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Challenges in the diagnosis of axial spondyloarthritis

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A B S T R A C T

With back pain as one of the most common complaints in the population and with no single disease feature with sufficient sensitivity and specificity to diagnose axial spondyloarthritis (axSpA) on its own, diagnosing axSpA can be challenging. In this article, we discuss clinical, laboratory, and imaging spondyloarthritis features that can be used in diagnosis and explain the general principles underlying an axSpA diagnosis. Moreover, we discuss three pitfalls to avoid when diagnosing axSpA: i) using classification criteria as diagnostic criteria, ii) making a diagnosis by simple counting of spondyloarthritis features, and iii) over-reliance on imaging findings. Finally, we have some advice on how to build diagnostic skills and discuss new developments that may help facilitate the diagnosis of axSpA in the future.

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disease that mainly affects the spine and sacroiliac (SI) joints. In addition to spinal inflammation, peripheral manifestations (arthritis in the limbs, enthesitis, and dactylitis) and extra-musculoskeletal manifestations (EMMs) (inflammatory bowel disease (IBD), psoriasis (PSO), and anterior uveitis (AU)) are common and contribute to the overall burden of axSpA (Fig. 1).

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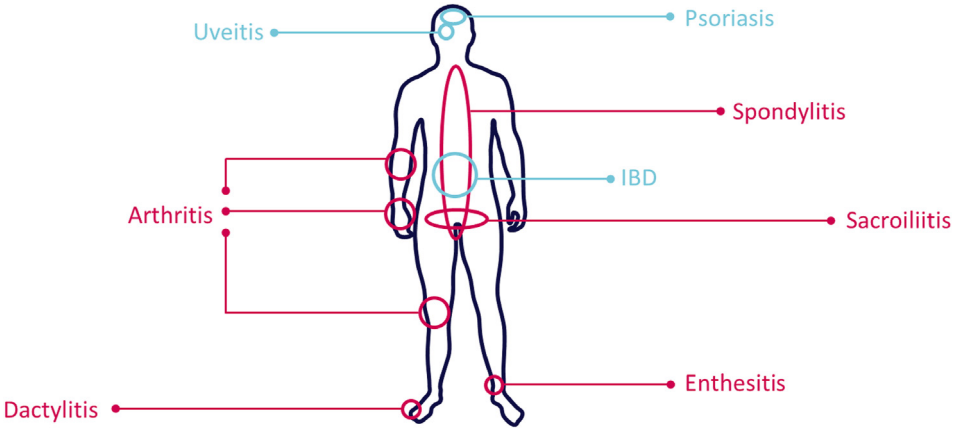

Fig. 1. Musculoskeletal (red) and extra-musculoskeletal (blue) manifestations of spondyloarthritis.

Axial spondyloarthritis (axSpA) can be subdivided into non-radiographic axSpA (nr-axSpA) and radiographic axSpA (previously called ankylosing spondylitis (AS). The difference between these two groups is that patients with radiographic axial spondyloarthritis have definite signs of sacroiliitis on conventional radiographs and patients with non-radiographic axial spondyloarthritis do not.

However, overall the clinical presentation and management of nr-axSpA and r-axSpA are very similar [1,2] with the possible exception of the subset of r-axSpA patients with extensive spinal damage. In these patients, prevention of progressive spinal damage and sometimes surgical correction of spinal deformation may be a part of management.

Nevertheless, the distinction between nr- and r-axSpA continues to be important because regulatory agencies such as the US Food and Drug Administration or the European Medicines Agency require clinical trials to be performed in both axSpA disease forms for approval of new pharmaceutical treatments. Also, progression rates of spinal damage vary between nr-axSpA and r-axSpA with damage mainly restricted to patients with r-axSpA [3].

General principles of diagnosis

AxSpA has a heterogenous presentation and unfortunately, no single feature from the patient's history, physical examination, laboratory testing, or imaging studies has sufficient sensitivity and specificity to diagnose axSpA. As a result, diagnosis involves the recognition of a pattern of features that taken together provide sufficient evidence to diagnose the disease. Importantly, with back pain usually the main complaint prompting a diagnostic procedure into axSpA as a possible cause of spinal symptoms, the diagnosis requires the exclusion of other potential causes of back pain.

In the following paragraphs, we will discuss the most useful clinical, laboratory, and imaging features that can be used to identify axSpA in patients with chronic back pain.

Building blocks of diagnosis

Age at onset of back pain symptoms

AxSpA usually starts in the second or third decade of life [4,5]) with age at onset of disease becoming uncommon after the age of 45 years [6]. As a result, age at onset of first back pain symptoms is very useful in identifying chronic back pain patients at risk of axSpA, as it is an easy and accessible piece of information that can be used in the first selection of patients.

The finding that the vast majority of axSpA patients develop back pain before the age of 45 years was made in European studies [5,7]. Recently, it has been shown that this is also true for patients in other parts of the world. Of the 2579 axSpA patients included in the Assessment of SpondyloArthritis International Society (ASAS)-PerSpA study, 92% had an age at onset of axial symptoms before the age of 45 years [8].

Strikingly, little variations were seen across geographical regions. Of 574 Asian axSpA patients 94% had had an age at onset of symptoms less than 45 years. In 998 European and North American patients this was 92%, in 246 patients from Latin America this was 89%, and in 771 patients from the Middle East and North Africa, this was 91%. In line with previous reports, age at onset of axial symptoms was consistently lower in HLA-B27-positive patients with a median of 25 years [interquartile range (IQR) 19–32] vs 31 years [IQR 22–39]} and in male patients with a median of 25 years (IQR 19–33) vs 28 years (IQR 21–37)]. However, in multivariable models, an additional statistically significant effect of male gender independent of HLA-B27 was only found in Asian patients. Taken together this means that around the world, the great majority of axSpA patients will have an age at onset of axial symptoms before the age of 45 years meaning that the onset of back pain well after the age of 45 years is unlikely to be due to axSpA.

Patient history and physical examination

The medical history of a back pain patient suspected of axSpA should always include inquiring about the duration and characteristics of back pain, in particular features that may suggest an inflammatory cause of the back pain.

Over time several sets of questions have been published aimed at defining a history suggestive of an inflammatory cause of back pain. The most recent one is the widely used ASAS expert criteria to identify patients with inflammatory back pain (IBP) [9] (Table 1).

In the original publication, the presence of four of the five features has a sensitivity and specificity of 80 and 74%, respectively, using overall expert judgment on IBP as the gold standard.

Given that IBP questions are easy to apply, IBP is commonly used in referral recommendations for other physicians to rheumatologists. As a result, IBP is very common in back pain patients referred to rheumatologists suspected of axSpA. The downside to this is that several publications have reported a reduced discriminative value of IBP in the rheumatologist's office [10,11].

In addition, medical history should include ascertainment of previous or current musculoskeletal SpA features i.e. arthritis, enthesitis, and dactylitis, and extra-musculoskeletal SpA features i.e. psoriasis, inflammatory bowel disease, and acute anterior uveitis. Patients should also be asked about a family history of SpA including uveitis and axSpA in family members. Although back pain of many causes may improve when treated with NSAIDs, marked improvement in pain within one or two days upon treatment of NSAIDs supports the diagnosis of an axSpA. Finally, medical history taking may also yield crucial pieces of information on the differential diagnosis of back pain such as—but certainly not limited to—questions about previous episodes of back pain or injury, back surgery, weight loss and fever, neurological symptoms, and widespread pain.

Physical examination is an important part of the diagnostic workup of patients with back pain suspected of axSpA. The joints need to be examined for arthritis, the heels for enthesitis of the Achilles tendon, the hands and feet for dactylitis, and nails and skin for psoriasis. Signs of active acute uveitis are

Table 1
ASAS experts Inflammatory back pain (IBP) criteria.

IBP if at least 4 out of 5 of the following parameters are 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 upon getting up)

Sieper et al. Ann Rheum Dis. 2009 Jun; 68(6):784-8.

not commonly detected by rheumatologists in patient with back pain suspected of axSpA but if present greatly increase likelihood of axSpA [12].

Restriction in spinal mobility can be measured in clinical practice. Commonly used measures are cervical rotation, chest expansion to measure the range of motion of the costovertebral joint, the Schober test for range of motion of the lower spine in the sagittal plane, and lateral spinal flexion in the coronal plane. Age-stratified reference intervals for various spinal mobility measurements in Europeans have been published [13] and are available through the ASAS website (https://www.asas-group.org/instruments/mobility-curves/).

Unfortunately, spinal mobility tests are of little diagnostic value as spinal mobility has a large variation in normal subjects and decreases with advancing age [13]. Moreover, in a cohort of chronic back pain patients suspected of early axSpA, impaired spinal mobility occurred as often in patients with early axSpA as in other forms of chronic back pain [14].

Laboratory testing

Acute phase reactants and in particular C-reactive protein (CRP) should be measured in patients suspected of axSpA. Elevated CRP levels are observed in about 25–40% of patients with axSpA [15,16]. Moreover, CRP levels are part of the AxSpA Disease Activity Score (ASDAS), the preferred composite measure of disease activity for axSpA, and over time elevated CRP is associated with spinal radiographic progression. Erythrocyte sedimentation rate (ESR) is an alternative when CRP is not available. Of note, a normal CRP or ESR does not exclude a diagnosis of axSpA and an elevated CRP or ESR may be caused by something other than axSpA.

AxSpA is a complex polygenetic disease but HLA-B27 is by far the most important single genetic risk factor for disease. Worldwide, HLA-B27 prevalence varies greatly between populations with prevalences of less than 1% reported in Sub-Saharan African studies [17] to over 30% in Northern Arctic communities such as Chukchi and Inuit [18]. Prevalence of HLA-B27 mirrors prevalence of axSpA in a given population highlighting the importance of pathogenesis. The diagnostic value of HLA-B27 testing lies in the fact that HLA-B27 is consistently far more common in axSpA patients than in the general population.

In the aforementioned PerSpA study, 89% of axSpA patients from Asia were HLA-B27 positive, 65% from Middle East and North Africa, 81% from Latin America, and 78% from Europe and North America [19]. For reference, the prevalence of HLA-B27 in the general population in Europe and North America is around 6 to 8%.

Imaging studies

Imaging studies play an important role in the diagnosis of axSpA. While inflammation may be present in the entire spine it is easiest to detect in the sacroiliac (SI) joints. In many centers, plain radiograph of the pelvis to visualize the SI joints continue to be the first imaging study as plain film radiography can be sufficient to identify sacroiliitis and is less expensive and resource-intensive than MRI.

On radiographs, the right and left SI joints should be evaluated and can be assigned a grade, based upon the degree of involvement (Fig. 2; Table 2). According to this grading system, a radiograph is regarded as positive for sacroiliitis if the score is greater than or equal to grade two bilaterally or is greater than or equal to grade three unilaterally [20].

Radiography may be the method most commonly used to assess involvement of the SI joints but it is often inadequate to detect early disease, as patients may have symptoms due to sacroiliitis for several years before abnormalities can be seen on radiography [21]. Moreover, as data is emerging that transition from non-radiographic to radiographic axSpA is a slow process, it is likely that many nr-axSpA may never develop abnormalities on radiographs of the SI joints [22,23]. Furthermore, interpreting radiographs of the sacroiliac joints in suspected axSpA is not always easy. Interobserver and intra-observer variations are substantial, which means that sacroiliitis can be missed or incorrectly assumed to be present [24].

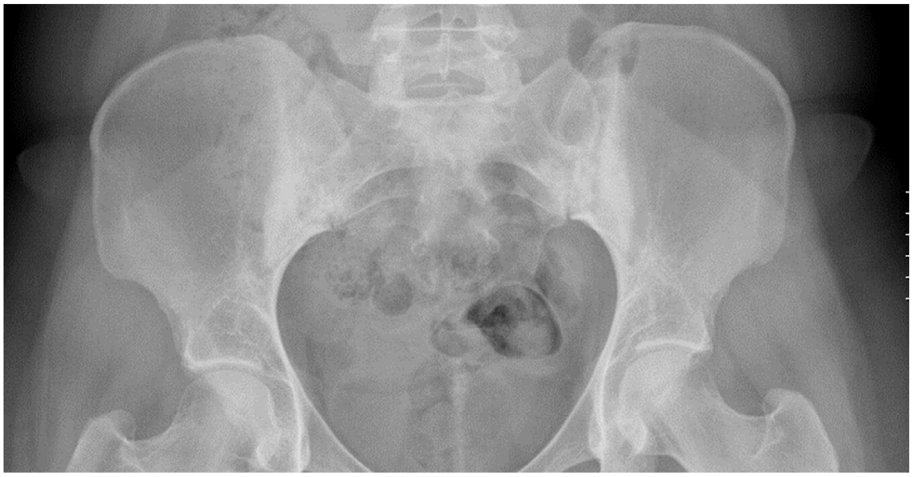

Fig. 2. Sacroiliitis on radiographs. Radiographs of the pelvis of a 32 year old female with HLA-B27 positive axial spondyloarthritis with peripheral arthritis and psoriasis. The radiologist graded both sacroiliac joints as grade 3. Patient gave written consent for use of the image for educational purposes.

Table 2
Grading of radiographic sacroiliitis.

Grade 0:	normal
Grade 1:	suspicious 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

Bennett PH, Burch TA: Amsterdam. Excerpta Medica Foundation International Congress Series 148, 1966:456–457.
Examples of radiographs with different grades of sacroiliitis can be found in the ASAS slide library under "X-ray" (www.asas-group.org/education/asas-slide-library/).

In patients with obvious sacroiliitis on radiography, additional imaging, such as an MRI, may not be necessary for diagnosis. MRI is capable of detecting inflammation in the SI joint in SpA before changes are seen on radiographs (Fig. 3). This is because MRI, unlike plain radiographs, can reveal inflammatory changes, fatty changes, and more subtle structural abnormalities. MRI also has better interreader reliability compared to conventional radiography [25].

In patients with a negative MRI of the sacroiliac joints (not showing sacroiliitis) at first diagnostic assessment, a follow-up MRI can generally be considered when axSpA is suspected. However, rates of a negative MRI of the sacroiliac joints becoming positive at follow-up after 3–12 months are very low, in particular for females (2.8%) and for HLA-B27 negatives (1.5%) and are only somewhat higher for males (12%) and for HLA-B27 positives (11%) [26].

MRI or radiography of the spine is not routinely used in the diagnosis of axSpA [27] but can be very useful when pathology other than SpA is suspected or to rule out other causes of back pain [28].

Differential diagnosis

Conditions that cause chronic spinal and low back pain may present in a similar way to axSpA. In the Spondyloarthritis Caught Early (SPACE) cohort which consists of chronic back pain patients referred to a rheumatologist with an onset of back pain before the age of 45 years and with a symptom duration of fewer than two years common diagnoses in patients with CBP who were not diagnosed with axSpA

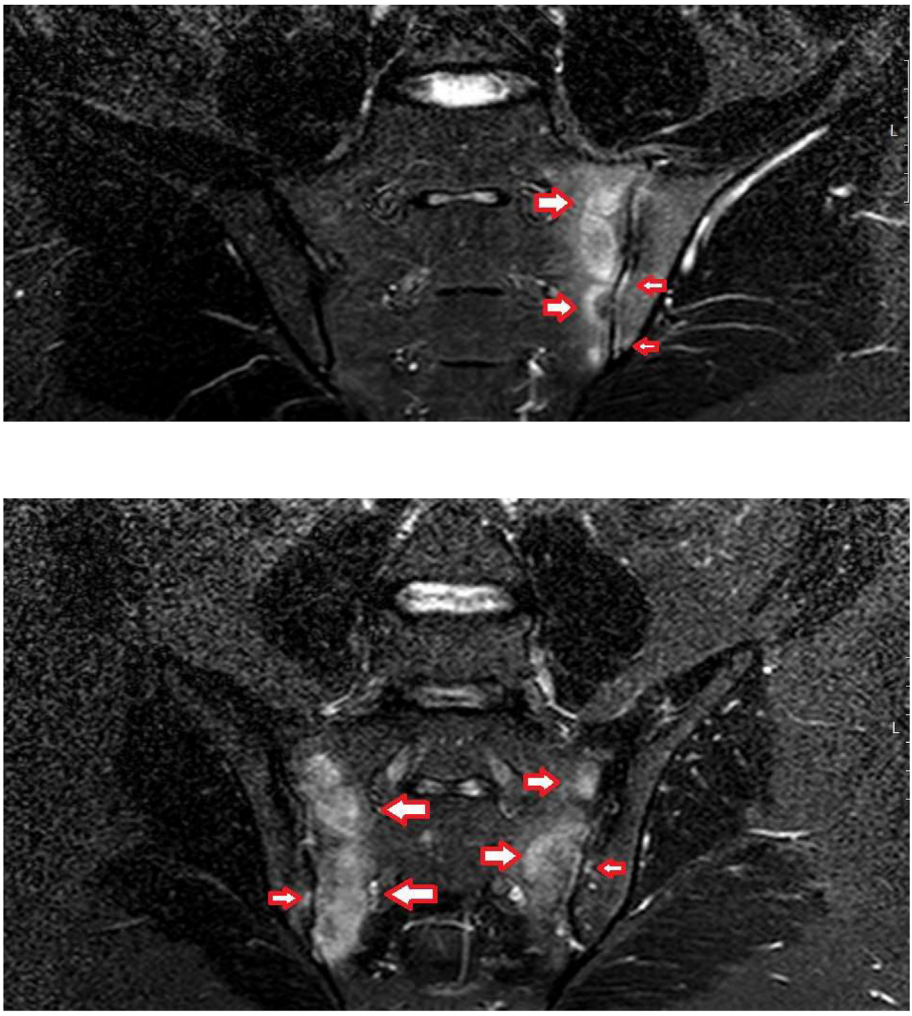

Fig. 3. Bone marrow edema on MRI of the sacroiliac joints. Two examples of bone marrow edema detected in the sacroiliac joint of patients diagnosed with axial spondyloarthritis. Upper panel: unilateral bone-marrow edema in the left sacroiliac joint. Lower-panel: bilateral bone-marrow edema in the sacroiliac joints. Patients gave written consent for use of the image for educational purposes.

were: non-specific back pain, mechanical back pain, IBP without SpA, degenerative disc disease and (fibro)myalgia [28]. Of note, in this cohort, CBP patients were young adults with a mean age of less than 30 years. In other groups of chronic back pain patients and in particular in older patients, other causes such as osteoporotic fractures, osteoarthritis of spine, malignancy, diffuse idiopathic skeletal hyperostosis are likely to be more common.

Approach to diagnosis

Having an idea of a typical disease presentation helps in identification and diagnostic workup. Although it cannot be stressed enough that axSpA has a heterogenous presentation, in our clinical practice in Western Europe, a typical presentation of axSpA is a young adult with chronic inflammatory

back pain (or at least some items associated with IBP) located at the lower back, starting before the age of forty to fifty, who is usually HLA-B27 positive with at least one or two other SpA features and clear signs of sacroiliitis on imaging. Spondyloarthritis exists in many forms, but we usually are very reluctant to diagnose a patient with axial SpA if no signs of active inflammation or post-inflammatory structural lesions can be found in SI joints or spine.

To help build diagnostic skills we highly recommend training on assessing clinical signs of SpA, pattern recognition, and interpreting images.

Many initiatives are being undertaken all around the world to educate rheumatologists on diagnosing and assessing SpA. One free-to-use example is the ASAS interactive online case library. This online case library contains over thirty clinical cases representing the entire spectrum of axSpA and the most common differential diagnoses (www.asas-group.org/education/asas-case-library). For all cases presented, imaging is discussed in the context of clinical findings and laboratory test results.

In the next section, we present three pitfalls to avoid in diagnosing axSpA. In our experience, these pitfalls are commonly encountered in clinical practice.

Pitfall one: using classification criteria for diagnosis

As with essentially all rheumatic and musculoskeletal diseases classification criteria have been developed for axSpA for research purposes. Classification criteria are standardized definitions that are primarily intended to create well-defined, relatively homogenous cohorts for clinical and laboratory research. The current classification criteria are the 2009 Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA [29].

In the ASAS axSpA classification criteria, a patient diagnosed with axSpA has to have chronic back pain for more than three months starting before the age of 45 years to fulfill the entry criterion (Fig. 4). In addition, the patient must have either sacroiliitis on imaging plus at least one other SpA feature or the patient must be HLA-B27 positive plus at least two other SpA features.

In the 2009 ASAS classification criteria all items previously discussed for diagnosis are listed.

At first glance, the classification criteria may give off the impression of being easy to use as diagnostic criteria, too. However, they are not.

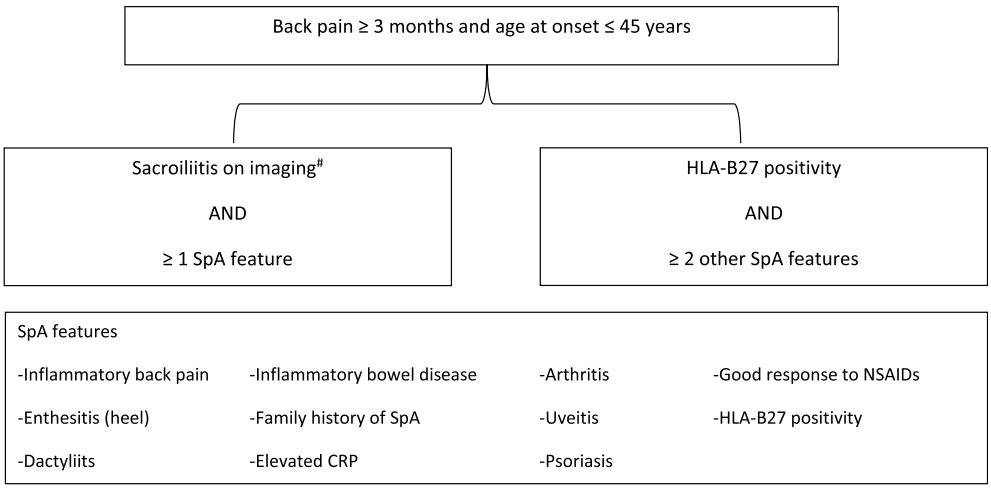

Fig. 4. Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis. Legend: #Imaging evidence of sacroiliitis includes active (acute) inflammation on magnetic resonance imaging highly suggestive of sacroiliitis associated with SpA or definite radiographic sacroiliitis according to the modified New York criteria for ankylosing spondylitis. CRP: C-reactive protein; HLA-B27: human leukocyte antigen B27: NSAIDs: nonsteroidal anti-inflammatory drugs. Adapted from M Rudwaleit et al . Ann Rheum Dis . 2009 Jun;68(6):777-83.

Using the classification criteria for diagnosis not only ignores the important issue of differential diagnosis but also leads to an unacceptable number of misdiagnoses both on axSpA patients incorrectly not diagnosed (due to too low sensitivity for diagnosis) and patients without axSpA incorrectly diagnosed as axSpA (due to too low specificity for diagnosis). The inherent limitations in both sensitivity and specificity of classification criteria in part result from the categorical character of classification criteria (either fulfilled or not fulfilled), whereas making a diagnosis in clinical practice allows for flexibility and encompasses a broad spectrum of diagnostic confidence [30].

Indeed, in a meta-analysis of 4990 patients from seven studies, the sensitivity of ASAS axSpA classification criteria was 82% (95% confidence interval 77%–96%), and the specificity 87% (95% confidence interval 78–92%) [31].

Pitfall two: diagnosis by simply adding up SpA features

In a patient with CBP, the presence of one or multiple SpA features increases the likelihood of axSpA: all SpA features have a certain diagnostic value, and the presence of multiple SpA features makes a axSpA increasingly more likely [32]. Indeed, in order to assist physicians in the diagnosis of axSpA a diagnostic algorithm has been developed. The ASAS-modified Berlin algorithm suggests a diagnosis of axSpA in patients with $\geq$4 SpA features without further imaging or HLA-B27 testing. However, it should be stressed that the ASAS-modified Berlin algorithm is only a tool in aiding rheumatologists in diagnosing axSpA and can and should not replace a differential diagnostic procedure in patients with CBP.

As SpA features are very diverse and range from genetic risk of disease (e.g. HLA-B27), to inflammation in the peripheral skeleton (e.g. arthritis), axial skeleton (e.g. sacroiliitis on MRI), and outside the joints (e.g. psoriasis) SpA features do have to be combined into a meaningful pattern pointing to inflammation in the axial skeleton. For example, if a patient with peripheral spondyloarthritis with psoriasis, arthritis, and dactylitis develops chronic back pain then that back pain does not automatically mean that back pain is caused by axSpA although that patient already has at least three SpA features.

Prompted by concerns from experts about the risk of overdiagnosis of axSpA when the diagnosis is made by simply counting the number of SpA features without clinical reasoning and without paying attention to an alternative diagnosis that may better explain the symptoms, in the SPACE cohort the association between the number of SpA features and an axSpA diagnosis was investigated. In 500 patients suspected of axSpA, a diagnosis of axSpA was made in 250 (50%) of the patients: The rate of axSpA was 24% in patients with $\leq$1 SpA feature, 43% with 2 SpA features, 62% with 3 SpA features and 85% with $\geq$4 SpA features. This shows that an increased number of SpA features indeed increases likelihood of axSpA but also that in rheumatological practice presence of numerous SpA features does not automatically lead to a diagnosis of axSpA [33].

Pitfall three: misdiagnosis through over-reliance on imaging

As mentioned, imaging whether through radiography or MRI as a means to detect inflammation or post-inflammatory changes in the spine and SI joints plays a very important role in diagnosing axSpA [34].

However -as already discussed-radiography of the SI joints is not able to detect cases of axSpA where structural damage to the SI joints has not happened and, in addition, suffers from substantial intra- and inter-reader variability. Therefore, MRI is increasingly used to visualize inflammation in the SI joints. While MRI can detect various lesions associated with axSpA, bone marrow edema has been and still is considered to be the most diagnostically useful.

While in the first definition of sacroiliitis on MRI in 2009 [35] only bone marrow edema reflecting active sacroiliitis was considered to be the only relevant lesion, knowledge of and experience with structural lesions on MRI has increased over time. Accordingly, the revised ASAS definition in 2016 [36] still focuses around detection of bone marrow edema typical of SpA but acknowledges the additional diagnostic value of concomitant structural lesions (e.g. erosions, bony ankylosis, fat metaplasia) on

MRI. In particular, in cases with doubtful bone marrow edema lesions, structural lesions may increase diagnostic confidence.

The usefulness of MRI is, however, limited by the difficulty of interpreting these images, especially without special training, and also by MRI needing to be interpreted in the context of the degree of clinical suspicion (Case).

Moreover, other causes of bone marrow edema in the SI joints such as mechanical stress should always be considered as over the years several articles have reported on SI joint BME in patients and individuals without axSpA. In 47 Dutch healthy volunteers, 23% had an MRI 'positive for sacroiliitis', compared to 92% of 47 axial SpA patients, and 6% of 47 patients with chronic back pain. In addition, 13% of 24 runners and 57% of the 7 women with postpartum low back pain had a 'positive MRI'. Yet, none of the BME findings in non-axSpA individuals included deep lesions (a homogenous signal extending at least 1 cm from the articular surface) and the higher the number of SI quadrants or MRI slices of the SI joints showing BME, the higher the likelihood of the lesion being due to axSpA [37].

A Danish study found that in recreational runners and elite ice-hockey players, BME fulfilling the ASAS definition was present in 30–41%, with the posterior lower ilium being the most often affected joint quadrant, and erosions being virtually absent in these individuals [38]. Making more disease-specific MRI definitions remains an important task for scientists.

Taken together, as with sacroiliitis on radiographs, MRI findings of BME alone are not necessarily diagnostic of axSpA and MRI should always be interpreted in the context of other clinical and laboratory findings.

Final thoughts

Pharmaceutical treatment options of axSpA are rapidly increasing. Key aims of axSpA management are to control symptoms, restore function and quality of life, and slow disease progression [2]. For obvious reasons, appropriate treatment must be preceded by a correct diagnosis. Notwithstanding the unresolved issue of getting people with suspected axSpA referred to a rheumatologist, diagnosing axSpA can be challenging despite clear improvements in diagnostic tools including MRI and more readily available HLA-B27 testing. Indeed, even under almost optimal diagnostic circumstances, diagnostic uncertainty remains in a number of patients with suspected axSpA due to the heterogeneous nature of the disease [39]. In patients in whom the diagnosis cannot be made with confidence, a definitive conclusion should be avoided. Regularly discussing cases with fellow rheumatologists and radiologists in particular those with expertise in musculoskeletal radiology is greatly recommended. For now, available data suggest that repeating MRI imaging at least within one year has a low yield and in general is not diagnostically useful [26].

Practice points

- With no pathognomonic feature, diagnosis of axial spondyloarthritis (axSpA) remains a skill that involves the recognition of a pattern of features that taken together provide sufficient evidence to diagnose the disease.
- Patient history, physical examination, and selected laboratory (HLA-B27, CRP), and imaging studies are used in diagnosing axSpA.
- Conditions that cause chronic spinal and low back symptoms may present in a similar way to axSpA and should be ruled out before making a diagnosis.
- Diagnostic pitfalls such as using classification criteria as diagnostic criteria, making a diagnosis by simply adding up SpA features or over-reliance on imaging must be avoided.

Research agenda

- There is room for improvement in diagnostic instruments for axSpA. Possibilities may lie in more disease-specific MRI definitions, polygenic risk scores [40], and new imaging techniques [41].
- There is a need for evidence-based guidance on managing diagnostic uncertainty including long-term follow-up of patients and for more data on the value of repeat assessments including imaging.

Declaration of competing interest

Dr. F.A. van Gaalen is currently a member of the ASAS executive committee and Prof. Dr. M Rudwaleit is the principal investigator of the ASAS CLASSIC study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.berh.2023.101871.

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