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The classification and diagnostic criteria of ankylosing spondylitis

Siba P. Raychaudhuri [a,b,*], Atul Deodhar [c]

[a] VA Sacramento Medical Center, Department of Veterans Affairs, Northern California Health Care System, Mather, CA, USA
[b] Department of Medicine, Division of Rheumatology, Allergy and Clinical Immunology, School of Medicine, University of California, Davis, USA
[c] Division of Arthritis & Rheumatic Diseases (OP09), Oregon Health & Science University, Portland, OR 97239, USA

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ABSTRACT

Ankylosing spondylitis is the prototype of immune-mediated inflammatory rheumatic diseases grouped under the term spondyloarthritis (SpA). An early diagnosis has now become increasingly important because effective therapies are available and anti-TNF drugs are even more effective if used in early stages of the disease. In ankylosing spondylitis, the 1984 modified New York criteria have been used widely in clinical studies and daily practice but are not applicable in early disease when the characteristic radiographic signs of sacroiliitis are not visible but active sacroiliitis is readily detectable by magnetic resonance imaging (MRI). Thus there has been a need for new classification or diagnostic criteria to identify inflammatory spondyloarthritis at early stage of the disease. This led to the concept of axial SpA to include the entire spectrum of patients with axial disease both, with and without radiographic damage. New classification criteria for the wider group of SpA have been proposed by ASAS (Assessment of Spondylo Arthritis International Society); and the patients are sub-grouped into (1) a predominantly axial disease, termed axial SpA including AS and non-radiographic axial SpA; (2) peripheral SpA. The clinical course and disease process of non-radiographic axial spondyloarthritis remains unclear. However the development of the SpA criteria by ASAS particularly for axial SpA, is an important step for early diagnosis and better management of these patients.

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1. Introduction

The term 'spondyloarthritis' (SpA) designates a group of diseases, which share common clinical and genetic features. These features include involvement of the axial skeleton (sacroiliac joints and spine), peripheral arthritis, enthesitis, dactylitis, acute anterior uveitis, associated psoriasis or inflammatory bowel disease, and presence of the HLA-B27 antigen [1–4]. Depending on the predominant clinical manifestations, SpA can be classified either as axial SpA (characterized by predominant involvement of the spine and/or sacroiliac joints) or as peripheral SpA (peripheral arthritis, enthesitis, and/or dactylitis) [5,6]. Axial SpA is characterized by chronic inflammatory back pain and based on clinical and radiological features can be separated into two groups – (i) ankylosing spondylitis (AS), which is defined by the presence of definite structural changes on radiographs in the sacroiliac joints, and (ii) nonradiographic axial SpA which is defined by the presence of sacroiliac inflammation as detected by MRI or the presence of HLA B27 in combination with the presence of features typical of spondyloarthritis. The spectrum of spondyloarthritis is described in Fig. 1. Ankylosing spondylitis is the prototype of immune-mediated inflammatory rheumatic diseases in the axial spondyloarthritis spectrum.

2. Prevalence of ankylosing spondylitis and spondyloarthritis as a group

Historically, AS was thought to be a disease that almost exclusively affected young men. More recent studies suggest a male-to-female ratio of about 2 or 3 to 1, although there can be considerable geographical and ethnic variation. AS has an estimated prevalence of about 0.5% [7,8] in the Caucasian population, whereas the estimated prevalence of SpA as a group is about 1.5%–2% [7,8]. Human leukocyte antigen (HLA)-B27 is strongly linked to disease susceptibility, and there is a close correlation between the frequency of several subtypes of this allele in a population and the prevalence of AS [4]. In the central European population, the HLA-B27 is as common as 6%–9% [7,9,10]; whereas, in Japanese or Central and South African populations its prevalence is 1% or less with a resulting low AS prevalence [11,12]. However AS can occur in the absence of HLA-B27 and only about 10% of HLA-B27-positive

* Corresponding author. VA Sacramento Medical Center, Department of Veterans Affairs, Northern California Health Care System, 10535 Hospital Way, Mather, CA 95655, USA. Tel.: +1 916 843 7096; fax: +1 916 366 5475.
E-mail address: sraychaudhuri@ucdavis.edu (S.P. Raychaudhuri).

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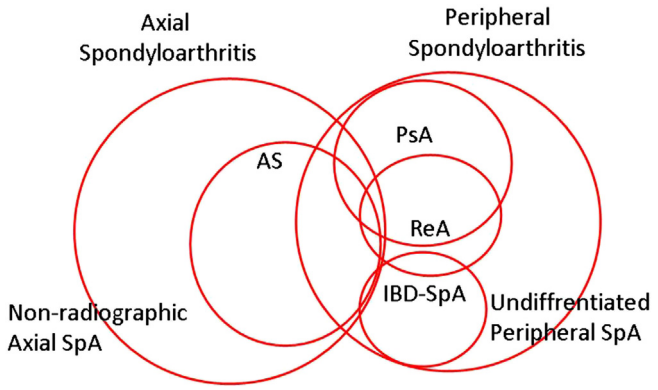

Fig. 1. Venn diagram showing the spectrum of Spondyloarthritis. AS – ankylosing spondylitis. PsA – psoriatic arthritis. ReA – reactive arthritis. IBD-SpA – inflammatory bowel disease associated arthritis.

subjects develop the disease [13], and even HLA-B27-positive identical twins can be discordant for disease incidence as well as severity [14,15].

3. Clinical features

The most characteristic clinical symptom of AS or axial SpA is inflammatory back pain [1,2,16]. The presentation of back pain is not an uncommon occurrence in the general population, making it important to differentiate inflammatory from non-inflammatory causes of back pain. Inflammatory back pain is characterized by stiffness and pain that is worse in the morning or after long periods of inactivity ("gel phenomenon") and is improved with exercise. Patients commonly complain of difficulty sleeping or pain that is not relieved with rest or lying down, or alternating buttock pain [17,18]. Alternating gluteal pain, a more specific feature of inflammatory back pain most likely represents sacroiliac involvement. Sometimes pain and stiffness in the mid-thoracic or the cervical region or chest wall pain may be the initial symptom, rather than the more typical low backache [18]. This may be a relatively more common presentation in women. In addition a major indicative for an inflammatory back pain could be significant pain relief in response to a non-steroidal anti-inflammatory drug (NSAID). The presence of inflammatory back pain alone may not be diagnostic but should trigger suspicion of ax-SpA. In addition certain known associated conditions such as psoriasis, inflammatory bowel disease and uveitis in a patient with inflammatory back may be indicative of ax-SpA. Thus it is important to gather these entire clinical features for an early diagnosis of AS or other forms of ax-SpA.

4. Diagnostic tests: there are no specific laboratory tests for AS or SpA

There are no laboratory findings that are diagnostic of AS. In contrast to other systemic inflammatory diseases such as Lupus and RA, acute phase reactants (erythrocyte sedimentation rate [ESR] and C-reactive protein) may be normal in majority population of SpA patients [19]. Rheumatoid factor and antinuclear antibodies are absent in SpA.

Almost 90% of the patients with AS [20,21] and nearly 70% of the patients with axial SpA [21] are positive for HLA-B27 whereas only 6–10% of the general white population is HLA-B27 positive [20]. This makes this marker relevant as a diagnostic tool. However as mentioned earlier, only a small fraction, about 10% of HLA-B27 positive subjects, develop the disease [13], and even identical twins who are HLA-B27-positive can be discordant for disease incidence as well as severity [14,15]. This clearly indicates that HLA-B27 is neither sufficient nor absolutely necessary for the occurrence of AS. Recently, two new loci related to AS, ERAP1 (ARTS1) and IL23R, have been identified [3]. These facts discourage the use of HLA-B27 as a diagnostic marker for AS or SpA. However HLA-B27 positivity is a key feature in the new ASAS classification criteria for axial-SpA [5,6] hence it is expected this laboratory test will be frequently used for AS and other SpA patients.

5. Diagnosis

In the absence of any diagnostic criteria, the modified New York Classification Criteria are the most widely used tool for the classification of ankylosing spondylitis and they continue to be used for diagnostic purposes too (Table 1) [22]. In most patients, the first symptoms of SpA (usually inflammatory back pain) start in the third or fourth decade of life. As mentioned earlier, inflammatory back is not enough to make the diagnosis; and the diagnosis of AS is based on clinical signs, symptoms along with the radiologic evidences of sacroiliitis. Following evaluations are done to determine the spinal involvement: (i) the modified Schober test is used to measure anterior lumbar spinal flexion (ii) lateral spine motion is assessed using lateral bending of the lumbosacral spine (iii) "Occiput-to-Wall" distance is measured to determine the cervical spine mobility and (iv) chest expansion is measured at the lower end of the xiphisternum to evaluate the rib cage movement. In addition palpation or percussion of the sacroiliac joints may elicit pain, but this does not reliably indicate the presence of sacroiliitis. Placing stress on the sacroiliac joints with the Flexion, Abduction, and External Rotation maneuver and the Gaenslen test can illustrate sacroiliac joint dysfunction and may also produce pain, though the specificity of these tests is not high. Examination and review of the eyes, skin and the cardiovascular and pulmonary systems may uncover extra-articular disease.

Sacroiliitis (Fig 2) is the required and the earliest radiographic manifestation of AS [23]. Thus, pelvic radiographs are essential to make the diagnosis of AS. Radiographic grading of sacroiliitis consists of 5 grades, ranging from 0 = normal to IV = complete ankylosis (Table 2). Due to oblique orientation of the sacroiliac (SI) joints, the standard anteroposterior radiographs of the pelvis may not allow for good visualization of the SI joints. Ferguson view, which is a 30° cephalad angled view of the SI joint may overcome this problem [23]. Isolated SI joint x-rays may result in increased amount of radiation and there is no evidence that this approach is actually superior to the standard pelvic x-ray [24]. Pelvic X-ray also allows to visualize the hip joints which are frequently affected in AS. The classic finding of "squaring" of the vertebral bodies is an important radiological hallmark induced by osteitis and subsequent erosions of the anterior superior and inferior surfaces [25]. Ossification of the spinal ligaments that bridge the intervertebral discs results in the characteristic bony protuberances called

Table 1
Modified New York criteria.

1 Radiological criterion
Bilateral sacroiliitis grade ≥ II or unilateral sacroiliitis grade III to IV
2 Clinical criteria
(a) Low back pain and stiffness of at least 3 months duration improved by exercise and not relieved by rest
(b) Limitation of motion of the lumbar spine in both the sagittal and the frontal planes
(c) Limitation of chest expansion relative to values normal for age and sex
Definite AS is diagnosed if the radiological criterion plus 2 of the 3 clinical criteria are present.

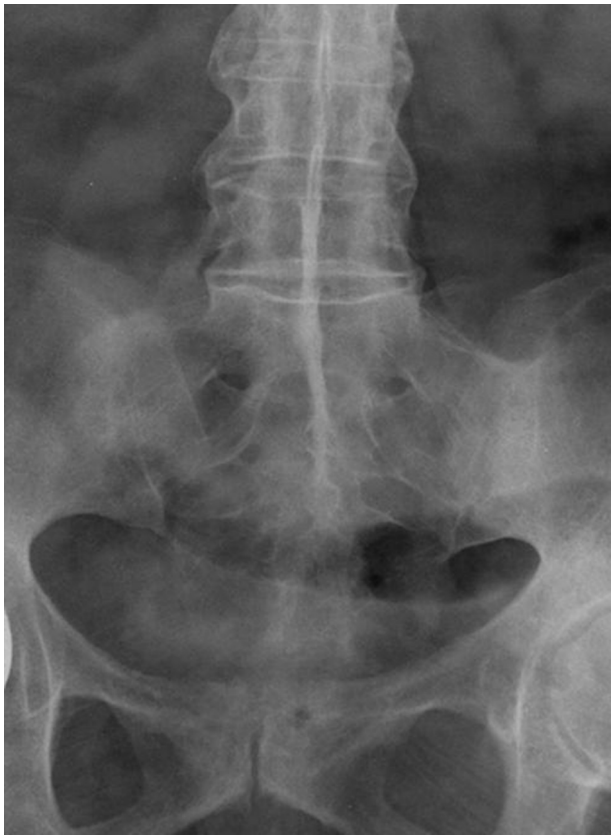

Fig. 2. Sacroiliitis and bamboo spine. Conventional radiograph of the pelvis in a 38 year old man demonstrating bilateral sacroiliitis along with fusion of the lumbar spine ("bamboo spine").

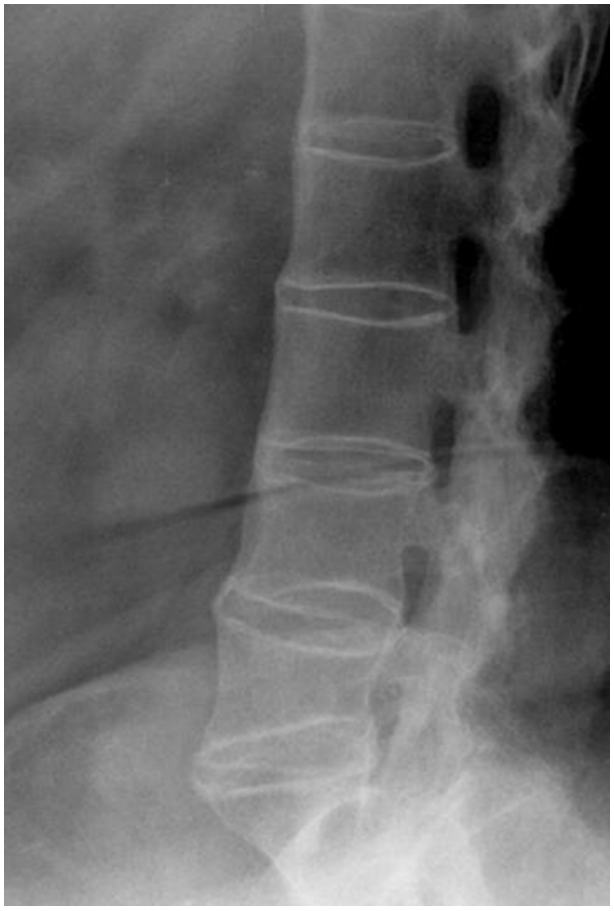

Fig. 3. Anterior syndesmophytes. Lateral radiograph of the lumbar spine shows anterior syndesmophytes bridging the vertebral bodies.

"syndesmophytes" (Fig 3). In long-standing and late stage AS, these syndesmophytes increase in size, the spine fuses and may give the appearance of a "bamboo spine" (Fig 1).

According to the modified New York classification criteria for AS, the patient requires to have X-ray evidence of sacroiliitis (defined as bilateral grade 2 or unilateral grade 3 or 4) [22]. However, interpretation of sacroiliac joint X-ray is difficult and open to interpretational variation, especially in the early stages of disease [23]. AS, requires X-ray evidence of sacroiliitis, and because of this requirement the diagnosis may get delayed as long as 10 years [26,27]. This is of great concern, since the diagnostic uncertainty increases disease morbidity and may leads to inappropriate investigations and delay in treatment.

CT and MRI demonstrate considerably higher sensitivity in identifying sacroiliitis in the early stages of AS [28,29]. CT appears to be superior to MRI for the visualization of chronic bony changes [24]. On the other hand, MRI is the only technique that can image acute inflammatory and chronic structural lesions simultaneously [24] and it seems to perform better than CT in revealing early cartilage changes and bone marrow edema [29]. A further advantage of MRI is that it does not involve radiation exposure. The presence of sacroiliac joint inflammation (sacroiliitis) on musculoskeletal imaging (X-ray or MRI) in the presence of clinical manifestations is virtually diagnostic of AS. The new definition of inflammatory back pain (IBP) and the use of the magnetic resonance imaging (MRI) to detect inflammation in the sacroiliac joints and the spine has helped in the early identification of axial SpA in the "non-radiographic stage" of the disease [20]. With the help of MRI inflammatory changes in the SI joints can be identified years before appearance of radiological changes in the conventional X-ray films.

Table 2
Radiographic grading of sacroiliitis.

Grade	Appraisal
0	Normal – normal width, sharp joint margins
I	Suspicious
II	Sclerosis, some erosions
III	Severe erosions, pseudodilatation of the joint space, partial ankylosis
IV	Complete ankylosis

6. Non-radiographic axial SpA – early diagnosis and its importance

Magnetic resonance imaging (MRI) is now considered to be an integral tool to aid in early recognition of inflammation of the axial skeleton, since it can detect active inflammatory changes at the sacroiliac joints with or without structural damage [30]. MRI scan of the SI joints is therefore vital for recognizing axial SpA at the stage when X-ray of the SI joints looks normal. It has been reported that a significant number of these patients will develop radiographic sacroiliitis, that is, structural damage of SI joints, and evolve into definite AS with time [21,27]. On the other hand, this concept also implies that a proportion of patients will remain at this stage with inflammation on MRI at some point during their disease, but without progressing to detectable damage on radiographs over subsequent years. At this point in time it remains unknown

whether all patients will develop radiographic evidence of sacroiliitis and spondylitis, and hence this stage of axSpA is defined as non-radiographic axial SpA (nr-axSpA), rather than pre-radiographic stage. Parameters which may predict the progression to definite radiographic sacroiliitis are currently under investigation.

A recent study of the German SpA Inception Cohort (GESPIC) revealed that 14.3% of patients with nr-axSpA showed spinal radiographic progression over a 2-year period, and the presence of baseline syndesmophytes, elevated erythrocyte sedimentation rate or C-reactive protein levels, and cigarette smoking were the independent predictors of the disease progression over 2 years [31].

Non-radiographic axial SpA is relatively a new concept so in respect to patient care an obvious question would arise how important it is to diagnose and identify this subset of SpA patients. It has been reported that compared to the established AS patients early (non-radiographic) axial SpA patients have the same level of pain and stiffness [21]. There is a substantial amount of evidence that therapeutic outcomes of the anti-TNF agents are better in patients with good functional status and in those at the early stage of the disease [32–34]. Thus, early diagnosis and an effective therapy should be a priority for proper care of the axial SpA patients that includes both non-radiographic and radiographic – or the established patients.

7. The new assessment of Spondylo Arthritis International Society (ASAS) classification criteria for spondyloarthritis

In contrast to the diagnostic criteria, classification criteria are for case identification for clinical research. Classification criteria are not intended for the diagnosis of individual patients in clinical practice. However, in the absence of true diagnostic criteria, classification criteria are often used for diagnostic purposes which may lead to inappropriate diagnosis. In clinical practice, diagnosis of a condition is dependent upon the prevalence of that condition in the population (pre-test probability) and is based on full history, physical examination, targeted investigations and recognizing the pattern that emerges from those. In making a diagnosis, common conditions are considered first and ruled out. Diagnostic criteria usually have some inherent uncertainty built in them with 'possible', 'probable' and 'definite' catagories after 'ruling out' common conditions. In contrast, the Classification Criteria are applied to patients who are already diagnosed by ticking "yes" or "no" boxes on clinical characteristic items. Till date, there are no diagnostic criteria developed for any diseases within the spondyloarthritis spectrum. Amor criteria [35] and the European Spondyloarthropathy Study Group criteria [36] have been widely used in SpA by clinicians for more than a decade. However these criteria suffer from two major limitations: (i) they do not separately identify axial and peripheral SpA (ii) widespread use of MRI was not available when these criteria were developed and hence it has not been used as an imaging tool. These limitations have paved the development of new classification criteria for axial [5,6] and peripheral SpA [37] by the Assessment of Spondylo Arthritis International Society (ASAS) group.

7.1. The ASAS classification criteria for axial SpA

To develop new ASAS classification criteria for axial SpA, candidate criteria were first developed based on clinical reasoning [5]. In a large prospective study involving more than 649 patients worldwide these candidate criteria were then validated [6]. ASAS classification criteria have been proposed for axSpA in subjects with chronic back pain with onset before age 45 (Fig 4). The new classification criteria for axSpA have two arms: the imaging arm and the clinical arm (Fig. 4). The imaging arm requires presence of sacroiliitis as detected by conventional radiography or by MRI (nonradiographic axial SpA; abbreviated as nr-axSpA) and at least one of the clinical features of SpA. The clinical arm requires presence of HLA-B27 and at least two of the clinical features (Fig. 4).

The sensitivity of the entire set of ASAS criteria for axial SpA was 82.9% and the specificity was 84.4%. The imaging arm that is the patients who had evidence of sacroiliitis on either MRI or radiographs, plus at least one further SpA feature showed excellent specificity (97.5%), but it has a low sensitivity (66.2%). Whereas the clinical arm (presence of HLA-B27 plus at least two further SpA features in a patient with chronic back pain and age at onset of <45 years) has reasonably good sensitivity and specificity (~80% for both). After the publication of the ASAS classification criteria for axSpA, the efficacy of anti-TNF treatments with adalimumab [38], infliximab [39], etanercept [40] and certolizumab [41] has been demonstrated in patients with nr-axSpA.

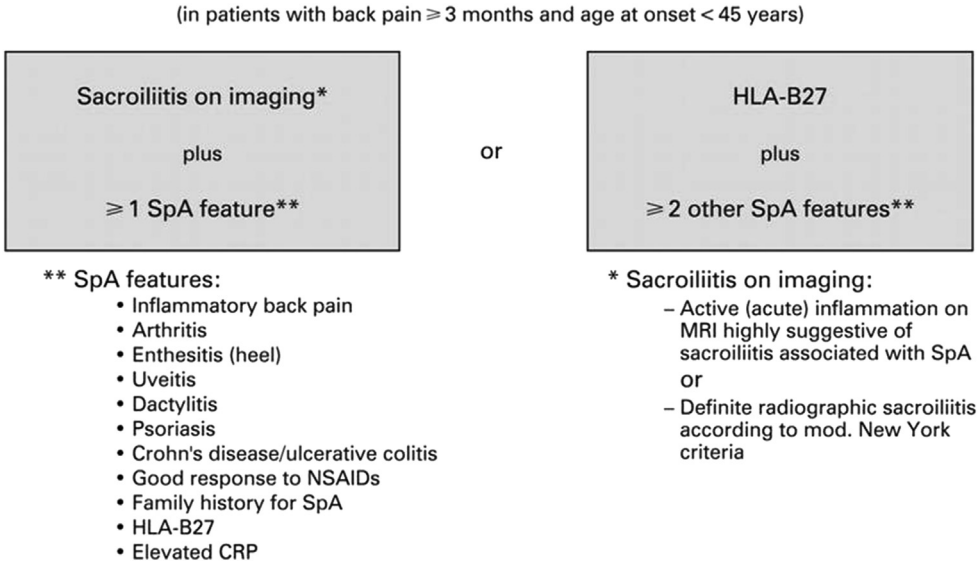

Fig. 4. Assessment of Spondylo Arthritis International Society (ASAS) classification criteria for axial and peripheral spondyloarthritis. (Adapted from Rudwaleit et al. [5,6,37]).

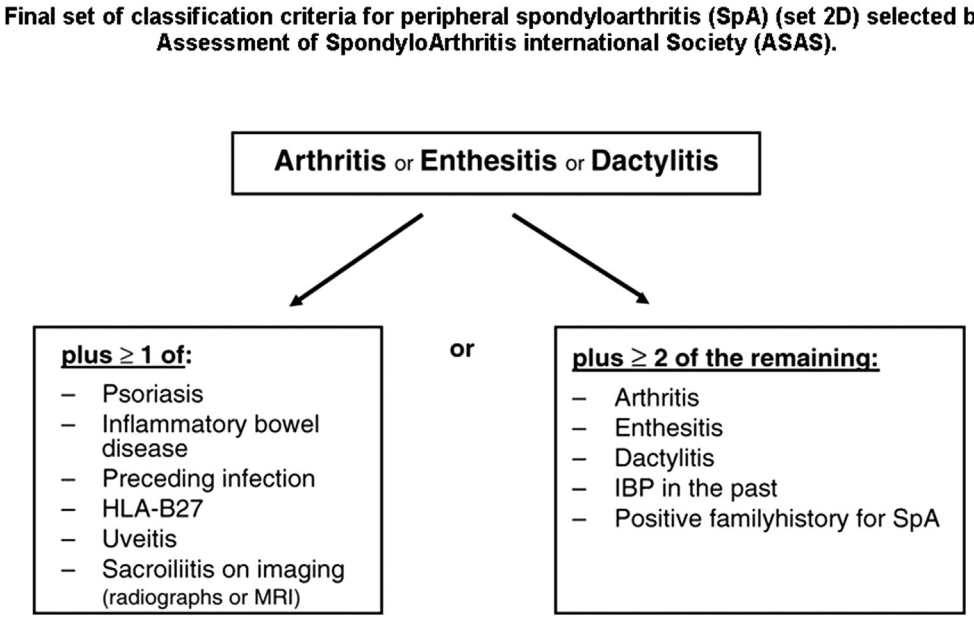

Fig. 5. Assessment of Spondylo Arthritis International Society (ASAS) classification criteria for axial and peripheral spondyloarthritis. (Adapted from Rudwaleit et al. [37]).

7.2. The new ASAS classification criteria for peripheral SpA

ASAS classification criteria (Fig. 5) have also been proposed for peripheral SpA [37]. According to these criteria in the presence of arthritis or enthesitis or dactylitis, one needs at least one or more of the "major" features that characterize psoriasis, inflammatory bowel disease, uveitis, HLA-B27, preceding infections, or sacroiliitis (X-ray or MRI), or two or more of the following features: arthritis, enthesitis, dactylitis, inflammatory back pain (IBP) in the past, and family history of SpA. The sensitivity of these criteria was 77.8% and specificity was 82.9% [37].

8. Limitations of ASAS classification criteria

The development of the new SpA classification criteria by ASAS is an important step towards a better definition of the early disease stage particularly in axial SpA. Therefore, the criteria can be used for the conduct of studies but also help establish a diagnosis by pointing out features that are highly relevant in SpA. However because of lack of diagnostic criteria, the ASAS classification criteria may be used by physicians inappropriately leading to over diagnosis of axial SpA. The specificity of the 'clinical criteria' (Fig 4) for non-radiographic axSpA has also been questioned. A good example will be, a 35 year old fibromyalgia patient who is HLA B27 positive could be misclassified as axial SpA based on soft and non-verifiable items such as positive family history, and response to NSAIDs ('Clinical Criteria' as mentioned in Fig 4). The importance of the subjective and objective features in the clinical criteria (Fig 4) may not necessarily be of same importance. However currently all items in these criteria have same weight – for example, objective criteria such as uveitis, IBD have equal importance to subjective criteria such as response to NSAIDs, non-verifiable criteria such as family history of SpA. Thus there is an unmet need for diagnostic criteria for axial SpA, peripheral SpA and even AS for clinicians to use in daily practice.

9. Conclusion

In recent years, important steps toward standardizing an early diagnosis of SpA have been made, including development of the new "SpA concept" encompassing both the axial and peripheral types, introduction of MRI as one of the key diagnostic imaging tools, development of the new classification criteria for SpA, and application of referral strategies. Further dissemination of these achievements and their consecutive application in clinical practice will contribute to shorten the long diagnostic delay and is likely to improve long-term outcome.

Contributions

SPRC and AD have designed the papers and they together have written this manuscript.

Declaration of conflicts of interest

None to declare.

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