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Early recognition of axial spondyloarthritis: imaging and genetic aspects

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Are additional tests needed to rule out axial spondyloarthritis in patients ages 16 - 45 years with short-duration chronic back pain and maximally one spondyloarthritis feature?

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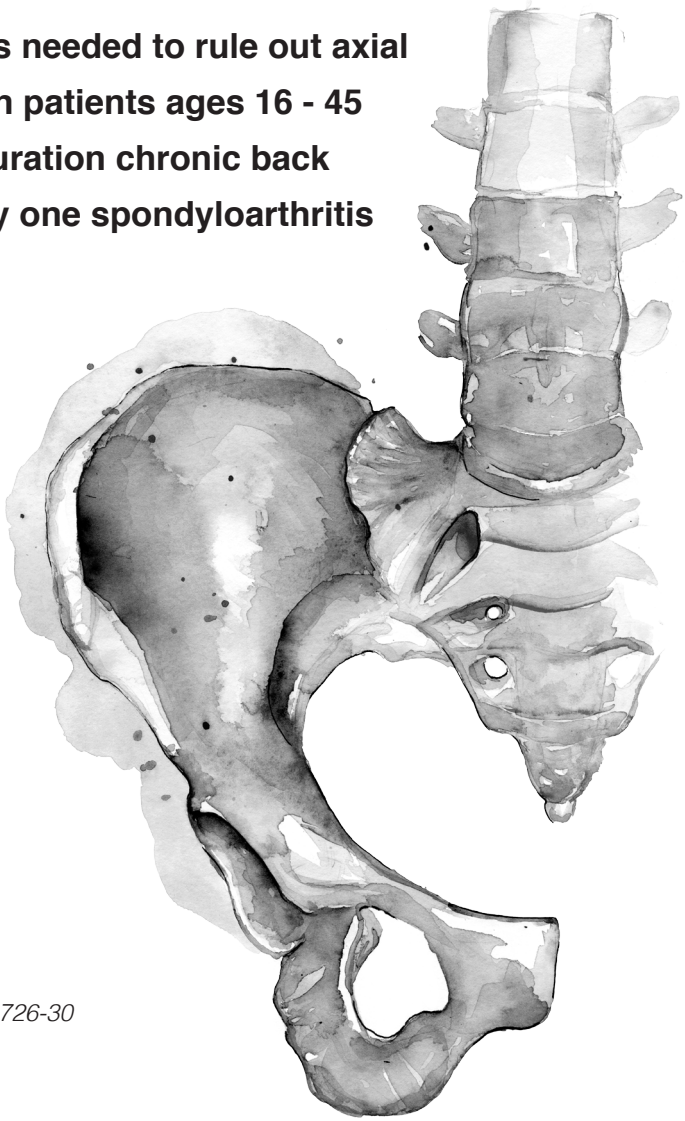

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ABSTRACT

Objective

To investigate whether HLA–B27 testing and imaging of the sacroiliac joints are needed in patients with ≤1 spondyloarthritis (SpA) feature, referred to a secondary care setting, after medical history collection, clinical examination, and measurement of acute phase reactants.

Methods

Baseline data from patients in the Spondyloarthritis Caught Early (SPACE) cohort visiting the rheumatology outpatient clinic of 5 centers across Europe (with back pain ≥3 months, ≤2 years, onset at ages <45 years) were used. All patients underwent a full diagnostic work-up: magnetic resonance imaging (MRI) and radiographs of the sacroiliac joints, HLA–B27 testing, and assessment of all other SpA features. Patients were diagnosed according to the treating rheumatologist and classified according to the Assessment of SpondyloArthritis international Society (ASAS) axial SpA criteria.

Results

Of the 354 patients, 133 (37.5%) showed 0 or 1 SpA feature after medical history collection, physical examination, and measurement of acute phase reactants (38 without SpA features, 95 with 1 SpA feature). Of the patients with ≤1 SpA feature, 18.4% (with 0 SpA features) and 17.9% (with 1 SpA feature) were diagnosed with axial SpA according to the rheumatologist after additional investigations (HLA–B27 testing and sacroiliac joint imaging). Additionally, 4 of 38 patients (10.5%) without SpA features fulfilled the ASAS axial SpA criteria (all according to the imaging arm only: 2 as MRI+/modified New York criteria (mNY)+,1 as MRI+/mNY-, and 1 as MRI-/mNY+). Of the 95 patients with 1 SpA feature, 22 (23.2%) fulfilled the ASAS axial SpA criteria (all according to the imaging arm only: 3 as MRI+/mNY+, 15 as MRI+/mNY-, and 4 as MRI-/mNY+).

Conclusions

In these patients in a secondary care setting with ≤1 SpA feature, axial SpA could not be ruled out without sacroiliac joint imaging and/or HLA–B27 testing.

INTRODUCTION

Axial spondyloarthritis (SpA) is a heterogeneous disease, and the diagnostic process can be challenging, since chronic back pain (CBP) is a very common symptom.[1] Nevertheless, diagnosis is important, as effective treatments are available and treatment at an early stage may lead to a better outcome, i.e., achieving low disease activity or even remission and possibly the prevention of structural damage as well.[2–6] Additionally, an early diagnosis reduces uncertainties in patients and prevents unnecessary diagnostic procedures.

In clinical practice, axial SpA can be diagnosed by recognition of a characteristic pattern of clinical, laboratory, and imaging findings. Through medical history collection, physical examination, and measurement of acute phase reactants, information on the presence of SpA features should be obtained in patients suspected of axial SpA (e.g., presence of enthesitis or uveitis anterior).[7] Additionally, testing for the presence of HLA–B27 and imaging of the sacroiliac (SI) joints using pelvic radiographs and/or magnetic resonance imaging may provide essential clues on the presence of axial SpA. The presence or absence of all those different SpA features determines the likelihood of diagnosis.[8] Unfortunately, there is no single SpA feature with sufficient specificity to establish the diagnosis early, and no formal diagnostic criteria exist.[9,10]

The modified Berlin algorithm may aid clinicians in establishing an early diagnosis of axial SpA with greater confidence.[11] According to the algorithm, an SI radiograph should be obtained in all patients with CBP (duration ≥3 months and ≤2 years, age at onset at ages <45 years) visiting the rheumatologist. Afterward, the presence of other SpA features should be evaluated. In case of 0 or 1 SpA feature, HLA–B27 testing is suggested, and if positive an MRI of the SI joints should be performed.

A downside of the algorithm is that radiographs are advised in all referred patients, regardless of the presence of other SpA features, meaning that all patients are subjected to ionizing radiation. Furthermore, after performing SI radiographs, medical history collection, physical examination, and measurement of acute phase reactants, the algorithm does not distinguish between patients with 0 or 1 SpA feature and recommends HLA–B27 testing in all patients, even though patients with no SpA features at that point may have a very low likelihood of axial SpA.

To address these issues, this study aimed to investigate whether additional investigations are useful in patients ages 16–45 years with back pain and ≤1 SpA feature (after clinical examination, physical examination, and C-reactive protein [CRP] level/erythrocyte sedimentation rate [ESR] measurement, but before HLA–B27 testing and imaging of the SI

joints). The study also aimed to investigate whether results are different in patients without SpA features or with 1 SpA feature.

METHODS

Study population

Baseline data from the Spondyloarthritis Caught Early (SPACE) cohort of patients included between January 2009 and October 2014 were used for this analysis. For this study, a subgroup of the SPACE cohort was used, namely patients with 0 or 1 SpA feature after medical history and physical examination, but before imaging and HLA–B27 testing. An extensive description of the cohort as a whole is available elsewhere.[12] In short, SPACE is a multinational, multicenter inception cohort study of young patients with CBP of a short duration (≥3 months but ≤2 years, with the onset at ages <45 years), with a suspicion of SpA referred to a rheumatologist.

Inclusion took place at 5 participating centers in The Netherlands (Leiden, Amsterdam, Gouda), Norway (Oslo), and Italy (Padua). Approval for the study was obtained from the local medical ethics committees. Patients were referred to the outpatient clinic of the different participating centers. All patients were first assessed by the rheumatologist. In case of suspected SpA, patients could be included in the SPACE cohort. Before inclusion, patients gave written informed consent in accordance with the declaration of Helsinki.

Diagnostic work-up

All patients underwent a full diagnostic work-up according to a fixed protocol. This work-up consisted of SI MRI and radiographs, HLA–B27 testing, and assessment of all other SpA features: inflammatory back pain (IBP), peripheral arthritis, enthesitis, acute anterior uveitis, dactylitis, psoriasis, inflammatory bowel disease (IBD), good response to nonsteroidal anti-inflammatory drugs (NSAIDs), a positive family history for SpA, and elevated CRP level and/or ESR.

Imaging of the SI joints

The MRIs were performed on a 1.5T machine. The acquired sequences were coronal oblique T1-weighted turbo spin-echo (repetition time [TR] 550/ echo time [TE] 10) and STIR (TR 2500/TE 60) with a slice thickness of 4 mm. The images were performed in a coronal oblique view. Radiologists of the different centers interpreted the radiographs and MRIs of the SI joints for the presence of sacroiliitis. This process was done as part of routine clinical practice, interpreting MRI using global assessment of the images (sacroiliitis yes/no) and interpreting radiographs according to the modified New York criteria. While reviewing the

images, radiologists took differential diagnoses such as hernia, osteoarthritis, and so on, into account.

Outcome: diagnosis of axial SpA and classification according to the Assessment of SpondyloArthritis international Society (ASAS) axial SpA criteria

Following the work-up discussed before (including HLA–B27 testing and imaging), the treating rheumatologist was asked to provide a diagnosis of axial SpA (yes/no) and provide a certainty of assessment for that diagnosis on a 1–10 scale. In addition, patients were classified according to the ASAS axial SpA criteria (yes/no).[13] This classification was done after all information, including imaging and HLA–B27 testing results, was obtained. Data were analyzed using Stata SE software, version 12.

RESULTS

In the SPACE cohort, after medical history collection, physical examination, and measurement of acute phase reactants, 133 of 355 patients (37.5%) had 0–1 SpA features, 44.7% had 2–3 SpA features, and 17.9% had ≥4 SpA features. For this study, the 133 patients with ≤1 SpA feature were included (95 with 1 SpA feature, 38 without SpA features). Patient characteristics for both groups are described in Table 1.

Table 1: Baseline characteristics of patients with ≤1 SpA feature

	Patients with 0 features Total number (n=38)	**Patients with 1 feature** Total number (n=95)	**All patients in the cohort** Total number n (n=354)
Age (years) at inclusion, mean (SD)	29.7 (9.6)	32.1 (8.4)	31.1 (8.4)
Male, n (%)	14 (36.8)	26 (27.4)	119 (33.6)
Symptom duration (months), mean (SD)	10.4 (6.1)	13.3 (7.5)	12.9 (7.2)
IBP, n (%)	-	38 (40.0)	220 (62.2)
Good response to NSAIDs, n (%)	-	12 (12.6)	119 (33.6)
Positive family history SpA, n (%)	-	20 (21.1)	130 (36.7)
Peripheral arthritis, n (%)	-	2 (2.1)	45 (12.7)
Dactylitis, n (%)	-	0 (0)	15 (4.2)
Enthesitis, n (%)	-	2 (2.1)	52 (14.7)
Uveitis, n (%)	-	1 (1.1)	26 (7.3)
IBD, n (%)	-	8 (8.4)	29 (8.2)
Psoriasis, n (%)	-	2 (2.1)	34 (9.6)
Elevated CRP, n (%)	-	8 (8.4)	76 (21.5)
HLA-B27 positive, n (%)	7 (18.4)	22 (23.2)	127 (35.9)
Sacroiliitis radiograph mNY, n (%)	3 (7.9)	7 (7.4)	36 (10.2)
Sacroiliitis MRI, n (%)	8 (21.1)	18 (19.0)	88 (24.9)

SpA, spondyloarthritis; IBP, inflammatory back pain; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; CRP, C-reactive protein; HLA-B27, human leukocyte antigen B27; mNY, modified New York criteria; MRI, magnetic resonance imaging.

Patients with 0 or with 1 SpA feature had a mean ± SD age of 29.7 ± 9.6 years and 32.1 ± 8.4 years, respectively. Mean duration of back pain was 10.4 ± 6.1 months and 13.3 ± 7.5 months, respectively. For comparison, disease characteristics of the SPACE cohort as a whole are shown in Table 1. In the group without SpA features, 18.4% was HLA-B27 positive versus 23.2% in the group with 1 SpA feature. Sacroiliitis on radiographs was seen in 7.9% and on MRI in 21.1% of patients without SpA features versus 7.4% and 19.0% (radiographs and MRI, respectively) of patients with 1 SpA feature (Table 1). Notable differences among the extra-articular manifestations in the group of patients with 1 SpA feature were seen: specifically, IBD (8.4%) was more frequently present, compared to uveitis (1.1%) and psoriasis (2.1%).

Of the 38 of 133 patients (28.6%) with no SpA features after additional investigations, 4 (10.5%) were classified according to the ASAS axial SpA criteria (Table 2). Three of those 4 were also diagnosed as having axial SpA by the rheumatologist. Four additional patients were diagnosed as having axial SpA by the rheumatologist but did not fulfill the ASAS axial SpA criteria.

A striking finding is that two of these patients were diagnosed as having axial SpA in the absence of both HLA–B27 positivity and sacroiliitis on both imaging modalities. In these two patients, certainty of diagnosis was 3 and 8, respectively (on a 1–10 scale, with 10 implying great certainty and 1 little certainty about diagnosis). Review of the MRI showed that the patient with a diagnosis of axial SpA with a high certainty (8 of 10) had clear evidence of SpA-associated structural lesions in the absence of inflammatory lesions on MRI or radiographic sacroiliitis. This evidence could have contributed to the SpA diagnosis.

Of the 95 of 133 patients (71.4%) with 1 SpA feature, 22 (23.2%) fulfilled the ASAS axial SpA criteria. Seventeen of the 95 patients (17.9%) were diagnosed as having axial SpA by the rheumatologist. Of these 17 patients, 14 were also classified via the ASAS axial SpA criteria, and the remaining 3 patients were not. In contrast, 5 patients were classified according to the ASAS axial SpA criteria, while not being diagnosed as having axial SpA according to the rheumatologist (data on diagnosis missing in 2 patients).

Of the patients with 1 feature who were classified according to the ASAS axial SpA criteria, the SpA features that were present before imaging and HLA–B27 testing were as follows: 7 patients had IBP, 5 had IBD, 4 had a positive family history for SpA, 3 had a good response to NSAIDs, 2 had elevated CRP levels and/or ESR, and 1 patient had enthesitis. The SpA features present in the patients who were diagnosed by a rheumatologist with axial SpA (among patients with 1 SpA feature) were as follows: 4 had a positive family history of SpA, 4 had IBP, 4 had IBD, 3 had an elevated CRP level and/or ESR, 1 had enthesitis, and 1 patient had a good response to NSAIDs.

In the 133 patients with ≤1 SpA feature, radiographic results were negative in 123 patients. Nineteen of those 123 patients (15%) were eventually diagnosed as having axial SpA after MRI and HLA–B27 testing were done. Of the 133 patients with ≤1 SpA feature, HLA–B27 was negative in 104 patients, of which 14 (13.5%) were eventually diagnosed with axial SpA. However, of the 133 patients, MRI was negative in 107, of which only 7 (6.5%) were diagnosed as having axial SpA.

Table 2: Effect of HLA–B27 testing and sacroiliac joint imaging on diagnosis and classification

Number of SpA-features	HLA-B27 status	Imaging status	SpA diagnosis yes	ASAS axSpA classification yes	SpA diagnosis no	ASAS axSpA classification no
0 (n=38)	HLA-B27 + (n=7)	MRI+ mNY+	2	2		
		MRI+ mNY-	1	1		
		MRI- mNY+		1	1	
		MRI- mNY-	2		1	3
	HLA-B27 – (n=31)	MRI+ mNY+				
		MRI+ mNY-	2		2*	5
		MRI- mNY+				
		MRI- mNY-			26	26
1 (n=95)	HLA-B27 + (n=22)	MRI+ mNY+		2	1*	
		MRI+ mNY-	3	4	1	
		MRI- mNY+		1	*	
		MRI- mNY-	2		12*	15
	HLA-B27 – (n=73)	MRI+ mNY+	1	1		
		MRI+ mNY-	8	11	3	
		MRI- mNY+	2	3	1	
		MRI- mNY-	1		57	58
Total			24	26	105	107

Asterisk (*) diagnosis by rheumatologist is missing.
SpA, spondyloarthritis; axSpA, axial spondyloarthritis; HLA-B27, human leukocyte antigen B27; ASAS, Assessment of SpondyloArthritis international Society; mNY, modified New York criteria; MRI, magnetic resonance imaging.

DISCUSSION

In patients with CBP referred to a rheumatologist and with ≤1 SpA feature, after full medical history collection, physical examination, and CRP level/ESR measurement, subsequent HLA–B27 testing and imaging led to a diagnosis of axial SpA in almost 20% of both patient groups. In both the group of patients with 0 SpA features and patients with 1 SpA feature, 20% were diagnosed with axial SpA, and therefore the number of SpA features present was not a differentiating factor in this study. Additionally, fulfilment of the ASAS axial SpA criteria was seen in 11% and 23% of the patients without SpA features and with 1 SpA feature, respectively.

Although we were expecting some patients to have a diagnosis of axial SpA, we were surprised by the relatively high percentages, in particular in the group with no SpA features. Several factors may have contributed to this unexpected finding. The preselection of patients could be an important explanation for this result: only patients ages <45 years were included and with a short duration of back pain (≤2 years). Diagnosis could also be influenced by the presence of SpA features that are not incorporated in the criteria, i.e., the presence of syndesmopohytes, inflammation on an MRI of the spine, or structural lesions on MRI of the SI joints. On the other hand, it is important to put the high percentages of an SpA diagnosis into perspective. Diagnosing SpA can be a challenge, especially in the absence of sacroiliitis on imaging. This clinical manifestation of SpA is heterogeneous, and diagnostic criteria are lacking.

A strength of this study is that we applied both diagnosis and classification. Taken together, these data support the ASAS modified Berlin algorithm in its recommendation to perform additional investigations in patients with 0 and 1 SpA feature in a secondary setting. Although differences exist between patients without and patients with 1 SpA feature, even in patients without SpA features, after medical history collection, physical examination, and CRP level/ESR measurement, we cannot entirely rule out axial SpA.

However, it should be taken into account that the SPACE cohort consists of patients with CBP with ≤2 years of symptoms. As radiographic changes may develop over time[14] radiography may not be the ideal first diagnostic step (as the modified Berlin algorithm suggests) in these young patients with a short symptom duration. This conclusion was underlined by the fact that the yield of radiographs was very low in this study, and as a comparison the yield of MRI is much higher. For future studies, investigating the additional benefit of structural lesions on a T1-weighted MRI of the SI joints should be relevant.

A limitation of this study is that the radiologists performed a global assessment of sacroiliitis rather than the ASAS definition for a positive MRI, and that we used this global assessment while applying the ASAS axial SpA classification criteria.[15] In addition, and in line with common clinical practice, only one reader interpreted the images instead of reading by several readers, although we assume that in the majority of cases the treating rheumatologist read the images as well.

An important strength of the study is that SPACE is an inception cohort for young patients with CBP (duration ≥3 months and ≤2 years, onset at ages <45 years), allowing us to investigate whether patients with very few symptoms can still be diagnosed and classified as having axial SpA. To our knowledge, SPACE is currently one of the very few, if not the only, sufficiently large longitudinal cohort study in the field of spondyloarthritis where patients without SpA features can also be included, which has allowed us to perform the current study. Since this study was performed in a secondary-care setting (patients referred to a rheumatologist, with a suspicion for axial SpA), we would like to emphasize that the results of this study cannot be extrapolated to CBP patients where the prevalence of axial SpA is much lower, as in primary care.

In conclusion, in a secondary-care setting, in patients with ≤1 SpA feature, after full medical history collection, physical examination, and CRP level/ESR measurement, axial SpA cannot be ruled out without additional imaging and/or HLA–B27 testing. In addition, these results also show that in selected cases diagnosis is entirely based on HLA–B27 testing and imaging.

REFERENCES

1. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain 2003;102: 167–78.
2. Landewé R, Braun J, Deodhar A, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing spondylitis: 24-week results of a double-blind randomized placebo-controlled Phase 3 study. Ann Rheum Dis 2014;73: 39–47.
3. Sieper J, Lenaerts J, Wollenhaupt J, et al. Efficacy and safety of infliximab plus naproxen versus naproxen alone in patients with early, active axial spondyloarthritis: results from the double-blind, placebo-controlled INFAST study, Part 1. Ann Rheum Dis 2014;73: 101–7.
4. Sieper J, Lenaerts J, Wollenhaupt J, et al. Maintenance of biologic-free remission with naproxen or no treatment in patients with early, active axial spondyloarthritis: results from a 6-month, randomised, open-label follow-up study, INFAST Part 2. Ann Rheum Dis 2014;73: 108–13.
5. Van der Heijde D, Joshi A, Pangan AL, et al. ASAS40 and ASDAS clinical responses in the ABILITY-1 clinical trial translate to meaningful improvements in physical function, health-related quality of life and work productivity in patients with non-radiographic axial spondyloarthritis. Rheumatology (Oxford) 2016;55: 80–8.
6. Claudepierre P. Spondyloarthritis: a window of opportunity? Joint Bone Spine 2014;81: 197–9.
7. Van Tubergen A, Weber U. Diagnosis and classification in spondyloarthritis: identifying a chameleon. Nat Rev Rheumatol 2012;8: 253–61.
8. Rudwaleit M, van der Heijde D, Landewé R, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2011;70: 25–31.
9. Rudwaleit M, van der Heijde D, Khan MA, et al. How to diagnose axial spondyloarthritis early. Ann Rheum Dis 2004;63: 535–43.
10. Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis: do we need new criteria? Arthritis Rheum 2005;52: 1000–8.
11. Van den Berg R, de Hooge M, Rudwaleit M, et al. ASAS modification of the Berlin algorithm for diagnosing axial spondyloarthritis: results from the Spondyloarthritis Caught Early (SPACE)-cohort and from the Assessment of SpondyloArthritis international Society (ASAS)-cohort. Ann Rheum Dis 2013;72: 1646–53.
12. Van den Berg R, de Hooge M, van Gaalen F, et al. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. Rheumatology (Oxford) 2013;52: 1492–9.
13. Rudwaleit M, van der Heijde D, Landewé R, et al. The development of Assessment of Spondyloarthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68: 777–83.
14. Poddubnyy D, Haibel H, Braun J, et al. Clinical course over two years in patients with early nonradiographic axial spondyloarthritis and patients with ankylosing spondylitis not treated with tumor necrosis factor blockers: results from the German spondyloarthritis inception cohort. Arthritis Rheumatol 2015;67: 2369–75.
15. Rudwaleit M, Jurik AG, Hermann KG, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009;68: 1520–7.

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