Classification and Diagnosis of Axial Spondyloarthritis — What Is the Clinically Relevant Difference?

Jurgen Braun, Xenofon Baraliakos, Uta Kiltz, Frank Heldmann, and Joachim Sieper

ABSTRACT. Objective. The Assessment of Spondyloarthritis international Society (ASAS) classification criteria for axial spondyloarthritis (axSpA) have added nonradiographic axSpA (nr-axSpA) to the classic ankylosing spondylitis (AS) as defined by the modified New York criteria. However, some confusion remains about differences between classification and diagnosis of axSpA. Our objective was to analyze differences between classification and diagnostic criteria by discussing each feature of the classification criteria based on real cases.

Methods. The clinical features of the ASAS classification criteria were evaluated in relation to their significance for an expert diagnosis of axSpA. Twenty cases referred to our tertiary center outpatient clinic were selected because of an incorrect diagnosis of axSpA: 10 cases in which axSpA had been excluded initially because the classification criteria were not fulfilled, and 10 patients who had been previously diagnosed with axSpA because the classification criteria were fulfilled. Upon reevaluation, the former were diagnosed with axSpA while the latter had other diseases.

Results. All items that are part of the classification criteria show some variability related to their relevance for a diagnosis of axSpA. There are clinical features suggestive of axSpA that are not part of the classification criteria. Misinterpretation of imaging procedures contributed to false-positive results. Rarely, other diseases may mimic axSpA.

Conclusion. Because the sensitivity and specificity of the axSpA classification criteria have been around 80% in clinical trials, some false-positive and false-negative cases were expected. It is hoped that their detailed description and discussion will help to increase the understanding of diagnosing axSpA in relation to the ASAS classification criteria. (First Release Nov 15 2014; J Rheumatol 2015;42:31–8; doi:10.3899/jrheum.130959)

Key Indexing Terms:
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Ankylosing spondylitis (AS) has long been considered the prototype of the partly heterogeneous group of spondyloarthritides (SpA). The SpA are genetically linked and share characteristic clinical features such as inflammatory back pain (IBP) due to sacroiliitis and spondylitis. Other SpA are enthesitis, arthritis, anterior uveitis, and organ manifestations such as psoriasis and chronic inflammatory bowel disease (IBD). In addition to clinical findings, imaging [mainly radiography and magnetic resonance imaging (MRI)] and laboratory data [mainly HLA-B27 and C-reactive protein (CRP)] are important diagnostic tools.

The publication of classification criteria for axial spondyloarthritis (axSpA) has widened the spectrum of this field, which had largely been determined by the 1984 classification criteria for AS — the established part of axSpA that has definite structural changes in the sacroiliac joints (SIJ), in addition to what has now been termed nonradiographic axSpA (nr-axSpA) — the subset in which no such changes are present. The main argument for developing new criteria has been the considerable delay until AS is diagnosed. Because imaging plays an important role in all criteria sets, the Assessment of Spondyloarthritis international Society (ASAS) has organized expert consensus groups to agree on definitions for inflammatory changes in the SIJ and the spine.

Patients with nr-axSpA, who seem to have fewer signs of inflammation in comparison to established axSpA, may represent axSpA in its early disease stages and may develop structural changes and AS in the near future; however, female patients, especially, may never develop such changes. The term undifferentiated SpA is therefore no longer used by the majority of experts for patients with nr-axSpA. Today it is sometimes used for...
patients with peripheral SpA who do not have psoriasis, IBD, or a preceding infection.

However, there is still some confusion about the differences between classification and diagnosis of axSpA. Although it is widely known that classification criteria are made for groups of patients and diagnostic criteria are usually made for individual patients, some clarification seems to be necessary on how established classification criteria might be used in daily clinical practice. When new classification criteria are developed and compared to already existing tools, they are usually tested against what is currently regarded as the gold standard. Even though it seems clear that by the introduction of new technologies such as MRI this view may change over time, the gold standard in rheumatology is often the opinion of the rheumatologist who is responsible for the patient, mostly but not always an expert in the field. If the developed criteria are good, the sensitivity and specificity are usually above 80%. This means that although the vast majority of patients is correctly classified, about 20% who fulfill the criteria are false-positive or false-negative. For classification criteria, a clear “yes” or “no” is the result, and negative findings are not taken into account. Responses are being developed for inclusion of a homogeneous group of patients into clinical studies. A positive diagnosis should already be present from the expert when it is tested whether the patient fulfills the criteria. A diagnostic approach is more flexible because it takes negative findings into account, and the final diagnosis is based on the expert’s opinion.

We examine here the use of clinical features for diagnosing axSpA and try to show the differences between classification and diagnosis. We show that there are situations when a diagnosis of axSpA — for example in the presence of other features typical for SpA — is appropriate, when the classification criteria are not fulfilled. On the other hand, we show that there are patients who, for various reasons, do not have axSpA even though they fulfill the classification criteria.

MATERIALS AND METHODS

Chronic back pain. Patients with axSpA may present with their first symptoms after some weeks. However, others may have been asymptomatic for long periods and may have forgotten about back pain at earlier timepoints, while still others may have had (inflammatory) chronic back pain for several decades but have not been diagnosed as axSpA yet. Chronic back pain may also occur intermittently. Indeed, for patients with AS, different courses of disease including flares have been described,16,17 or had been present in the past, there are situations where diagnosis of axSpA, in the presence of other typical features, will be potentially appropriate. For example, patients may have had back pain for a long time before visiting a rheumatologist and may show definite radiographic alterations at first presentation. Further, the prevalence of IBP in patients with anterior uveitis, psoriasis, and IBD is quite high.18 Some of these patients have axSpA, but back pain is not reported as a predominant symptom.

Although in such cases a diagnosis of peripheral SpA should be considered,19 it is well known that there is considerable overlap between the 2 SpA entities,19 which may make it difficult to determine the predominant symptom. Accordingly, a mixed set for classification has been proposed. This, however, is infrequently used mainly because the approval of medications has followed the route of differentiating axial versus peripheral SpA. Based on historical experience, this makes sense because at least conventional disease-modifying antirheumatic drugs such as sulfasalazine clearly work better for peripheral arthritis than for IBP,20 and tumor necrosis factor (TNF) blockers work well in both conditions.

The localization of back pain is not part of the classification criteria. However, there is some evidence that this matters clinically. The most common location in the first years after symptom onset is the lower back. However, inflammatory changes in all parts of the spine may cause symptoms. In patients with established AS, the lower part of the thoracic spine was the most frequent anatomic location,23 but other parts of the axial skeleton are also frequently involved.24-25 In a study on referral variables for axSpA, the lower back turned out to be the best.26

Age at onset. Although this is clearly not frequently the case, the age at first onset of typical symptoms of axSpA may be older than 45 years. Indeed, several papers have reported on patients with late-onset axSpA.27-29 Patients may also start to have IBP before the age of 18, although these patients would still fulfill the classification criteria if they were already 18 years old at time of first presentation. In juvenile SpA, patients frequently show SpA with peripheral symptoms and develop back pain some years later.30

Sacroiliitis on imaging. According to the ASAS classification criteria, patients with axSpA may not have inflammatory lesions on MRI suggestive of sacroiliitis associated with SpA. Also, definite radiographic sacroiliitis according to modified New York criteria is not a requirement. In those cases, patients need to be HLA-B27–positive to be classified as axSpA.31 On the other hand, patients may have inflammatory (MRI) and or structural changes (radiography) in the spine that are not so clear in the SIJ. How frequently this occurs has not yet been defined. Reported percentages vary between 5% and 50%.32 However, theoretically, a patient with chronic back pain who does not have sacroiliac changes and who is HLA-B27–negative could well be diagnosed with axSpA when clear-cut spondylitis is present along with other variables characteristic for axSpA. Further, recent histologic studies have shown that the sensitivity and specificity of MRI to detect sacroiliac inflammation is clearly far below 100%.31,32,33 The role of conventional radiography and MRI is central in the classification criteria, and many rheumatologists are reluctant to make a diagnosis of axSpA without a positive imaging finding. The ASAS definitions of sacroiliitis and spondylitis have played an important role in the standardization of imaging.31,32,33 The problem of the widespread performance of sophisticated imaging procedures in primary care has been discussed.31,34 Because imaging in axSpA requires experience and knowledge, application of the wrong techniques (excluding short-tau inversion recovery or T1 post-gadolinium) and misinterpretation of imaging results may frequently lead to false-positives and false-negatives. In addition, the difficulty of diagnosing definite structural changes in the SIJ, and of separating AS from diffuse idiopathic skeletal hyperostosis, is well known, and the velocity of new bone formation is similar.35,36

Concern has been raised that in the “clinical arm” of the ASAS criteria, where patients are classified based on a positive HLA-B27 finding plus 2 additional SpA features without a positive imaging result, patients will be falsely classified with axSpA, for example, those with fibromyalgia. This seems possible and is a good example of the differences between classification and diagnosis. Some experience, including a good clinical history and evaluation, will often, but not always, help to make that distinction.

HLA-B27. In the evaluation trial for the ASAS classification criteria, only 66% of the patients were HLA-B27–positive.37 As reported, an
HLA-B27–negative patient with a normal MRI is unlikely to have axSpA; however, it is known that a substantial number of the HLA-B27–negative patients is likely to have psoriasis or chronic IBD. On the other hand, the prevalence of HLA-B27 in the population is around 6%–8% in Central European countries and the United States,36,37 > 90% of those people are healthy and do not develop SpA.38 Based on the high prevalence of back pain in the population,22,39 one can expect many healthy (in terms of axSpA) HLA-B27–positive patients with back pain. Thus, these patients are per se likely to receive a diagnosis of axSpA, but two-thirds of them will not have this disease.40 Indeed, the differential diagnosis may not be easy, especially because degenerative disc disease may also cause morning stiffness in the lower back.41 On the other hand, in countries with a low background prevalence of HLA-B27 and of axSpA, such as Japan,42 or a low HLA-B27 prevalence in patients with AS, such as Lebanon43 (in contrast to other Arab countries44), these estimates and calculations will be less relevant. In Europe, HLA-B27 has been shown to be of critical importance for referral strategies in primary care.55,46,47

The likelihood of false-positive or false-negative testing for HLA-B27 has been found to be comparatively low with established techniques (< 5%), and using PCR methodology, this may be even lower.48 The fact that more than 100 HLA-B27 subtypes have now been recognized has no practical influence on diagnosis and classification.38

In general, all musculoskeletal and other organ-related symptoms occurring in patients under suspicion of SpA or with SpA may well have a cause unrelated to SpA. But symptoms suggestive of SpA may occur in patients who do not have that disease. The relative frequency of SpA-associated symptoms and disease manifestations can be seen roughly as occurring in 3 groups: 1 group (prevalence around 70%) covers back pain, IBP, positive imaging, a good response to nonsteroidal antiinflammatory drugs (NSAID), and HLA-B27 positivity; the second group (prevalence about 50%) covers arthritis, enthesitis, and elevated CRP; and the third (prevalence about 30%) covers anterior uveitis, dactylitis, psoriasis, IBD, and a family history of SpA.40

IBP. While the prevalence of IBP seems to be in the range of 70%–80% in patients with AS, it is less well investigated in nr-axSpA. Although a similar prevalence can be assumed,30,49,50,51 data-based prevalence rates remain to be demonstrated. In such studies, it will be important to use the opinion of experienced rheumatologists rather than classification criteria as the gold standard. Further, there is currently no general agreement on which criteria for IBP should be used in daily practice. Nevertheless, this does not seem to matter much because the proposed criteria perform similarly well in daily rheumatology practice. This is most likely related to the high pretest probability of patients with axSpA who get to see a rheumatologist. However, the probability is different in other settings, such as in primary care, where the pretest probability of axSpA is around 5% in the group of patients with back pain and the resulting posttest probability for a diagnosis of axSpA is no higher than 20%.39 Indeed, there is some evidence that the performance of the ASAS criteria may differ in different clinical situations.46,49 Further, IBP is a frequent complaint in the population.48,36 For example, morning stiffness of the lower back alone has been shown to not differentiate well between patients with axSpA and other patients with chronic back problems in primary care.26 Finally, in the diagnostic pyramid published some years ago, IBP versus chronic back pain did not contribute substantially more to a diagnosis of axSpA.52 However, data from another study on IBP in AS suggested that the presence of 3 out of 4 IBP items had high specificity (97%) for a diagnosis of AS — of course the sensitivity was low in that calculatory approach.46,49

IBP is a characteristic symptom of patients with SpA in the offices of rheumatologists but has limited sensitivity and specificity in other settings. Arthritis. Every experienced rheumatologist knows how difficult it can be to diagnose arthritis, because many patients report arthralgia. Because the physical examination may be misleading, different imaging procedures are used to provide “objective” evidence of joint inflammation. Indeed, MRI and ultrasound including Doppler techniques are increasingly used, and scintigraphy is frequently performed. However, all these depend greatly on the expertise of the examiner. Thus, false-positive and false-negative results are relevant matters of concern.

The asymmetric pattern of the most frequently presented oligoarthritis and the predominance of the lower extremities are relevant in relation to a possible diagnosis of SpA.54. There is currently no ideal assessment tool for the quantification of arthritis in SpA, because the joint counts that are used to assess polyarthritis in rheumatoid arthritis (RA) do not work well in oligoarticular disease in SpA.

Clinical examination and imaging may lead to false-positive and false-negative findings in the assessment of arthritis and may have an influence on the diagnosis of SpA. Enthesitis (heel). Although involvement of entheseal structures is regarded as a characteristic sign of SpA, it is clear that it also occurs in other inflammatory rheumatic diseases such as RA.55. Clearly, there are many more sites of enthesitis than the heel in SpA.56. For example, the shoulder may be involved.57 On the other hand, sites such as the epicondyles of the elbow are frequent locations of symptoms in patients who have mechanical stress other than SpA. Further, currently used assessment tools for clinical enthesitis vary substantially.53,55,39. However, because enthesitis and painful entheses may not appear to be very impressive in the clinical examination, imaging is a relevant tool to provide “objective” evidence of inflammation — especially for the plantar fascia, where MRI techniques are used. For other entheses, such as the pes anserinus and the great trochanter, ultrasound is the most reliable tool. Imaging studies using power Doppler have suggested that subclinical enthesitis may be frequent at various sites.50 However, the clinical relevance of this finding remains to be demonstrated.

False-positive and false-negative findings in clinical examination and imaging in the assessment of enthesitis may influence the diagnosis of SpA. Uveitis. A high prevalence of anterior uveitis (in the range of 30%–40%) has been reported for AS,61,62 while this number seems to be lower for nr-axSpA,69 probably because patients are earlier in the course of their disease, and the rate of HLA-B27 is somewhat lower. Anterior uveitis associated with SpA usually occurs acutely and unequally and is easily treated with local corticosteroids in the majority of cases.62,63 Anterior uveitis may also occur in other rheumatic diseases such as sarcoidosis and Lyme disease,44 but in other rheumatic diseases such as Behçet disease it is more the posterior compartment of the uvea or both compartments (panuveitis) that become involved. In other rheumatic diseases, the conjunctiva (reactive arthritis), the sclera, and the retina (in RA) may become affected.48 Because the rheumatologist is usually not able to exactly differentiate the anatomic localization of an inflammatory eye disease, such symptoms are usually handled in cooperation with the ophthalmologist. Indeed, in many countries, it is the usual attitude of eye specialists to refer patients with anterior uveitis to the rheumatologist to identify SpA.

An incorrect diagnosis of uveitis may clearly affect the diagnostic examination in patients suspected of SpA. In the diagnostic pyramid proposed some years ago, anterior uveitis was the strongest multiplicative clinical factor (RR > 7).

Dactylitis. Although occurring in all SpA subtypes, the usually impressive clinical finding of dactylitis (sausage finger or toe) has its highest prevalence in psoriatic arthritis (PsA).59. An assessment tool specifically for quantifying dactylitis has been proposed.66 While the overall sensitivity of dactylitis in SpA is not very high, its specificity is good, because it does not usually occur in other rheumatic diseases. Rarely, active osteoarthritis (OA) of the proximal interphalangeal joints may cause such diagnostic problems. The main differential diagnosis of dactylitis is trauma — which can be ruled out easily when taking the patient’s history. Psoriasis. Psoriasis is a relatively frequent finding in the population (2%–3%), and in patients diagnosed with SpA.58,69. The diagnosis usually requires the cooperation of an experienced dermatologist. The diagnostic approach may be difficult and the diagnosis may remain unclear for some time. There are different kinds of psoriasis, including vulgaris, guttata, and palmaris et plantaris; they should be differentiated by the dermatologist.
who may not find this easy in all cases. In addition, other skin and nail diseases such as neurodermitis and tinea pedis may have a similar appearance. In the new classification criteria for PsA\(^{55}\), the written diagnosis of the dermatologist is usually mandatory. In contrast, the rheumatologist may decide in individual cases that the apparent squamous skin efflorescence in combination with a very suggestive clinical sign of dactylitis and arthritis may be sufficient for a diagnosis of SpA or PsA. The rheumatologist may not find it very easy to differentiate OA occurring in a patient having psoriasis from PsA — especially if proximal and distal interphalangeal joints as well as the back\(^{70}\) are involved. The presence of psoriasis predominantly palmar or plantar may be associated with a special subtype of SpA and PsA that has been named SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis)\(^{71}\).

Importantly, based on other suggestive clinical and/or imaging findings, PsA may be diagnosed even without an apparent skin disease\(^{72}\). Some but not all of these patients may have a family history of psoriasis. Further, the onset of psoriasis can come before or after the onset of musculoskeletal symptoms\(^{72}\).

The presence of psoriasis in connection with other symptoms suggestive of SpA is a clinically relevant finding that may significantly support a diagnosis of axSpA. Indeed, psoriasis was even identified as an item of a 2-step referral program for the early identification of axSpA\(^{46}\). However, patients with psoriasis may well have musculoskeletal symptoms that are not explained by an underlying SpA.

**Chronic IBD (Crohn disease/ulcerative colitis).** In comparison to psoriasis, Crohn disease and ulcerative colitis are less prevalent in the overall population\(^{73}\). Patients under suspicion of SpA with gastrointestinal symptoms should undergo endoscopy. The diagnosis always requires cooperation with an experienced gastroenterologist who cooperates with a pathologist, but even so, the diagnostic approach may prove difficult, and the diagnosis may remain unclear for some time. Although the association of IBD with SpA is in general well established\(^{74}\), it seems that not all patients with musculoskeletal symptoms in conjunction with IBD have a condition in the spectrum of SpA. The largest study of the association of all kinds of arthritis with IBD suggested that there are 2 types, one showing some association with SpA including HLA-B27, and one not\(^{75,76}\). This study was based on clinical and genetic findings. A completely different approach has been the systematic search for macroscopic and microscopic colitis in patients with different types of SpA\(^{74}\). However, this approach has not made its way to a clinical pathway related to making a diagnosis of SpA.

In addition, similar to the situation in psoriasis, the onset of symptomatic IBD may be before, after, or in parallel to arthritis or other musculoskeletal symptoms\(^{77}\). The gastroenterologist makes the diagnosis of IBD. The presence of IBD in connection with other symptoms suggestive of SpA is a clinically relevant finding that may significantly support a diagnosis of axSpA. However, patients with IBD may well have musculoskeletal symptoms not explained by an underlying SpA. Differential features of SpA between IBD and psoriasis have been described\(^{77}\).

**Good response to NSAID.** This item has been included based on the publication of Amor\(^{78}\) and on clinical experience with the partly impressive clinical responses of patients with axSpA. The problem with the item is that it is not very precise in its quantitative aspect and raises the question, “what is a good response?” This has not been precisely defined to date. However, it is clear that, for example, patients with nonspecific low back pain respond poorly to NSAID and only about 20%–25% report clinically relevant improvement\(^{79}\). Because the success rates reported for patients with axSpA are in the range of 70%–80%, this item fits quite well among the diagnostic variables for axSpA\(^{55}\). However, it is clear that both false-positive and false-negative results may influence the diagnostic approach to patients under suspicion of axSpA.

**Family history of SpA.** A positive family history is usually defined as having first-degree relatives in whom a diagnosis of SpA has been made\(^{80}\). Patients with SpA report a positive family history in about a third of the cases\(^{49,50,81}\). In the last set of the classification criteria\(^{50}\) this has included the presence in first-degree or second-degree relatives of any of the following: AS, psoriasis, uveitis, reactive arthritis, or IBD.

Thus, there is some variance in how family history is handled at least in the classification but also in the diagnostic approach to SpA.

**Elevated CRP.** While the role of elevated CRP serum levels to indicate higher disease activity has recently become more and more established — especially in predicting response to anti-TNF therapy\(^{82,83,84}\) and response to NSAID therapy regarding the prevention of radiographic progression in the spine\(^{85,86}\) — it has also been shown that the correlation of clinical disease activity and serum CRP levels is relatively weak\(^{87,88}\). Further, in patients with extraarticular manifestations, especially IBD but also psoriasis, CRP levels may be raised just because of the underlying disease and not because of the musculoskeletal involvement. This can be difficult to differentiate but should be always tried. Of course, in daily clinical practice one always has to rule out other reasons for an elevated CRP.

**RESULTS**

An online supplement available at jrheum.org presents descriptions and images of cases misclassified to axSpA (false positive) or for which classification was missed despite the designation of axSpA (false negative).

**DISCUSSION**

Because diagnosis of axSpA may be difficult among a large population with back pain, and the use of classification criteria for diagnosing patients is often misunderstood, we used our experience in the field to give examples of patients evaluated for a potential diagnosis of axSpA in our clinic. We present examples of both false-positive and false-negative diagnoses in patients who had been evaluated for axSpA. Because imaging is an important part of the classification criteria, it was not surprising to find several cases in which interpretation of the images rather than the ASAS criteria themselves impeded correct diagnosis. These examples should help to further understand the problems potentially associated with classifying and diagnosing axSpA.

However, it was not possible to cover all important differential diagnoses in the examples described. Therefore we looked into our database and the literature (Table 1) to show other rheumatic diseases in which sacroiliitis or similar sacroiliac changes may occur\(^{89,90,91,92,93,94}\). The scarcity of related publications and our own experience suggest that these cases are relatively rare. A major differential diagnosis that can be complicated, osteitis condensans\(^{95}\), clearly needs more study.

Another important differential diagnosis that has not been mentioned in detail is infectious sacroiliitis or spondylitis due to a bacterial infection\(^{96,97,98}\). Although staphylococci and streptococci are clearly the most frequent microbes detected (for example, in patients with drug dependency), cases of tuberculosis and brucellosis have also been reported, albeit more frequently in countries with high background rates\(^{97,98}\). These pathologies are usually characterized by mialgias and fever in addition to back pain —
sacroiliitis. We stress that the absence of radiographic changes excludes a diagnosis or a classification of axSpA. The differential diagnosis of sacroiliitis is wide and includes a spectrum of inflammatory and non-inflammatory processes, each with its own peculiar clinical features. Infections such as Staphylococci, streptococci, Mycobacterium tuberculosis, Brucella species, or postinfectious structural changes in the sacroiliac joint may occur. Pelvic fractures, malignant neoplasms, and inflammatory processes such as sacroiliitis in gout, osteoarthritic changes in the axial skeleton, and Sacroiliitis in familial Mediterranean fever may also cause symptoms substantially less frequent in patients with axSpA.

What may cause a diagnostic challenge is the clinical situation in which patients have a history of pyogenic infection in the SIJ, because the structural changes that usually occur in bacterial infection may mimic the changes known in AS. Osteoarthritis changes in the SIJ are known to occur more frequently with increasing age. Thus, this differential diagnosis to axSpA usually does not cause problems before the age of 40 years.

Another important differential diagnosis is a pelvic fracture, most frequently seen in postmenopausal women but also in younger patients after minor trauma. Rarely, a malignancy such as lymphoma, leukemia, or even sarcoma may occur. Severe pain and nonresponse to standard therapies should increase suspicion of such diagnoses.

Our aim was to put the diagnosis and classification of axSpA into perspective. We have shown that a diagnosis of axSpA can be made in patients not fulfilling the ASAS classification criteria and that patients fulfilling the criteria may ultimately not be diagnosed with axSpA. Importantly, we stress that the absence of radiographic changes excludes neither a diagnosis nor a classification of axSpA.

ONLINE SUPPLEMENT
Supplementary data for this article are available online at jrheum.org.

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