 from grade 2 sacroiliitis is notably difficult (Figure 1). It is inherently difficult to grade radiographs of the sacroiliac joints, leading to frequent misclassification, and improvements in performance are difficult to achieve even after appropriate training sessions.[41]

MRI is of major interest in the assessment of SIJ when an axSpA diagnosis is suspected, for two main reasons. Firstly, it is a more reliable imaging technique than radiographs when structural damage is already stablished,[42] having a documented superior performance even in juvenile SpA patients.[43] Second, inflammatory changes which may be present in nr-axSpA are not apparent in radiographs, but may only be observed by MRI. MRI is therefore the only imaging technique capable of detecting both active (inflammatory) and chronic (structural) lesions as well as their anatomical distribution, contributing to the early diagnosis of axSpA. MRI correlates with histological findings in axSpA,[44] is a predictor of response to therapy[5, 45] and can be used to monitor disease activity over time.

The main goal of an early diagnosis is to provide patients with efficient control of their symptoms, better physical function and more quality of life. However, as there is evidence associating high disease activity states with radiographic progression, mainly in the early phases of the disease,[46, 47] we may be contributing to slowing down radiographic progression of our patients when treating them early. As there is increasing evidence suggesting that both corner inflammatory lesions and fatty lesions of the spine may predict progression of structural damage of the spine,[48-50] inflammation on MRI of the SIJ is also highly predictive of structural radiographic SIJ progression.[51] MRI assumes increased importance on the identification of patients who could benefit from better disease control. The summary of recent evidence regarding prevention of structural damage in axSpA is reviewed below.

Radiographs of the spine are useful to assess disease severity and progression although of limited value for diagnostic purposes at early disease stages. The presence of erosions, squaring and

sclerosis, and more importantly syndesmophytes or complete bony bridging are important features that can suggest axSpA. However syndesmophytes/ankylosis tend to be a late feature that is rarely seen (less than 5% of patients) in the absence of radiographic sacroiliitis.[49]

E. How to interpret MRI findings in axSpA

MRI lesions in the context of suspected axSpA are broadly classified into active and structural lesions (Table 3). [52, 53] Figure 2 shows examples of active and structural MRI SIJ lesions in a patient with nr-axSpA. The performance of MRI in the diagnosis of axSpA was recently systematically reviewed by Jones et al.[54] This systematic literature review (SLR) served as evidence to support recommendations for acquisition and interpretation of MRI of the spine and sacroiliac joints in the diagnosis of axSpA.[55] The manuscript addresses the use of MRI in the assessment of patients with suspected axSpA, covering topics including recommended sequences, anatomical coverage, acquisition parameters and interpretation of active and structural MRI lesions. The full list of recommendations can be found in the article but two key messages should be highlighted: 1) the full range and combination of active and structural lesions of the SIJs and spine should be taken into account when deciding if the MRI scan is suggestive of axSpA or not (i.e. contextual interpretation of active and structural lesions is key to enhancing diagnostic utility of MRI is patients with suspected axSpA), and 2) imaging cannot be viewed in isolation and needs to be interpreted in the context of clinical presentation and results of laboratory investigations.

MRI evaluation of the SIJ can be quite challenging even for experienced radiologists, due to several pitfalls. For example, in T2-weighted fat suppressed sequences, normal anatomical structures may appear more hyperintense than what they should, due to inadequate fat suppression. This is especially noted at the posterior part of the sacrum, and sometimes at the iliac bone. Pelvic and iliac vessels may cause pulsation artefacts, and incomplete ossification observed in children may be mistaken for BMO.[56] In addition, a prevalence of up to 27% of lesions suggestive of SpA in the spine and SIJ have been found in healthy controls.[57, 58] Similar findings have been found in non-specific back pain,[59] postpartum women,[59] runners,[59] soldiers [38],[60] athletes,[61] and the general population.[62] Furthermore, in patients with chronic low back pain recruited from primary care without previous rheumatological assessment, 21% met the MRI classification criteria based on SIJ BMO alone, but 42% of these lesions were small and of questionable clinical relevance as they showed no association with clinical SpA features.[63]

Classification criteria for a “positive” MRI have been proposed for research purposes. In 2009, ASAS developed a definition of active sacroiliitis on MRI for classification of axSpA. BMO/osteitis lesions suggestive of axSpA are typically located in subchondral bone marrow (periarticular location), and comparison with the sacral interforaminal bone marrow signal as reference might help their identification. Such lesions can be present in association with structural lesions, such as sclerosis or bone erosions. Authors of this consensus were well aware of the lack of specificity of MRI inflammation, as they are also present in other conditions such septic sacroiliitis, insufficiency bone fractures, and primary or secondary bone tumours. Differential diagnosis of such lesions also includes other frequent diseases, such as osteoarthritis, osteitis condensans ilii, and some pitfalls (blood vessels surrounding ligaments may be erroneously interpreted as active inflammation).[64]

More recently, the ASAS definition of a positive MRI was updated. Authors concluded that the previously proposed definition of active sacroiliitis “performs satisfactorily for the classification of axSpA according to the ASAS axSpA criteria”. However, this update also highlighted the importance of simultaneously reviewing sequences designed to identify inflammatory and structural lesions. If equivocal BMO is present, the decision may be influenced by the presence of concomitant structural lesions, especially erosions.[52] However, authors considered that there was still not enough evidence for the benefits of adding structural damage features to the definition of active sacroiliitis (for classification purposes). Similarly, there was no evidence of a significant benefit in the evaluation of spine MRI for classification purposes (not for diagnostic purposes).[52]

In summary, taking into account the limitations of MRI in terms of specificity, rheumatologists must always keep in mind the clinical context of the patient when a diagnosis of axSpA is suspected. Pre- and post-test probabilities must always be accounted for during clinical judgment, as demographic, clinical, and laboratorial factors may outweigh the importance of the MRI findings. Importantly, the ASAS definition of a positive MRI for sacroiliitis was first designed for classification purposes and it is of limited value in clinical practice. Once again, the differences between classification and diagnostic criteria must always be kept in mind by treating physicians.

On the other hand, MRI assessment of SIJ may also present some limitations regarding sensitivity, when compared with physician expert opinion and histology.[65, 66] These limitations have also been suggested by reports of axSpA patients with active disease requiring treatment with TNF inhibitors (TNFi) pointing to a frequency of 15-20% of patients without detectable active lesions on their baseline MRI scans.[67, 68] These findings highlight the importance of a clinical diagnosis,

and suggest that a normal SIJ MRI should not rule out early axSpA in patients with significant elements to trigger the suspicion of this condition. MRI is a very important tool on axSpA assessment, but clinicians should be aware of its limitations.

F. Evidence on prevention of structural damage

The first line drugs in the treatment of axSpA are non-steroidal anti-inflammatory drugs (NSAIDs). However, their effect on slowing radiographic progression remains controversial. Continuous use of NSAIDs may have an effect on the reduction of radiographic progression, mainly in patients with elevated CRP, as suggested in two trials and a cohort study.[69-71] However, a more recent randomised multicentre trial failed to show this effect.[72]

Despite the evidence pointing to an association between disease activity and radiographic progression,[46, 73] the first studies which attempted to demonstrate the effect of TNFi on the progression of structural damage failed to accomplish such goal. These studies consisted in open-label extensions of randomised controlled trials (RCT) comparing those patients against others enrolled in historical cohorts.[74-76] However, a recent long-term observational study described a reduction on spinal radiographic progression in patients with AS treated with TNFi who were followed for 10 years.[77] This study also suggested that this effect was mediated through a reduction in disease activity (with the AS Disease Activity Score-CRP (ASDAS-CRP) outperforming BASDAI and CRP alone,[77] confirming data from previous studies).[46, 73] In the same study, achievement of an inactive disease status (ASDAS ≤1.3) while on treatment with TNFi resulted in almost complete inhibition of radiographic spinal progression during the subsequent 2 years. More recent clinical trials have been pointing to a low radiographic progression after 4 years of follow-up for certolizumab and secukinumab, the first non TNFi biologic disease-modifying antirheumatic drug (bDMARD) approved for AS.[78, 79] This observation may be related to differences in the characteristics of the patients currently recruited for axSpA clinical trials compared to older trials, with earlier diagnosis and the recruitment of a wider spectrum of patients being potential contributing factors. Despite emerging evidence suggesting the possibility of prevention of structural damage in axSpA, treatment recommendations, including ASAS-European League Against Rheumatism (EULAR) management recommendations for axSpA, are still based on disease activity criteria, rather than aiming for prevention of radiographic progression regardless of patients' symptoms.[80]

G. Proposal of an algorithm to investigate chronic back pain

Low back pain is a frequent symptom in the population (global age-standardised point prevalence of 9.4%; 15% in males and 14.5% in females in Western Europe).[34] As SpA is much less prevalent - between 0.2% to 1.6% depending on geographic region/ethnic background (prevalence between 0.32% to 1.4% for axSpA),[28, 81-84] we must differentiate between patients complaining of chronic non-specific back pain and those who may benefit from further investigation. In patients with chronic back pain, clinical and laboratorial assessment is required, searching for SpA features, which, if present, increase the suspicion of axSpA.

At any point during patient evaluation, should a red flag be identified, physicians should promptly request adequate investigations in order to exclude the possibility of a disease requiring more urgent intervention. For example, a patient suffering from night sweats, weight loss, fatigue, and white blood count abnormalities should be investigated for a neoplasm. Another example would be a patient with high fever, continuous, localised back pain, and very high inflammatory markers, in whom an infectious spondylodiscitis should be ruled out.

MRI availability varies widely (between countries and within countries), and physicians should select patients for MRI assessment who could benefit from it the most. Thresholds for requesting an MRI may also vary depending on the organisation of local healthcare systems, specific costs and resources available. Excluding from MRI assessment patients with a low risk of SpA and those who have already the diagnosis of AS based on clinical symptoms and pelvic X-Ray, the accessibility of this exam could be increased for patients who will need it to confirm or exclude a diagnosis of axSpA.

In 2013, ASAS published a diagnostic algorithm for axSpA (ASAS modification of the Berlin algorithm for diagnosing axSpA).[85] Figure 3 shows a proposed variation of this algorithm with additional clinical practice and contextual considerations. Patients with chronic back pain with an early onset (less than 45 years old), pelvic X-Ray without definite radiographic sacroiliitis, and a moderate to high risk of axial SpA based on the presence of SpA features, are the best candidates for MRI assessment.

H. Summary

Scientific advances in the field of axSpA have allowed the identification of patients in early states of disease, even before structural damage is made apparent. However, there is still significant diagnosis delay in axSpA, and greater awareness among non-rheumatologists is required in order to trigger earlier referral. The new ASAS criteria for axial and pSpA are now widely used. However, clinicians must keep in mind that classification criteria should not replace clinical judgment in routine clinical practice. The benefit of identifying patients early in order to reduce the rate of structural damage is still a topic under discussion in axSpA. However, the identification of such patients is undoubtedly beneficial, considering the availability of highly effective therapies and the possibility to improve patients' outcomes. MRI can provide important diagnostic and prognostic information in axSpA but contextual interpretation is required. A diagnostic algorithm is proposed, but the physician's experience and clinical judgement will always play the most important role in the diagnostic process.

Practice points

- Clinical judgement remains the mainstay for diagnosis of axSpA.
- Physicians should not misuse classification criteria, avoiding their use before a clinical diagnosis is made.
- MRI and genetic testing opened new perspectives in this area, allowing identification of early disease.
- Contextual interpretation of MRI is required and clinicians must keep in mind MRI limitations, not excluding or making a diagnosis solely based on MRI findings.
- Treatment escalation in axSpA is still guided by disease activity measures and not by an intention to prevent radiographic progression or the presence of MRI activity.

Research agenda

- Establishment of public health initiatives to educate non-rheumatologists on how to identify patients with potential axSpA.
- Identification of patients at risk of progression who could have more significant benefit with more intensive treatment.
- Further evidence on the prevention/retardation of structural damage with the available therapies, and potential differences between drugs, namely biologic drugs with different mechanisms of action.
- Investigation of treat-to-target strategies in axSpA and their potential in prevention/retardation of structural damage.
- Investigation of the use of imaging (MRI) remission as a treatment target in axial SpA.

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Table 1. Published classification criteria for spondyloarthritis*				
mNY criteria for AS	**Amor criteria for SpA**	**ESSG criteria for SpA**	**ASAS criteria for axSpA**	**ASAS criteria for pSpA**
Entry criterion:				
Imaging criterion plus ≥1 clinical criterion	Sum of points of items below must be ≥6; a sum of points ≥5 classifies for probable SpA	IBP (modified Calin)[25] or synovitis (asymmetric or predominantly in the lower limbs), and ≥1 clinical or radiological criterion	CBP (≥3 months) with an onset <45 years of age and: a) Imaging criterion plus ≥1 the clinical criteria or b) Positive HLA-B27 plus ≥2 other clinical criteria	Peripheral arthritis, enthesitis or dactylitis and: a) Imaging criterion or ≥1 clinical SpA feature from group A or b) ≥ 2 other clinical SpA features from group B
Imaging criterion:				
Radiographic sacroiliitis†	Radiographic sacroiliitis† (3 points)	Radiographic sacroiliitis†	Radiographic sacroiliitis† or MRI sacroiliitis‡	Radiographic sacroiliitis† or MRI sacroiliitis‡
Clinical criteria:				
▪ Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest ▪ Limitation of motion of the lumbar spine in the sagittal and frontal planes ▪ Limitation of chest expansion relative	▪ Lumbar or dorsal pain during the night, or morning stiffness of lumbar or dorsal spine (1 point) ▪ Asymmetric oligoarthritis (2 points) ▪ Buttock pain (1 point), if affecting alternately the right or the left buttock (2 points) ▪ Dactylitis (2 points)	▪ Buttock pain alternating between right and left gluteal areas ▪ Urethritis, cervicitis, or acute diarrhoea within one month before arthritis	▪ IBP (ASAS)[24] ▪ Arthritis ▪ Enthesitis (heel) ▪ Uveitis ▪ Dactylitis ▪ Psoriasis	**Group A** ▪ Uveitis ▪ Psoriasis ▪ Crohn's/ulcerative colitis ▪ Preceding infection ▪ HLA-B27

to normal values correlated for age and sex	▪ Enthesitis (2 points) ▪ Iritis (2 points) ▪ Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis (1 point) ▪ Acute diarrhoea accompanying, or within 1 month before, the onset of arthritis (1 point) ▪ Presence or history of psoriasis, balanitis, or IBD (Crohn's/ulcerative colitis) (2 points) ▪ Good response to NSAIDs in less than 48h, or relapse of the pain in less than 48h if NSAIDs discontinued (2 points) ▪ Presence of HLA-B27, or familial history of AS, Reiter syndrome, uveitis, psoriasis, or chronic enterocolopathies (2 points)	▪ Inflammatory bowel disease ▪ Psoriasis ▪ Positive family history	▪ Crohn's/ ulcerative colitis ▪ Elevated CRP ▪ Good response to NSAIDs ▪ Family history of SpA ▪ HLA-B27	**Group B** ▪ Arthritis ▪ Enthesitis ▪ Dactylitis ▪ IBP ever (ASAS)[24] ▪ Family history for SpA

*Please note that the definition of IBP and some SpA features varies between different criteria sets; for details please consult the original publications. †Defined as radiographic sacroiliitis grade ≥2 bilaterally or grade 3-4 unilaterally: grade 0 = normal; grade 1 = suspicious changes; grade 2 = minimum abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width); grade 3 = unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankylosis; grade 4 = severe abnormality (total ankylosis). ‡Defined as bone marrow oedema (short tau inversion recovery sequence) or osteitis (T1 post-gadolinium sequence) highly suggestive of SpA, clearly present and located in the typical anatomical areas (subchondral or periarticular bone marrow); if there is only one signal (lesion) per MRI slice suggesting active inflammation, the lesion should be present on at least two consecutive slices; if there is more than one signal (lesion) on a single slice, one slice may be sufficient. Abbreviations: AS, ankylosing spondylitis; ASAS, assessment of spondyloarthritis international society; axSpA, axial spondyloarthritis; CBP, chronic back pain; CRP, C-reactive protein; ESSG, European spondyloarthropathy study group; HLA, human leukocyte antigen; IBD, inflammatory bowel disease; IBP, inflammatory back pain; mNY, modified New York; MRI, magnetic resonance imaging; NSAIDs, non-steroidal anti-inflammatory drugs; pSpA, peripheral spondyloarthritis; SpA, spondyloarthritis.

Table 2. Comparison between the ASAS, MASTER and EpiReumaPt referral strategies

Strategy	IBP	HLA-B27	Good response to NSAIDs	Family history of SpA	Other criteria	Refer if	IBP definition
ASAS	+	+	+	+	(1) Peripheral manifestations (arthritis, enthesitis and/or dactylitis) (2) Extra-articular manifestations (uveitis, psoriasis and/or IBD) (3) Elevated acute phase reactants (CRP and/or ESR)	≥1/7 positive	ASAS IBP criteria i.e. IBP if ≥4/5 back pain features present: (1) Age at onset <40 years (2) Insidious onset (3) Improvement with exercise (4) No improvement with rest (5) Pain at night (with improvement on getting up)
MASTER	+	+	+	+ (AS only)	-	≥2/4 positive	IBP if ≥1/3 back pain features present: (1) Morning stiffness in the lower part of the spine >30 min (2) Improvement by exercise, not by rest (3) Awakening in the night because of back pain, with improvement by exercise
EpiReumaPt	+	-	-	-	(1) Previous SpA/PsA diagnosis by a physician (2) LBP ≥3 months, starting <45 years and ≥1/6 SpA features* (3) Dactylitis (4) Heel enthesitis	≥1/5 positive	IBP if ≥3/8 back pain features present: (1) Onset of LBP ≤40 years (2) Insidious onset (3) Improvement with exercise (4) No improvement with rest (5) Occurs at night and improves in

							the morning (6) Wakes patient in the second half of the night (7) Morning stiffness ≥30 minutes (8) Alternating buttock pain

*The six SpA features considered are: (1) family history of SpA, (2) previous diagnosis of uveitis by an ophthalmologist, (3) previous diagnosis of psoriasis by a physician, (4) previous diagnosis of IBD by a physician, (5) good response to NSAIDs, (6) informed by a physician to be HLA-B27 positive. AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis international Society; CRP, C-reactive protein; EpiReumaPt, Portuguese nationwide epidemiological study; ESR, erythrocyte sedimentation ratio; HLA, Human Leukocyte Antigen; IBD, inflammatory bowel disease; IBP: inflammatory back pain; LBP, low back pain; MASTER: Multicentre Ankylosing Spondylitis survey Trial to Evaluate and compare Referral parameters in early SpA; PsA, psoriatic arthritis; NSAIDs, non-steroidal anti-inflammatory drugs; SpA, spondyloarthritis;

Table 3. MRI lesions in the context of suspected axSpA		
Anatomical area	**Acute lesions**	**Structural lesions**
Sacroiliac joints	(1) Bone marrow oedema (2) Capsulitis (3) Joint space enhancement (4) Inflammation at the site of erosion (5) Enthesitis (6) Joint space fluid	(1) Erosion (2) Fatty deposition (also known as fat metaplasia) (3) New bone formation/fat deposition in the joint space (also known as metaplasia in an erosion cavity or "backfill") (4) Sclerosis (5) Ankylosis (6) Non-bridging bone-bud/spur.
Spine	(1) Anterior/posterior spondylitis (anterior/posterior corner inflammatory lesions) (2) Spondylodiscitis (endplate/disc inflammation) (3) Arthritis of costovertebral joints (4) Arthritis of zygoapophyseal/facet joints (5) Enthesitis of spinal ligaments (6) Inflammations of other bony structures (e.g. pedicles, transverse processes and spinous processes).	(1) Erosion (2) Fatty deposition (3) Sclerosis (4) Syndesmophytes (5) Ankylosis

Figures

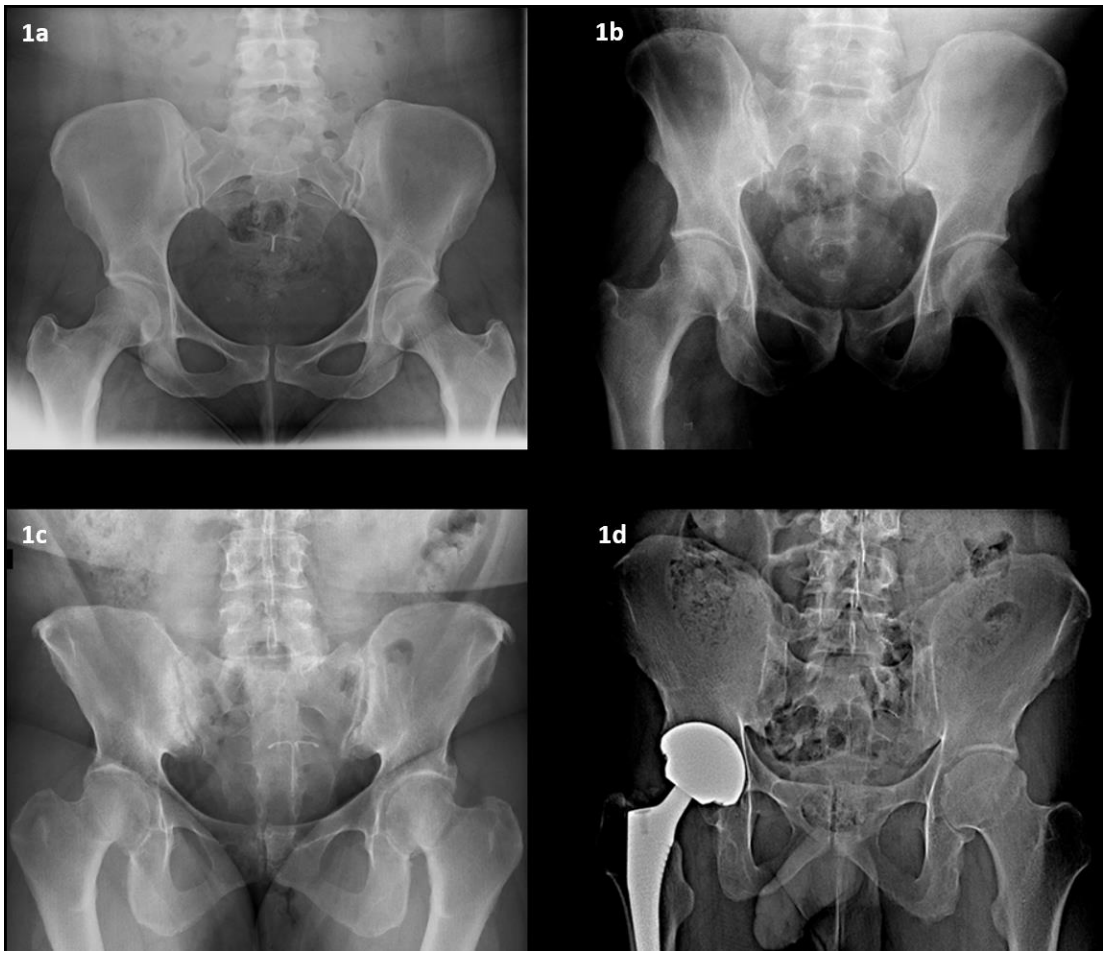

Figure 1. Grading of sacroiliitis according to modified New York criteria. 1a) Bilateral grade 0; 1b) Grade 1 right, grade 0 left; 1c) Grade 3 right, grade 2 left; 1d) Bilateral grade 4. Grade 0: Normal; Grade 1: Suspicious (but not definite) changes; Grade 2: Minimal abnormality - small localized areas with erosions or sclerosis, without alteration in the joint width; Grade 3: Unequivocal abnormality – moderate or advanced sacroiliitis with one or more of the following: erosions, sclerosis, joint space widening, narrowing, or partial ankylosis; Grade 4: Total ankylosis.

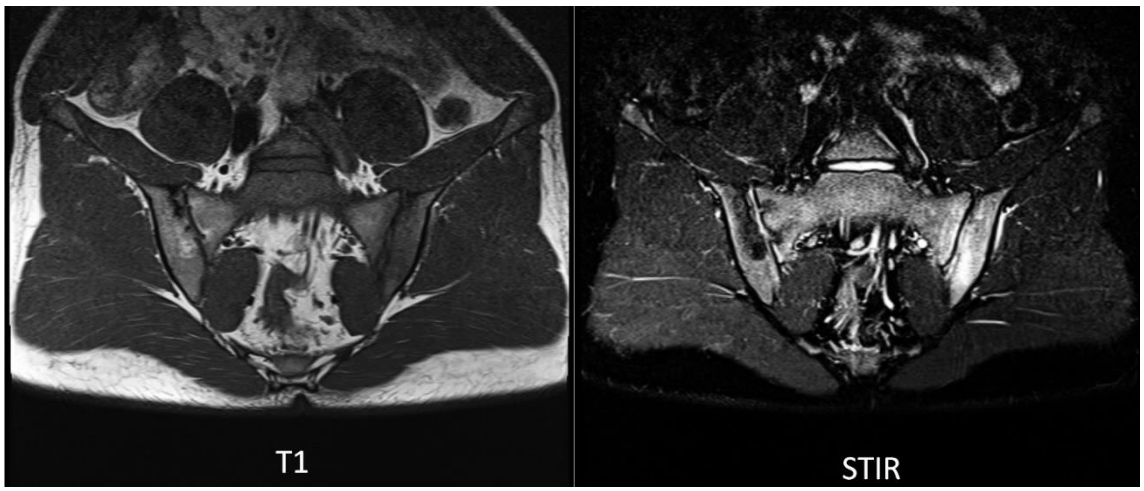

Figure 2. MRI of the sacroiliac joints (SIJ). Typical active and structural lesions in a patient with non-radiographic axial spondyloarthritis (X-ray did not fulfil modified New York criteria). The short tau inversion recovery (STIR) sequence shows abnormal increased signal in the left SIJ, typical for bone marrow oedema (BMO) due to inflammatory sacroiliitis. The BMO is subchondral in location, lesions are of a significant size, margins are poorly defined and there are corresponding areas of hypointensity on the T1-weighted sequence. The T1-weighted sequence also shows erosion and fat deposition of the right SIJ. Erosion can be seen as a defect in subchondral bone associated with full thickness loss of the dark appearance of the subchondral cortex at its expected location, with loss of signal on the T1-weighted sequence. The hyperintense signal on the T1-weighted sequence, located in the subchondral bone and surrounding some of the erosions represents fat deposition. Sclerosis of the right SIJ can also be seen (very low signal on all sequences located in the subchondral area.

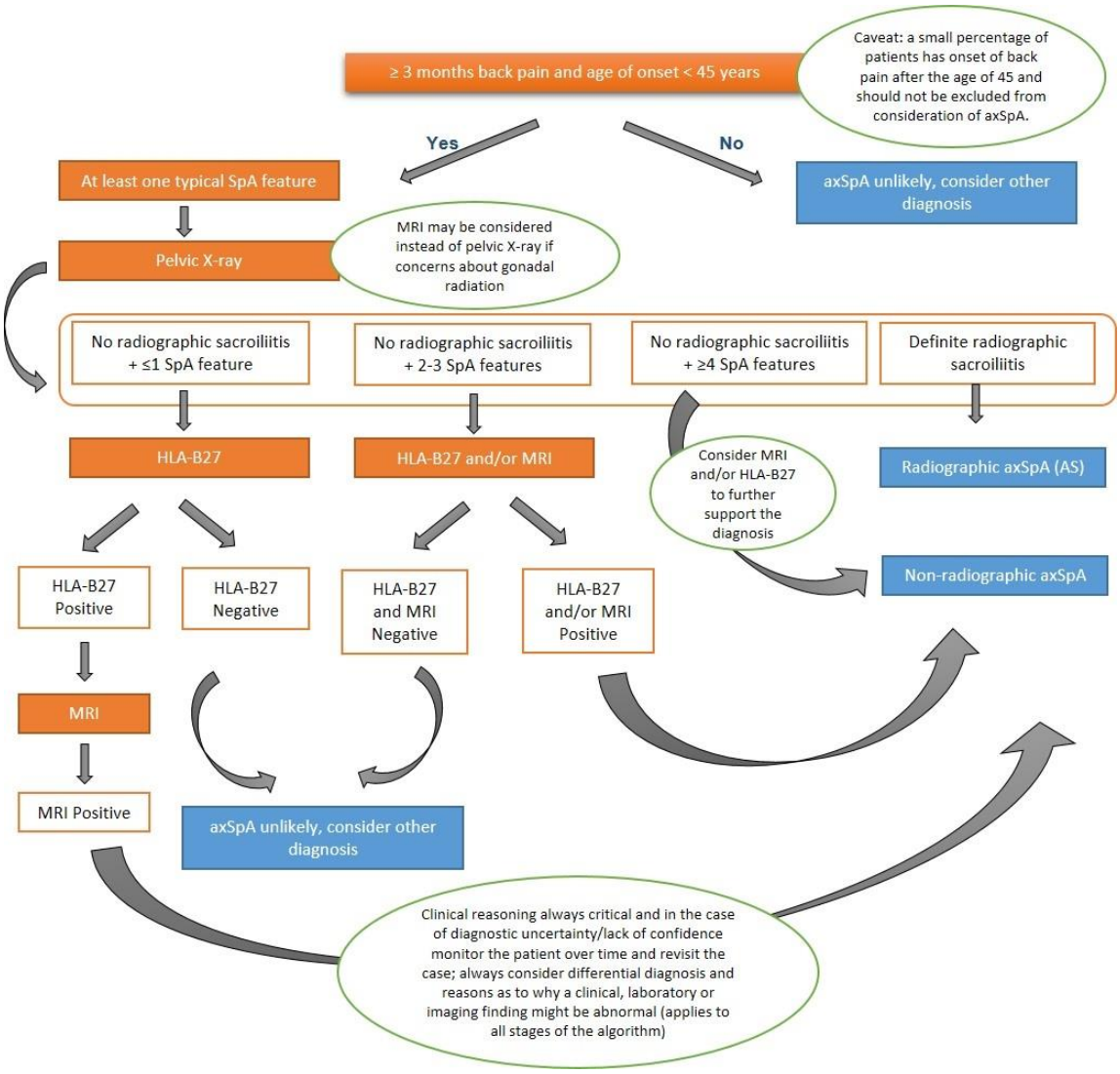

Figure 3. Flow chart representing a proposed clinical algorithm to assess patients with chronic back pain (after careful medical history, physical examination and consideration of differential diagnosis [that may elicit other investigations]). Typical SpA features: IBP, heel pain (enthesitis), dactylitis, uveitis, positive family history of SpA, inflammatory bowel disease, alternating buttock pain, psoriasis, asymmetric arthritis, good response to NSAIDs, elevated acute phase reactants (ESR or CRP). Thresholds for requesting and MRI may also vary depending on the organisation of local healthcare systems, specific costs and resources available.

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