Published in final edited form as:

Curr Opin Rheumatol. 2010 September ; 22(5): 603–607. doi:10.1097/BOR.0b013e32833c7255.

Early axial spondyloarthritis

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Abstract

Purpose of review—To summarize recent advances in the classification of preradiographic axial spondyloarthritis (SpA).

Recent findings—Inflammation in the sacroiliac joints precedes radiographic damage that is necessary to establish a diagnosis of ankylosing spondylitis (AS). Preradiographic axial SpA refers to patients with SpA who exhibit signs and symptoms of axial involvement, but lack criteria for AS. Patients with axial SpA can have remarkably similar clinical features and disease activity as those with early AS. MRI is a sensitive method for detecting sacroiliac joint inflammation, which is useful in predicting the development of AS. Whole-body MRI has emerged as a means to visualize additional areas of involvement. However, it may be less sensitive than conventional MRI, and thus its added value will need to be further assessed. The incorporation of MRI evaluation of the sacroiliac joints and HLA-B27 testing into criteria for identifying individuals with preradiographic axial disease has led to the development of criteria for classifying axial SpA.

Summary—The development of classification criteria for axial SpA will aid in the identification of patients suitable for clinical trials testing whether early intervention will slow the development and/or progression of structural changes in that lead to AS.

Introduction

Ankylosing spondylitis (AS) often begins as an undifferentiated disease with clinical features of spondyloarthritis (SpA) but lacking sufficient axial skeletal involvement and radiographic damage to the sacroiliac joints to fulfill the modified New York criteria [1,2]. Furthermore, although many individuals with undifferentiated SpA will develop progressive axial disease, this is not always the case. This article reviews recent advances in the recognition and classification of preradiographic axial SpA in adults, focusing on the use of MRI and other criteria to identify individuals who are at greatest risk of eventually fulfilling criteria for AS.

Characteristics of early axial disease

The SpA concept encompasses patients with phenotypic features such as inflammatory bowel disease, dactylitis, and psoriasis that are largely distinct from those seen in other inflammatory arthropathies such as rheumatoid arthritis. At one end of the spectrum lies AS, the prototypic form of SpA in which sufficient damage has accumulated in one or both sacroiliac joints to be evident on plain radiographs (erosions, sclerosis, and/or ankylosis). Individuals with these abnormalities together with additional clinical criteria that reflect

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There are no conflicts of interest.

axial involvement will meet modified New York criteria and can be classified as having AS. However, delays of 8–11 years between the onset of symptoms and a diagnosis are not uncommon in both adults [3] and children [4]. Patients with clinical features of SpA who fail to meet criteria for AS can often be classified as undifferentiated SpA by applying either European Spondyloarthropathy Study Group (ESSG) [5] or Amor [6] criteria. However, undifferentiated SpA is not simply an early presentation of AS; long-term outcome studies suggest that more than 40% of patients with undifferentiated SpA may not develop AS even after 10 years of follow-up [7]. This has underscored the importance of recognizing early forms of AS involving the axial skeleton, but in a preradiographic stage when definite sacroiliitis is not apparent on plain radiographs [2].

In an effort to identify characteristics that might distinguish individuals with nonradiographic disease from those with AS, Rudwaleit *et al.* [8•] examined a large group from the German Spondyloarthritis Inception Cohort (GESPIC). Patients were required to have a clinical diagnosis of axial SpA by the treating rheumatologist. (Note that this designation was made prior to the publication of criteria for axial SpA as discussed below.) Classification of AS was based on the modified New York criteria, whereas axial SpA was defined by a modified version of the ESSG criteria for undifferentiated SpA, and the absence of definite radiographic sacroiliitis. The ESSG modification incorporated HLA-B27, acute anterior uveitis, and dactylitis as minor criteria that could accompany the major criterion of inflammatory back pain (IBP).

There were remarkably few differences between the group with early AS ($n = 236$) and those with axial SpA ($n = 226$). Notably, the presence of HLA-B27 and the frequency of arthritis, enthesitis, uveitis, and IBP were the same. Measures of disease activity such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), morning stiffness, fatigue, and night pain were also the same. HLA-B27 was associated with a younger age at disease onset in both groups. However, male sex and an elevated C reactive protein (CRP) were associated with radiographic sacroiliitis (odds ratios of 2.38 and 1.85, respectively) and the presence of syndesmophytes, whereas no such relationship was found for HLA-B27. This study suggests that obtaining plain radiographs in patients with signs and symptoms of AS such as IBP, enthesitis, arthritis, uveitis, HLA-B27, and an elevated BASDAI does not provide definitive classification if the radiographs are negative. Indeed, individuals with nonradiographic axial SpA have many of the same clinical features, emphasizing that radiographic confirmation of AS in the sacroiliac joints should not be used as a criterion in defining patients with axial involvement.

Although the AS cohort included individuals with up to 10 years of disease (vs. ≤ 5 years for the axial SpA cohort), a subanalysis of AS patients with less than or equal to 5 years of disease resulted in similar findings. The current study suggests that elevated CRP may be a marker for the evolution of nonradiographic axial SpA to AS. Interestingly, three cytokines strongly correlated with CRP elevations are interleukins (IL)-6, IL-1, and IL-17 [9], two of which (IL-6 and IL-17) have been implicated in AS pathogenesis [10–14], including evidence for IL-6 overexpression in inflamed sacroiliac joints [11] and in serum where it correlates with CRP and with disease activity [10]. It will be of interest to learn whether neutralizing these cytokines is beneficial in axial SpA and AS.

Imaging early disease

Inflammation in the caudal region of the sacroiliac joint is one of the earliest features of spinal disease in AS. Often this begins on the iliac side of the joint and then involves the sacral side as inflammation progresses. Frank erosions become evident, but may not appear for months to years after inflammation has begun. Sclerosis occurs and is often progressive,

eventually resulting in fusion of the joint. Plain radiography is insensitive to most of the early inflammatory changes in the sacroiliac joints in AS, yet to fulfill the modified New York criteria [1], sacroiliitis must be present as either grade 2 (erosion and sclerosis) or greater bilaterally, or grade 3–4 (erosion, sclerosis, and/or ankylosis) unilaterally. In one study, it took 5–10 years for 36 and 59%, respectively, of patients with IBP and radiographically normal (or suspicious) sacroiliac joints to develop radiographic sacroiliitis [7]. Although there are many examples of more rapid progression [15], the problem of detecting early changes in the sacroiliac joint with plain radiography remains.

MRI has emerged as a powerful tool for evaluating patients with SpA. This topic has been reviewed recently [16,17, 18], and thus the focus here will be its utility in early axial disease. MRI is highly sensitive for detecting bone marrow edema reflecting inflammation in its earliest stages, and well before the appearance of radiographic changes. Typically, this is best seen on fat suppressed T2-weighted or short tau inversion recovery (STIR) sequences, where increased water content due to cellular infiltration or replacement of bone marrow fat raises the signal intensity. Alternatives involving the use of contrast agents include fat-suppressed T1-weighted images after intravenous Gadolinium (Gd) administration. Increased signal intensity with Gd enhancement reflects changes in tissue perfusion from alterations in vascular composition and permeability. Gd use requires intravascular access, and thus increases the time and cost for the procedure. Although rare, Gd administration is also associated with nephrogenic systemic fibrosis [19], and thus carries some risk.

Bone edema detected by MRI around the sacroiliac joints has been shown to be useful in predicting development of AS [20]. In this study of patients with early disease defined as IBP of less than 2 years' duration, severe bone edema (affecting >75% of an SI quadrant) together with HLA-B27 produced a likelihood ratio of 8.0 for developing AS in less than 8 years. Less severe bone edema was less predictive.

A comparison of patients with 'early' disease (defined as undifferentiated SpA with axial involvement; average disease duration of 1.5 years) to individuals with 'late' disease (defined as AS; average disease duration 9.6 years) from several years ago revealed a similar number of inflamed structures on MRI (4.5 ± 3.2 vs. 5.2 ± 2.3 , respectively) and no absolute differences in the regions involved [21]. However, there was a tendency for more frequent involvement of the dorsal and caudal regions of the joint and adjacent bone marrow in early disease, with a tendency for the iliac side to be involved initially. The absence of major differences between early and late disease argues against fundamentally different processes. Early dorsocaudal involvement implicates the synovial part of the sacroiliac joint, consistent with a study of histopathologic changes [22]. In this study, the STIR sequence was less sensitive than Gd-enhanced MRI for finding inflammation, particularly in the joint space [21].

A recent study of patients with 'very early' IBP (median duration of disease 24 weeks; range 2–260) who had not received disease modifying anti-rheumatic drugs or steroids revealed bone marrow edema in the sacroiliac joints of 85% (46/54) of the IBP group [23]. Interestingly, 23.5% had bone marrow edema in the lumbosacral region of the spine, although only two individuals had lesions solely in this region. Surprisingly, 41% (9/22) of the control group also had areas of bone marrow edema, although it was less severe than the IBP group. The majority of these lesions were found in controls with mechanical back pain, with only two lesions in healthy controls. The severity and number of sacroiliac lesions correlated strongly with the presence of HLA-B27 in the IBP group, but there was no correlation with disease activity (BASDAI, BASFI, or CRP) or duration. The co-occurrence of sacroiliac and lumbosacral lesions in about one fourth of the patients led the authors to

speculate that the notion that disease begins in the sacroiliac joints and ascends the spine may not always be the case. More studies will be needed to assess the frequency of spinal involvement in the absence of sacroiliitis at the onset of disease.

Whole-body MRI

Whole-body MRI offers advantages over more focused approaches in that it is more comprehensive and additional clinically relevant lesions may be found [24]. Multichannel technology enables information to be obtained from sacroiliac joints, spine, anterior chest wall, and shoulder and pelvic girdles in approximately 30 min. In order to validate this approach, Weber *et al.* [25•] compared acute inflammatory sacroiliac lesions visualized with whole-body and conventional MRI in 32 AS patients with active disease (BASDAI ≥ 4). Whole-body MRI detected all the inflammatory lesions seen with conventional MRI. Correlation coefficients between the two approaches ranged from 0.87 to 0.94 for three readers, whereas the interobserver coefficients were between 0.79 and 0.96 for whole-body MRI compared with 0.69 and 0.95 for conventional MRI. The biggest difference was in mean sum scores, which were consistently higher for conventional MRI among all readers. The authors opined that the differences were due to visualization of a larger portion of the joint with the more focused approach, as a consequence of different slicing angles (oblique rather than strictly coronal) or possibly slightly narrower slices obtained with conventional MRI. They concluded that as a consequence of some of these limitations, the use of whole body MRI in routine evaluation of AS patients is not yet justified.

The diagnostic utility of additional information obtained from whole-body MRI that included the spine has also been assessed [26]. In 35 AS patients, 25 IBP patients (lacking radiographic criteria for AS) with similar disease activity, and 35 healthy controls, the presence of vertebral corner inflammatory lesions (CILs) was of diagnostic utility in patients with AS, particularly when two or more lesions were present. Sensitivity and specificity were 69 and 94%, respectively, with a positive likelihood ratio of 12. For IBP patients, CILs were 32 and 96% sensitive and specific, respectively, with a positive likelihood ratio of 8. Although lateral inflammatory lesions had high specificity (97%), sensitivity was low (31%). Interestingly, nine out of 35 controls (~26%) had one more CIL, but only two controls had more than two CILs, whereas AS patients had a median of five to six. This study suggests whole-body MRI has utility for diagnosing AS, particularly when two or more CILs are found.

With the increased use of MRI to visualize inflammation and treatment responses, it is important to recognize the strengths and weaknesses of various methodologies. In 40 SpA patients with a mean duration of symptoms of 7 years, Madsen *et al.* [27] reported a significant positive correlation between scores for bone marrow edema in sacroiliac joints visualized with T1-weighted Gd-enhanced vs. fat-suppressed STIR images. There was complete agreement in the evaluation of 60 of the 80 joints: 35 with bone marrow edema and 25 normal joints. For the 20 discrepant joints, 11 were positive on STIR but not with Gd enhancement, whereas nine were positive only on Gd enhancement. The location of the lesions may have played a role in the differences. The STIR sequence revealed marrow activity on the periphery of chronic fatty changes, whereas Gd enhancement picked up small subchondral lesions not visualized on STIR due to slightly lower resolution. The authors suggested that it may be possible to substitute STIR for T1-weighted post-Gd imaging, which may be beneficial in terms of time, cost, and safety.

Classification of axial spondyloarthritis

The Assessment of SpondyloArthritis International Society (ASAS) recently developed criteria to identify patients who have axial SpA in the context of chronic back pain [28•,

29••]. The sensitivity and specificity were 82.9 and 84.4%, respectively, which is better than versions of ESSG or Amor criteria modified to incorporate MRI findings. The process involved development of candidate classification criteria to capture patients with and without radiographic sacroiliitis. Twenty expert ASAS members evaluated 71 'paper' patients with chronic back pain of unknown cause with a possible diagnosis of SpA. The vast majority (97.2%) did not meet modified New York criteria for AS, but 38% had bone marrow edema or osteitis in or around the sacroiliac joint on MRI, and thus were considered to have active sacroiliitis [30•]. Patients were unequivocally classified on the basis of aggregate opinion as SpA or no SpA. Logistic regression revealed that MRI information was strongly contributory for classification by expert opinion [odds ratio (OR) = 45 with 95% confidence interval (CI) 5.3–383]. From this exercise, sets of criteria for identifying axial SpA were developed based largely on a positive MRI plus one clinical feature, or IBP plus two clinical features [28•].

To refine and validate the sets of criteria for axial SpA, 649 patients under the age of 45 who had at least 3 months of back pain were used. Forty percent of the patients were randomly selected for the refinement phase and then the remaining 60% were used for validation. Axial SpA was considered to be present in 60.2% of 649, with 70% of these not fulfilling modified New York criteria for AS, and thus considered as nonradiographic axial SpA. Further refinement established criteria with an 'imaging arm', where the presence of sacroiliitis by radiography or MRI plus one SpA feature was considered axial SpA. In the 'clinical arm', criteria consisted of HLA-B27 plus two SpA features. Applying both arms resulted in sensitivity and specificity of 82.9 and 84.4%, respectively. The ASAS criteria performed better than the MRI-modified ESSG and AMOR criteria, which had approximately 85/65 and 83/78% sensitivity and specificity, respectively. Elimination of laboratory or clinical features such as the CRP, dactylitis, or IBD did not compromise the criteria, yet they were retained as recognizable domains of the SpA concept. The authors emphasized that the criteria need to be tested in a setting where the prevalence of SpA is lower than that in the chronic back pain population.

Weisman *et al.* [31] have recently developed a case ascertainment tool to help identify patients with AS from those with chronic back pain. Items such as sex, presence of neck or hip pain/stiffness, duration of pain, reduction of pain/stiffness with activity, and pain relief with non-steroidal anti-inflammatory drugs were particularly informative. The tool demonstrated a sensitivity of 67.4% and a specificity of 94.6% and may help to identify undiagnosed patients who have AS.

Considerations for juvenile spondyloarthritis

Juvenile SpA occurs predominantly in older (>6 years of age) male children and tends to affect the larger joints of the lower extremities. Enthesitis is common, as is the HLA-B27 gene, and there is a tendency to develop sacroiliitis and eventually AS. However, compared with adult SpA, there is less axial involvement at disease onset and more hip arthritis and enthesitis. Currently, classification of juvenile SpA is problematic (reviewed in [32]). On the basis of the International League of Associations for Rheumatology (ILAR) criteria used to classify the major forms of juvenile (idiopathic) arthritis (JIA) [33], many children with SpA are classified as enthesitis-related arthritis (ERA). However, if they have clinical features such as psoriasis, or dactylitis and nail pits along with arthritis, they are excluded from ERA and may be classified as psoriatic arthritis or undifferentiated arthritis [32,33]. Thus, the approach to classification of SpA in children differs substantially from adults, where criteria such as ESSG or Amor include other features of SpA. In addition, similar to the situation in adults, there is a need to identify children with early axial involvement. However, apart from sacroiliac joint tenderness or inflammatory lumbosacral pain that constitute a minor criterion

in the ERA set [33], there is no way to identify individuals with acute sacroiliitis. Interestingly, there is evidence of ‘silent sacroiliitis’ in up to 20% of children with SpA, where MRI detected evidence of sacroiliitis in individuals with no history of back pain [34].

Conclusion

MRI is now recognized as a sensitive tool for detecting axial inflammation in SpA. Information from MRI of the sacroiliac joints, together with HLA-B27 testing and the presence of clinical features of SpA, has been used to develop and validate criteria for diagnosing preradiographic axial SpA in adults with chronic back pain. The identification and treatment of patients with early axial SpA offer our best opportunity to change the outcome. It will be important to develop and validate criteria that can be used to diagnose axial SpA in children.

Acknowledgments

R.A.C. is supported by the Intramural Research Program of the National Institute of Arthritis Musculoskeletal and Skin Diseases at the NIH. He thanks Dr M. Ward for critical evaluation of the manuscript.

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