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SPONDYLOARTHRITIS (M KHAN, SECTION EDITOR)

An Update on Diagnosis and Classification of Axial Spondyloarthritis

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Abstract
Purpose of Review To summarize the most relevant recent progress to diagnose and classify patients with axial spondyloarthritis (axSpA).
Recent Findings A substantial proportion of new studies focused on the diagnosis and classification of patients with axSpA. Efforts have been concentrated on setting the best strategy to refer patients with suspected axSpA and evaluating the utility of different tools during the diagnostic work-up, especially of imaging techniques. On top of this, researchers have worked on addressing some concerns raised about the employment of the Assessment of SpondyloArthritis international Society classification criteria, especially those related to the validity and misuse of the criteria, providing valuable data on this regard.
Summary Recent findings emphasize that classification should serve a completely different purpose than diagnosis. In addition, they highlight the importance to consider the limitations for imaging acquisition, the appropriate context, and differential diagnosis when interpreting imaging findings during the diagnostic work-up of patients with suspected axSpA.

Keywords Axial spondyloarthritis · Non-radiographic axial spondyloarthritis · Diagnosis · Classification · Ankylosing spondylitis · Review

Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease comprising radiographic axSpA (r-axSpA) and non-radiographic (nr-axSpA) forms. In most cases, back pain is the initial manifestation of the disease, which is associated with inflammation of the spinal and sacroiliac joints. Over a long time, if this inflammation persists, the disease leads to irreversible structural damage and disability, causing a great impact on physical and social quality of life of the patients and even on their relatives [1].

During the last couple of decades, the field of axSpA has enormously evolved through the development of new diagnostic tools and measurements for evaluating disease activity and its outcomes and, especially, the discovery of new efficacious therapies [2–5]. Nevertheless, in order to apply all these clinical developments in patients with axSpA, it is essential to make an early diagnosis. Otherwise, all the tremendous efforts and progress concerning the follow-up and management of this disease will not be feasible to implement in clinical practice.

Despite an early diagnosis has become indispensable in patients with axSpA, performing an early diagnosis has been identified as one of the main unmet needs in the axSpA field [6]. The current analysis shows that this essential aim is far from being achieved. According to a recent meta-analysis, the mean diagnostic delay in patients with SpA is 7 years [7•]. There are many reasons behind this unacceptable diagnosis delay but one of the most relevant is the "typical" journey that patients with axSpA usually go through until they are finally diagnosed, which includes many visits to other specialists and performance of useless complementary examinations that in most cases do not lead to the correct diagnosis [8]. This situation has been identified to be even worst in females compared with males, with a mean (95% confidence interval) diagnostic delay of 8.8 (7.4–10.1) versus 6.5 (5.6–7.4) years, respectively. The reasoning behind this gender-disparity is unclear but recent data show that this disparity could be explained by a lower percentage of HLA-B27 carriers among female axSpA

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patients and also due to the existence of a medical bias, related to the traditional thought that axSpA, especially ankylosing spondylitis (AS), is primarily a male-disease [9, 10].

Furthermore, on top of achieving an early diagnosis, as more research is performed in the field of axSpA, a proper classification of patients with the disease is becoming more and more relevant. In this sense, new classification criteria were developed a decade ago, named the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA, that are being used in most of the clinical trials and research studies in this disease [11].

In order to provide an update about the recent progress related to this topic, this manuscript aims to review the most recent findings concerning the diagnosis and classification of patients with axSpA.

Diagnosis

As mentioned earlier, an early diagnosis is becoming essential but it still is an unmet need for patients with axSpA. So many of the recently performed studies have focused on the evaluation and development of new tools to help physicians make an early diagnosis by the identification of efficient screening procedures or referral strategies, evaluation, and possible redefinition of some of the typical SpA features, and also on the development of new biomarkers. The tool in which researchers have invested most of their effort is on the employment of imaging techniques within the diagnostic work-up of patients with suspected axSpA.

Clinical Features

One of the main reasons that could explain the long diagnostic delay is that chronic back pain (CBP), the leading symptom of axSpA, is also a very common symptom among the general population. In this sense, among patients with CBP, the presence of inflammatory characteristics has been shown to be quite specific of axSpA. Traditionally, it has been assumed that most patients with inflammatory back pain (IBP) either have or will develop SpA, but there was no evidence to certainly support this assumption. In fact, taking into account that the prevalence of axSpA is much lower than the prevalence of IBP, the numbers of this assumption did not match. To provide some insight in this regard, a recent retrospective study based on the Rochester Epidemiology Project determined the proportion of patients with new-onset IBP who progress to a diagnosis of SpA [12, 13]. After 15 years, only approximately 30% of patients with IBP progressed to SpA, while IBP symptoms resolved in almost half of the patients. Additionally, the most important predictor to develop SpA identified in patients with IBP was the presence or history of acute anterior uveitis (AAU), and a positive family history of SpA or related features. Currently, a positive family history is defined as the presence in first- or second-degree relatives of AS, psoriasis, reactive arthritis, and inflammatory bowel disease (IBD) [11]. However, a recent study analyzing data from two recent-onset axSpA cohorts, SPondyloArthritis Caught Early (SPACE), and DEvenir des Spondylarthropathies Indifférenciées Récentes (DESIR), suggests that an update of the ASAS definition of a positive family history is needed because a positive family history of reactive arthritis, IBD, or psoriasis did not contribute to identifying axSpA in CBP patients suspected of suffering from axSpA (Table 1) [14].

To date, several referral strategies for patients with suspected axSpA have been developed, comprising at least 13 strategies combining different features, including a positive family history, IBP, and other features typical of SpA. But no study had evaluated all these referral strategies in the same population. In the SPACE cohort, this comparison was performed, and the conclusion of this study revealed that most of the strategies perform well but the selection of the ideal strategy depends on the purpose and on the health system structure where this is meant to be applied. If no patient is to be missed, the ASAS strategy (≥ 1 SpA feature in the presence of CBP with onset at ≤ 45 years of age) would be most preferable because this was shown to have 98% sensitivity. But if the number of referrals needs to be limited, the MASTER strategy seems to perform best [15]. This strategy is defined as the presence of at least two of the following four features: IBP, HLA-B27, good response to non-steroidal anti-inflammatory drugs, and a positive family history of AS, because it will have the highest positive likelihood ratio (LR+ = 2.68) [15].

Biomarkers

So far, the only biomarkers employed in routine clinical practice within the diagnostic procedures for axSpA are HLA-B27 and acute phase reactants. However, their sensitivity and specificity are limited. Previous studies had shown that anti-CD74

Table 1 Presence of AS and/or AAU defines a "positive family history"

	SPACE ($n = 438$)		DESIR ($n = 647$)	
	OR	p value	OR	p value
Any positive family history	2.5	< 0.001	1.4	< 0.05
Ankylosing spondylitis	5.9	< 0.001	3.3	< 0.001
Acute anterior uveitis	9.8	< 0.001	21.6	< 0.01
Reactive arthritis	0.8	0.7	0.1	< 0.1
Inflammatory bowel disease	0.9	0.7	0.8	0.6
Psoriasis	1.1	0.8	0.8	0.2

SPACE, SPondyloArthritis Caught Early; *DESIR*, DEvenir des Spondylarthropathies Indifférenciées Récentes; *OR*, odds ratio. Data from Ez-Zaitouni Z et al. Arthritis Res Ther 2017;19:118

IgA antibodies are elevated in patients with established axSpA, and a recent study including patients from the SPACE cohort has observed that it is also increased in patients with short-disease duration. But unfortunately, the research also concluded that the serum elevation of these antibodies did not yield significant or enough diagnostic value in patients with early CBP [16]. Serum levels of sclerostin and anti-sclerostin antibodies to help identify axSpA in patients with IBD have been investigated in an Italian cohort [17]. Patients with IBD and axial manifestations of SpA had serum levels of sclerostin that did not differ from AS patients (mean ± standard deviation: 129.3 ± 38.6 vs. 126.4 ± 36.93 pg/ml, respectively), but it did differ significantly from IBD patients with peripheral manifestations of SpA (248.9 ± 55.7 pg/ml, $p < 0.001$), and those without SpA (242.5 ± 87.48 pg/ml, $p < 0.01$), and rheumatoid arthritis (249.6 ± 61.33 pg/ml, $p < 0.05$), and healthy controls (263.6 ± 75.5 pg/ml, $p < 0.01$). According to these findings, serum levels of sclerostin might become a useful biomarker to assess the presence of axial involvement in patients with IBD, and require further research studies.

Imaging

Imaging Acquisition

Probably, because of the lack of clinically useful biomarkers, most studies have focused on the application of imaging techniques to identify patients with axSpA in an early phase of the disease. In this regard, researchers first addressed the clinical question of whether or not there is room to improve imaging acquisitions. Conventional radiography of the sacroiliac (SI) joints is recommended as the first imaging method to diagnose sacroiliitis as part of axSpA. But clinicians constantly face problems employing this imaging technique because of its limitations. Firstly, the pelvic anatomy is complex which makes it difficult to get an appropriate image. And secondly, there is moderate inter-reader variability that does not seem to increase with training [18]. Therefore, in order to solve these shortcomings, researchers have evaluated if the use of dedicated sacroiliac views or cross-sectional techniques such as magnetic resonance imaging (MRI) and computerized tomography (CT) can improve imaging acquisition to detect structural lesions. A Canadian study recently evaluated if the employment of the Ferguson view could help to decrease inter-reader variability compared to the anteroposterior pelvic view [19]. There was agreement between both views regarding the interpretation of the readers, with similar but at the same time poor values of intraclass correlation coefficient (0.64–0.75) and kappa (0.5 and 0.3, respectively) scores for both modalities. Thus Ferguson view is not superior to the standard view and therefore either of them can be employed. A comparison of T1-weighted MRI with radiography for detecting structural lesions of the SI joints using low-dose CT as standard of reference (SIMACT study) found the MRI to be superior to radiography and recommend future studies for reaching a consensus to define a positive T1-weighted MRI of the SI joints for structural lesions [20•].

Imaging Abnormalities in Non-axSpA Population

With no doubt, from all published data during the last couple of years, the hot topic has been the examination of imaging abnormalities "typical" of axSpA (bone marrow—BM edema, fat metaplasia, bone sclerosis, erosions, ankylosis) in non-SpA population, especially on MRI (Table 2) [21•, 22••, 23, 24•].

A Dutch study showed the presence of inflammatory lesions at the SI joints in healthy individuals, runners, and women with postpartum back pain. Interestingly, a substantial proportion of this population had an MRI positive for sacroiliitis according to the ASAS definition: 23% of healthy individuals, 13% of runners, and 57% of postpartum women [21•]. However, deep (extensive) BM edema lesions were almost exclusively found in axSpA patients [21•]. Another study also assessed the frequency and anatomic distribution of imaging features in the SI joints of young athletes (hockey players and recreational runners) [22••]. MRI was performed before and after running. BM edema and fat metaplasia were observed in both groups but these lesions did not increase after running. Interestingly, between 30 and 40% of this population fulfilled the ASAS definition for a positive MRI but the most affected region was the posterior lower ilium. In contrast, bone erosions were almost absent in this non-SpA population, which indicates that this type of lesion may be specific for axSpA [22••, 23].

Table 2 Healthy population with a positive magnetic resonance imaging according to ASAS definition included in the recent research studies

	N	Positive MRI (%)
de Winter et al		
Healthy controls	47	23
Frequent runners	24	13
Postpartum women	7	57
Weber et al.		
Hockey players	22	35
Recreational runners (before running)	20	30
Recreational runners (after running)	"	41
Varkas et al.		
Military recruits (before training)	22	23
Military recruits (after training)	"	36

MRI, magnetic resonance imaging. Data from de Winter J et al., Arthritis Rheumatol 2018;70:1042–8; Weber U et al., Arthritis Rheumatol 2018;70:736–45; Varkas G et al., Rheumatology (Oxford) 2018;57:508–13

Also, the influence of possible factors on the detection of MRI abnormalities in non-SpA population has been investigated. A Belgium study did not observe any effect of mechanical stress in military recruits evaluated before and 6 weeks after intensive physical training; neither the inflammatory nor the structural MRI lesions increased after the intensive training [24•]. Furthermore, the possible influence of age on MRI structural lesions occurrence was investigated by a retrospective German study including over 450 participants [25]. This study concluded that sclerosis, osteophytes, and especially fat metaplasia are observed on the MRI of sacroiliac joints in people without SpA, while erosions were almost not observed. Of interest, the extent of fat metaplasia clearly increased with age, being present in more than 75% of patients older than 75 years (Fig. 1) [25].

Finally, the presence of inflammatory and structural lesions in athletes has also been evaluated using ultrasound technique, employing the Madrid Ankylosing Spondylitis Enthesitis Index (MASEI) [26]. In this study, a group of non-athlete controls and a group of patients with SpA were also included. Both, inflammatory and structural lesions were found in all groups but the MASEI score was significantly higher in patients with axSpA while no significant differences were observed between athletes and non-athletes control groups: (mean ± standard deviation 26.3 ± 13, 12.2 ± 7, and 10.4 ± 6, $p < 0.0001$; respectively) [26].

All these findings in the non-SpA population (Table 2) highlight the importance of considering the clinical context in the interpretation of images acquired through the diagnostic procedure in patients with suspected axSpA. In fact, a recent study has shown that imaging of the SI joints is important for diagnosing early axSpA but it is not all-decisive [27••]. Therefore, it is essential to think about other possible diseases causing changes in the SI joint, such as osteiitis condesans ilii, gout, and diffuse idiopathic skeletal hyperostosis (DISH) [28–30]. So, in summary, we can conclude that it is true that a picture is worth a thousand words, but when this refers to axSpA, we need to remember that imaging is important for diagnosing early axSpA but not pathognomonic.

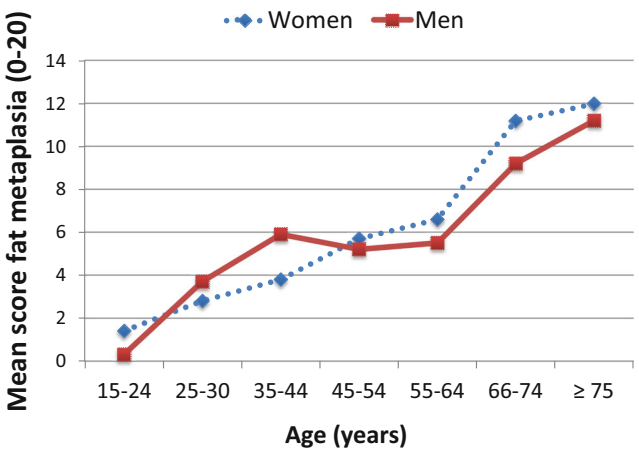

Figure 1 Patterns of bone marrow fat metaplasia according to age, stratified for gender. Data from Ziegeler K et al. J Rheumatol 2018;45:915–21

Classification

The classification criteria employed in most of the current clinical trials and research studies are the ASAS classification criteria for axial SpA [11]. These were published in 2009 and have an entry requirement of presence of low back pain for at least 3 months that has its onset before age 45. The criteria have two possible entry arms: the imaging arm (through the presence of sacroiliitis on radiography or MRI) and the clinical arm (through the presence of HLA-B27). To classify a patient as axial SpA, in addition to one of these entry criteria, the presence of at least one (or two, in case of the clinical arm) of the typical characteristics of SpA is required. These characteristics include the following: inflammatory back pain, inflammatory arthritis, enthesitis, uveitis, dactylitis, psoriasis, inflammatory bowel disease, good response to non-steroidal anti-inflammatory drugs, family history of SpA, presence of HLA-B27, and elevated CRP. Despite the fact that ASAS criteria are well implemented, several concerns have been raised during the last years. Accordingly, recent studies have focused on providing scientific evidence to clarify these concerns.

Imaging

The use of imaging to properly classify patients has been an important topic of research in recent years. As it is well known, to define a positive MRI according to ASAS criteria only, BM edema and the SI region are considered. So, the question that arises is what would the impact (if any) be if other type of lesions or regions is included under this definition.

To answer this question, two studies were recently performed. The first one analyzed SPACE cohort data to investigate any impact of replacing radiography by MRI to observe structural lesions of the SI joints, or adding these lesions to the ones observed on radiography when classifying patients with axSpA [31]. It concluded that this often did not result in a different ASAS classification as most patients just changed from one subcategory to another, rather than becoming ASAS axSpA criteria positive or negative. The second study analyzed data from SPACE and DESIR cohorts to investigate if adding inflammatory lesions on MRI of the spine has an effect on the classification of patients with axSpA [32]. In patients with suspected axSpA without sacroiliitis on MRI of the SI joints, a positive MRI of the spine was found to be rare (in less than 2% of these patients). So, according to these

results, the addition of MRI of the spine to the ASAS axSpA criteria has a low yield of newly classified patients and therefore is not recommended for this purpose.

Validity of ASAS Criteria

In the original study, the ASAS criteria for axial SpA showed an overall sensitivity of 83% and a specificity of 84%. However, during the last years, some experts had raised some concerns related to the criteria, including the lack of worldwide validation and the insufficient specificity of the clinical entry arm. Recently, a meta-analysis compromising more than 5500 patients from eight different cohorts worldwide has been published [33••]. The results support good performance of these criteria as tested against the rheumatologist's diagnosis, with an observed sensitivity of 82% (95% confidence interval 77–86%) and specificity of 89% (95% confidence interval 78–92%). Furthermore, a recent study analyzed data from the ASAS-COMOSPA study, which included more than 3000 patients from 26 different countries across the world [34]. In this population, most patients with a clinical diagnosis of axSpA fulfilled several classification criteria, including the ASAS criteria, and patients fulfilling the clinical arm were similar to patients fulfilling the imaging arm [34]. Remarkably, large inter-regional differences were not found.

Nevertheless, despite these data, the Spondyloarthritis Research and Treatment Network (SPARTAN) from North America and ASAS have finally agreed to run the "Classification of Axial Spondyloarthritis Inception Cohort" (CLASSIC) study. Its aim is not to develop new criteria but to validate the ASAS axSpA classification criteria in a worldwide study, which will run with appropriate sample size calculations for North America and the rest of the world. A minimum sensitivity and specificity have been established. If this is achieved, the ASAS classification criteria will be considered as validated worldwide. But if this is not achieved, further actions will be taken in order to improve the sensitivity and specificity of the criteria.

Overdiagnosis

Despite the fact that classification criteria should not be employed for diagnostic purpose, one of the major concern raised after the development of the ASAS axSpA classification criteria was the possible overdiagnosis of axSpA by physicians erroneously using these classification criteria to diagnose the disease, and subsequent erroneous treatment decisions leading to the administration of expensive and potentially hazardous biological therapy to non-SpA patients [35]. In this context, the main concern was the specificity of the clinical arm of the ASAS criteria, and especially the possibility of over-treating women with fibromyalgia (FM).

Recently, Baraliakos et al. analyzed the similarities and differences among patients diagnosed with axSpA and those with FM, with the objective of determining if patients with FM can be classified erroneously as having axSpA when applying the ASAS classification criteria for axSpA in clinical practice [36••]. Importantly, they observed that patients with FM rarely fulfilled the ASAS criteria, and, also, that patients with established AS fulfilled FM criteria more often than patients classified as nr-axSpA. This study provided relevant data to clarify the concerns related to the possible overtreatment of patients with FM as a consequence of biological therapy approval for nr-axSpA, but further research studies are needed to clarify this point.

Conclusions

This review summarizes the most relevant recent findings of diagnosis and classification of axSpA. Based on the published data, it is clear that this topic provokes great interest for clinicians and researchers working in the field of axSpA. A number of studies have focused on setting the best strategy for early referral of patients with suspected axSpA. All available strategies for referral seem to perform well but the model to be selected depends on the context. In this regard, it is important to keep in mind that IBP is neither necessary nor sufficient to diagnose axSpA. The most recent studies have concentrated on evaluating the diagnostic utility of different tools employed during the diagnostic work-up, with special interest in imaging techniques. In this sense, imaging has shown to be important for diagnosing axSpA but is not all-decisive. When interpreting imaging findings of the SI joints, it is important to consider the limitations of imaging acquisition, the appropriate context and also other possible differential diagnoses. Moreover, while dedicated views of the SI joints have not shown to be superior to the standard anteroposterior radiograph of the pelvis, MRI has higher sensitivity and better inter-reader agreement to detect bone erosions compared to conventional radiographs. Finally, posterior lower ilium BM edema and fatty lesions may be frequently found in non-SpA population, but bone erosions and deep BM edema seem to be specific of axSpA.

Last but not least, researchers have also addressed some concerns raised about the implementation of the ASAS classification criteria, especially those related to the validity and misuse of the criteria. Recent data support the worldwide validation of the ASAS classification criteria. Only a minority of patients with FM fulfill the ASAS criteria. But most importantly, we need to keep in mind that classification criteria can never substitute the complex process of clinical diagnosis making, which is an art combining pattern recognition and clinical reasoning.

Compliance with Ethical Standards

Conflict of Interest Dr. Victoria Navarro-Compán has received unrelated honoraria or research grants from Abbvie, BMS, Lilly, MSD, Novartis, Pfizer, Roche, and UCB. She is also a member of ASAS.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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