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Keep an Eye on the Back: Spondyloarthritis in Patients With Acute Anterior Uveitis

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Objectives. This study was undertaken to analyze the prevalence of spondyloarthritis (SpA) in patients with acute anterior uveitis (AAU), to identify parameters associated with the presence of SpA, and to evaluate the performance of referral algorithms for identifying patients with a high probability of having SpA.

Methods. Prospectively recruited consecutive patients with noninfectious AAU underwent structured rheumatologic assessment including magnetic resonance imaging of the sacroiliac joints, allowing a definitive diagnosis/exclusion of concomitant SpA. Fisher's exact test and Mann-Whitney U test were used to compare AAU patients with SpA and AAU patients without SpA. Furthermore, logistic regression analyses were performed. The predictive performance of SpA referral strategies was analyzed by calculating the sensitivity, specificity, positive predictive value, and positive and negative likelihood ratios.

Results. Among the 189 AAU patients evaluated, 106 (56%) were diagnosed as having SpA. The majority of SpA patients (93%) had predominantly axial SpA and 7 patients had peripheral SpA. In 74 patients (70%), the SpA diagnosis was established for the first time. In multivariable logistic regression analysis, psoriasis (odds ratio [OR] 12.5 [95% confidence interval (95% CI) 1.3–120.2]), HLA–B27 positivity (OR 6.3 [95% CI 2.4–16.4]), elevated C-reactive protein level (OR 4.8 [95% CI 1.9–12.4]), and male sex (OR 2.1 [95% CI 1.1–4.2]) were associated with the presence of SpA. None of the ophthalmologic parameters were found to be predictive of SpA. The Dublin Uveitis Evaluation Tool (DUET) showed higher specificity for SpA recognition than the Assessment of SpondyloArthritis international Society (ASAS) tool for the early referral of patients with a suspected diagnosis of axial SpA (specificity for SpA 42% versus 28%), whereas the sensitivity of the ASAS tool was slightly higher than the DUET tool (sensitivity for SpA 80% versus 78%). However, more than 20% of the AAU patients in this study who were diagnosed as having SpA would have been missed by both referral strategies.

Conclusion. Our study revealed a high prevalence of SpA in AAU patients overall, as well as a high prevalence of previously undiagnosed SpA in AAU patients. Therefore, we propose rheumatologic evaluation for all AAU patients with musculoskeletal symptoms.

INTRODUCTION

Acute anterior uveitis (AAU) and spondyloarthritis (SpA) are inflammatory diseases with clear association and concomitance. Both are supposed to result from a complex interplay between genetic predisposition (mainly HLA–B27 positivity) and external triggers such as mechanical stress, microbiome, and/or infection that subsequently lead to the activation of the immune system (1). The

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linkage between uveitis and both SpA and HLA–B27 positivity was already known in 1973 (2). AAU is the most frequent extramusculoskeletal manifestation in SpA, occurring in up to one-third of patients (3,4). Uveitis develops more frequently in HLA–B27–positive SpA patients, and its prevalence increases with the duration of disease. Moreover, concomitant AAU is associated with peripheral manifestations in SpA patients (5). The reported prevalence of SpA in AAU patients ranges widely between 20% and 78% (6–15), which may be the result of differences in the designs of previous studies, as some studies focused on subgroups of AAU patients (e.g., with recurrent AAU or HLA–B27 positivity) and some focused on patients without a known diagnosis of SpA.

Axial SpA remains one of the rheumatic diseases with the longest diagnostic delay (16). The presence of uveitis is associated with longer time between symptom onset and diagnosis (17,18). Early diagnosis is essential for effective treatment and prevention of structural damage. Moreover, the diagnosis of underlying SpA introduces the option of treating with biologic disease-modifying antirheumatic drugs (bDMARDs) that are not approved for the treatment of AAU, but which are efficacious for treating acute flares and preventing the recurrence of symptoms (1). As ophthalmologic manifestations might be the first reason to consult a specialist, effective referral strategies for AAU patients could reduce the delay in the diagnosis of SpA.

Different referral strategies have been proposed. Wach et al suggested rheumatologic evaluation of AAU patients with back pain even if they did not fulfill the criteria for inflammatory back pain (IBP) (11). Sykes et al recommended referring patients with chronic back pain beginning before the age of 45 years (12), which follows the Assessment of SpondyloArthritis International Society (ASAS) recommendation for the referral of patients with suspected axial SpA by non–rheumatology specialists (19). In a study in which AAU patients were evaluated for referral with the Dublin Uveitis Evaluation Tool (DUET) (6), it was recommended that AAU patients with either chronic back pain starting before the age of 45 years or those with joint pain requiring medical care should be sent to rheumatologists if they are either HLA–B27–positive or they have psoriasis (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42315).

The objectives of our study were to analyze the prevalence of concomitant SpA in an unselected cohort of noninfectious AAU patients, to identify parameters associated with the presence of SpA, and to evaluate the performance of existing referral algorithms (DUET and ASAS) in identifying patients with a high probability of SpA.

PATIENTS AND METHODS

Patients. Consecutive patients with AAU attending the ophthalmologic clinics of Charité–Universitätsmedizin Berlin, an academic medical center, or from practice-based ophthalmologists in Berlin were prospectively included in this cross-sectional study between July 2017 and April 2021. The inclusion criterion for this study was having an ophthalmologic diagnosis of noninfectious AAU according to the Standardization of Uveitis Nomenclature (SUN) for reporting clinical data (20), and the exclusion criterion was age below 18 years. All patients provided written informed consent. The study was approved by a local ethics committee and conducted according to the Declaration of Helsinki and the Principles of Good Clinical Practice.

Ophthalmologic assessment. Ophthalmologists were asked to provide an ophthalmologic examination of the included patients. The SUN grading scheme was used to assess cells and haze in the anterior chamber and the vitreous body (21). Intraocular pressure and visual acuity were measured in both eyes. The presence of hypopyon, synechia, and fibrinous reaction was recorded.

Rheumatologic examination and imaging. Patients underwent a structured examination by a rheumatologist at the dedicated SpA clinic of the Charité, which included the collection of demographic data and disease history, the evaluation of SpA parameters, spinal mobility (Schober's test and lateral flexion), patient-reported outcomes, and laboratory parameters (HLA–B27, C-reactive protein [CRP] level, and erythrocyte sedimentation rate [ESR]), and imaging. A CRP level of ≥5 mg/liter was defined as being elevated. IBP was classified according to the ASAS criteria for IBP (22). Disease activity was assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (23), patient global assessment, and the Ankylosing Spondylitis Disease Activity Score (ASDAS) (24). Functional status was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI) (25).

Patients were diagnosed by the rheumatologist as having predominantly axial or peripheral SpA based on all obtained data. Pelvic radiography was performed only in patients with back pain. Axial SpA was graded as nonradiographic or radiographic, with the latter being chosen if definitive sacroiliitis fulfilling the modified New York criteria for ankylosing spondylitis (26) was present on radiography.

All patients without contraindications irrespective of back pain underwent magnetic resonance imaging (MRI) of the sacroiliac (SI) joints with STIR, T1-weighted, and volumetric interpolated breath-hold examination (VIBE) sequences in semicoronal planes.

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For diagnosis, the rheumatologist assessed all clinical, laboratory, and imaging information, including MRI of the SI joints. After the study enrollment, all MRIs were anonymized and independently scored by 7 experienced and calibrated readers. The presence of active inflammatory and structural lesions was determined by reader consensus (≥4 of 7 readers) and lesions were scored according to the updated ASAS MRI working group definitions of MRI lesions in the SI joints of patients with SpA (27). Additionally, readers indicated if MRI changes were globally compatible with axial SpA.

Statistical analysis. Fisher's exact test was used for categorical variables and the Mann-Whitney U test was used for continuous variables in the comparisons of AAU patients with SpA and AAU patients without SpA, as well as in the comparisons of AAU patients with known SPa and AAU patients with newly diagnosed SpA. Univariable and multivariable logistic regression analyses were performed for selected parameters based on those used in the referral tools. *P* values of less than 0.05 were considered statistically significant.

Agreement between MRI readers was assessed with Fleiss' kappa coefficient. The predictive performance of the DUET and ASAS referral algorithms for the identification of patients with a suspected diagnosis of SpA was analyzed by calculating the sensitivity, specificity, positive predictive value (PPV), and positive and negative likelihood ratios. Analyses were performed with IBM SPSS Statistics version 26.

RESULTS

Initially, 204 patients with noninfectious AAU that was diagnosed by an ophthalmologist were included in this study. We lost 11 patients to follow-up before MRI, and 4 patients had contraindications for MRI. The remaining 189 patients either had available MRIs of the SI joint (n = 185) or had radiographs showing definitive sacroiliitis (n = 4) (allowing for a reliable diagnosis) and were included in the subsequent analyses (Figure 1 and Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42315). The mean age of the 189 AAU patients included in this study was 40.8 years, and 55% of the patients were men (Table 1). AAU was mostly unilateral (86%). Nearly one-third (32%) of the included patients had experienced only 1 episode of AAU. Most patients had already experienced back pain, while 68% of patients reported current back pain. On average, back pain started 6.5 years before the first AAU episode. One-third of the included patients received immunomodulating therapy, which was mainly in the form of systemic glucocorticoids (22%). Eleven patients were receiving treatment with conventional synthetic DMARDs (csDMARDs), and 8 patients were receiving treatment with bDMARDs (6 patients receiving monoclonal tumor necrosis factor inhibitors and 1 patient each receiving etanercept and interleukin-17 inhibitors).

Prevalence of SpA. More than half of the patients included in this study (n = 106 [56%]) either were diagnosed as having SpA after rheumatologic evaluation (n = 74) or received confirmation of their previous SpA diagnosis (n = 32). In 2 patients, the previously established SpA diagnosis was dismissed. While only 7 patients were diagnosed as having peripheral SpA without axial involvement, the vast majority presented with predominantly axial SpA (n = 99 [93%]). Pelvic radiographs were available for 88 (89%) of the axial SpA patients, 66% of whom were classified as having radiographic axial SpA.

A total of 79 SpA patients (75%) fulfilled the respective ASAS classification criteria: 78 patients for axial SpA and only 1 patient

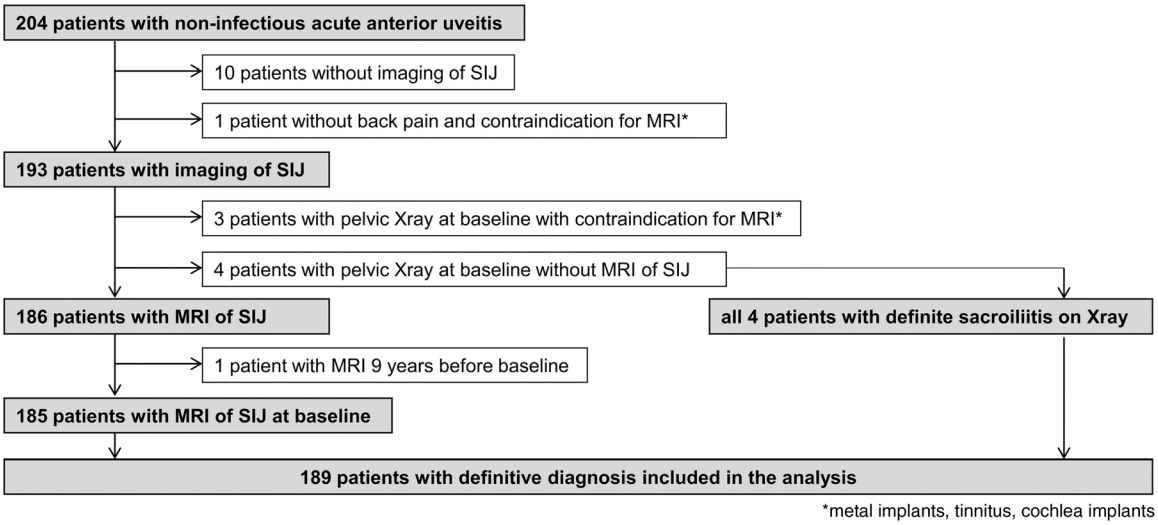

Figure 1. Flow chart of patient selection in a study evaluating the predictive performance of referral strategies for identifying acute anterior uveitis (AAU) patients with a high probability of having axial spondyloarthritis (SpA). MRI = magnetic resonance imaging; SIJ = sacroiliac joint.

Table 1. Demographic and clinical characteristics of acute anterior uveitis (AAU) patients with spondyloarthritis (SpA) and AAU patients without SpA*

	All AAU patients (n = 189)	Patients missing data	AAU and SpA (n = 106)	AAU, no SpA (n = 83)	P†
Age, mean ± SD years	40.8 ± 12.3	0	41.9 ± 11.6	39.5 ± 13.0	0.129
Male sex	103 (54.5)	0	67 (63.2)	36 (43.4)	0.008
Smoking ever	100 (52.9)	0	61 (57.5)	39 (47.0)	0.186
HLA–B27–positive	153 (81.0)	0	98 (92.5)	55 (66.3)	<0.001
Uveitis					
Time since first episode, mean ± SD years	5.9 ± 8.0	0	6.6 ± 7.9	5.1 ± 8.2	0.164
First episode of uveitis	60 (31.7)	0	33 (31.1)	27 (32.5)	0.876
Number of AAU episodes, mean ± SD	6.9 ± 11.7	0	7.7 ± 13.5	5.8 ± 8.9	0.774
Unilateral uveitis	162/188 (86.2)	1	95/105 (90.5)	67 (80.7)	0.059
Synechia ever	59/98 (60.2)	91	32/59 (54.2)	27/39 (69.2)	0.148
Hypopyon ever	12/139 (7.9)	50	6/75 (7.4)	6/64 (8.6)	>0.999
Fibrinous reaction ever	55/151 (36.4)	38	30/81 (37.0)	25/45 (35.7)	>0.999
Back pain					
Back pain ever	177 (93.7)	0	101 (95.3)	76 (91.6)	0.372
Current back pain (last week)	129 (68.3)	0	79 (74.5)	50 (60.2)	0.041
Duration of back pain, mean ± SD years	12.6 ± 10.3	12 (no back pain)	13.7 ± 10.6	11.1 ± 9.7	0.070
Time between back pain and first AAU episode, mean ± SD years	6.5 ± 10.6	12 (no back pain)	7.0 ± 11.5	5.8 ± 9.4	0.453
Age at back pain onset <45 years	163 (86.2)	0	95 (89.6)	68 (81.9)	0.095
Chronic back pain (>3 months)	150 (79.4)	0	85 (80.2)	65 (78.3)	0.857
Inflammatory back pain	121 (64.0)	0	76 (71.7)	45 (54.2)	0.015
Modified Schober test, mean ± SD cm	4.2 ± 2.0	2	3.9 ± 1.8	4.7 ± 2.1	0.002
Lateral flexion, mean ± SD cm	16.6 ± 5.6	3	16.0 ± 6.1	17.2 ± 4.9	0.221
Disease activity parameters					
PhGA score, mean ± SD (range 0–10)	3.1 ± 2.5	0	3.4 ± 2.5	2.6 ± 2.3	0.016
PtGA score, mean ± SD (range 0–10)	3.5 ± 3.1	2	4.0 ± 3.2	2.9 ± 2.8	0.014
BASDAI, mean ± SD (range 0–10)	3.1 ± 2.0	1	3.3 ± 2.2	2.9 ± 1.8	0.416
BASFI, mean ± SD (range 0–10)	1.7 ± 3.0	1	2.2 ± 3.7	1.1 ± 1.4	0.011
ASDAS-CRP, mean ± SD	2.0 ± 0.9	4	2.2 ± 1.0	1.7 ± 0.8	0.004
CRP level, mean ± SD mg/liter	4.5 ± 8.7	2	5.9 ± 10.5	2.6 ± 5.2	<0.001
ESR, mean ± SD mm/hour	14.7 ± 14.1	7	17.7 ± 16.3	10.9 ± 9.7	0.002
Treatment					
NSAIDs	65/171 (38.0)	18	48/100 (48.0)	17/71 (23.9)	0.001
Systemic steroids	41 (21.7)	0	23 (21.7)	18 (21.7)	>0.999
csDMARD	11 (5.8)	0	7 (6.6)	4 (4.8)	0.758
bDMARD	8 (4.2)	0	7 (6.6)	1 (1.2)	0.081
bDMARD naive	170 (89.9)	0	89 (84.0)	81 (97.6)	0.003
SpA features					
Psoriasis‡	17 (9.0)	0	16 (15.1)	1 (1.2)	0.001
IBD§	5 (2.6)	0	5 (4.7)	0	0.068
Peripheral manifestation ever	78 (41.3)	0	51 (48.1)	27 (32.5)	0.037
Arthritis ever	53 (28.0)	0	37 (34.9)	16 (19.3)	0.022
Peripheral manifestation current	16 (8.5)	0	12 (11.3)	4 (4.8)	0.124
Arthralgia requiring medical care	67/161 (41.6)	28	44/89 (49.4)	23/72 (31.9)	0.036

* Except where indicated otherwise, values are the number (%) of patients or number/total number of patients with available data (%). PhGA = physician global assessment; PtGA = patient global assessment; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Disease Functional Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score using the C-reactive protein level; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal antiinflammatory drugs; csDMARD = conventional synthetic disease-modifying antirheumatic drug; bDMARD = biologic DMARD; IBD = inflammatory bowel disease.
† Mann-Whitney U test for numerical variables and Fisher's exact test for categorical variables.
‡ Psoriasis ever diagnosed by a dermatologist.
§ Inflammatory bowel disease (IBD) ever diagnosed by a gastroenterologist.

for peripheral SpA (28). The reasons patients did not fulfill the classification criteria for axial SpA were as follows: back pain in 1 patient started after 45 years, 11 patients did not experience chronic back pain, and 9 patients fulfilled neither of these criteria. Six of the 7 peripheral SpA patients did not fulfill ASAS classification criteria, as they reported current back pain.

Follow-up data were available for 80 of the 106 SpA patients. In 41 of the patients for whom follow-up data were available, treatment was changed within 1 year after baseline: 24 patients started treatment with bDMARDs, 23 patients started treatment with NSAIDs, and 2 patients started treatment with csDMARDs.

Evidence of axial SpA on MRI of the SI joints. MRIs of the SI joints were available for 185 patients (Table 2). Agreement between readers was moderate to substantial (Supplementary Table 2, http://onlinelibrary.wiley.com/doi/10.1002/art.42315). Active inflammatory lesions and/or structural changes compatible with a diagnosis of axial SpA were present in 89 AAU patients (48%), 83 (93%) of whom were diagnosed as having axial SpA. Sixty-three of the 95 axial SpA patients with available MRIs had active inflammatory lesions, and 58 of these patients fulfilled the ASAS definition of an MRI positive for axial SpA. Structural changes such as erosions, fatty lesions, fat metaplasia in an erosion cavity, bony buds, ankylosis, and sclerosis were present in 79 axial SpA patients. None of the peripheral SpA patients had changes compatible with a diagnosis of axial SpA. Among patients without a clinical diagnosis of SpA, 4 had active inflammation and 6 had structural changes compatible with a diagnosis of axial SpA.

Factors associated with the presence of SpA. AAU patients with concomitant SpA compared to patients without systemic disease were more often men (63% versus 43%) and HLA–B27–positive (93% versus 66%) (see Table 1 for exact *P* values). Although back pain was frequent in the whole cohort, current back pain was seen more frequently in AAU patients with SpA compared to AAU patients who did not have SpA (75% versus 60%), and more AAU patients in the SpA group had IBP compared to those without SpA (72% versus 54%). Moreover, back pain was more often located in the SI joint in patients with SpA compared to patients who did not have SpA (63% versus 35%; $P < 0.001$). Only 5 of the included patients had inflammatory bowel disease (IBD) and they were all diagnosed as having SpA. Psoriasis was significantly more frequent in patients with SpA compared to patients who did not have SpA (15% versus 1%).

At study inclusion, only 16 patients (9%) presented with peripheral manifestations, but 41% reported that they had experienced at least 1 episode of arthritis, enthesitis, or dactylitis in the past. The presence of arthritis and any peripheral manifestation was associated with SpA.

SpA was further associated with increased disease activity based on common parameters of inflammation, the CRP and ESR, patient and physician global assessments of disease activity, and ASDAS scores, which all were higher in AAU patients who were diagnosed as having SpA. Patients with SpA also presented with reduced spinal mobility and function compared to patients who did not have SpA, which was reflected by higher BASFI scores (mean BASFI score 2.2 versus 1.1) and decreased range of motion by modified Schober test (mean score 3.9 cm versus 4.7 cm).

In our cohort, AAU patients with SpA and AAU patients without underlying SpA showed no differences in the results of their ophthalmologic examination; SpA was equally frequent in patients experiencing their first episode of AAU and in AAU patients with recurrent disease. No difference was observed regarding visual acuity, intraocular pressure, the presence of hypopyon, the presence of synechia, or the presence of fibrinous reaction.

We evaluated the parameters included in the ASAS and DUET referral strategies using a multivariable analysis model by including those parameters in addition to age and sex. However, as chronic back pain starting before the age of 45 years was not associated with the presence of SpA in our cohort, we included IBP as a parameter instead. In the multivariable analysis, instead of using the variable of arthralgia requiring medical care (as used in the DUET), we substituted it with the presence of any peripheral manifestation ever, because data on arthralgia requiring medical care were missing for 28 patients. In multivariable logistic regression analysis (Table 3), psoriasis (odds ratio [OR] 12.5 [95%

Table 2. Imaging characteristics of AAU patients with SpA and AAU patients without SpA*

	All AAU patients (n = 189)	AAU and axial SpA (n = 99 [52.3])	AAU and peripheral SpA (n = 7 [3.7])	AAU, no SpA (n = 83 [43.9])	False positive rate
Radiography					
SI joint radiograph available	119 (63.0)	88 (88.9)	3 (42.9)	28 (33.7)	–
Definitive radiographic sacroiliitis according to the modified New York criteria	58 (48.7)	58 (65.9)	0 (0)	0 (0)	0
MRI					
SI joint MRI available	185 (97.9)	95 (96.0)	7 (100)	83 (100)	–
Active inflammatory changes compatible with SpA	67 (36.2)	63 (66.3)	0 (0)	4 (4.8)	4.4
Inflammatory lesions fulfilling the ASAS definition of positive MRI of SI joint	61 (33.0)	58 (61.1)	0 (0)	3 (3.6)	3.3
Structural changes compatible with SpA	85 (45.9)	79 (83.2)	0 (0)	6 (7.2)	6.7
Presence of changes (active and/or structural) compatible with axial SpA	89 (48.1)	83 (87.4)	0 (0)	6 (7.2)	6.7

* Values are the number (%) of patients. ASAS = Assessment of SpondyloArthritis international Society; MRI = magnetic resonance imaging; SI = sacroiliac joint (see Table 1 for other definitions).

Table 3. Parameters associated with the presence of SpA in patients with AAU*

	Univariable OR (95% CI)	Multivariable OR (95% CI)
Psoriasis, ever	14.6 (1.9–112.4)	12.5 (1.3–120.2)
HLA–B27–positive	6.2 (2.7–14.6)	6.3 (2.4–16.4)
Elevated CRP level (≥5 mg/liter)	4.1 (1.8–9.0)	4.8 (1.9–12.4)
Male sex	2.2 (1.2–4.0)	2.1 (1.1–4.2)
Inflammatory back pain (ASAS definition)	2.1 (1.2–3.9)	1.9 (0.9–4.0)
Any peripheral manifestation, ever	1.9 (1.1–3.5)	1.9 (0.9–3.8)
Age	1.0 (1.0–1.0)	1.0 (1.0–1.0)

* Odds ratios (ORs) with 95% confidence intervals (95% CIs) for the probability of having SpA in patients with AAU were determined in univariable and multivariable logistic regression analyses. See Table 1 for other definitions.

confidence interval CI (95% CI) 1.3–120.2]), HLA–B27 positivity (OR 6.3 [95% CI 2.4–16.4]), male sex (OR 2.1 [95% CI 1.1–4.2]), and elevated CRP level (OR 4.8 [95% CI 1.9–12.4]) were significantly associated with the presence of SpA in AAU patients. In contrast, IBP and the presence of peripheral manifestations were associated with SpA solely in univariable analyses.

Predictive performance of referral strategies for SpA. All of the information needed for the evaluation of both the DUET and the ASAS referral strategies was available for 185 AAU patients. In assessing the probability of a diagnosis of SpA among all AAU patients, use of the ASAS referral tool had a slightly higher sensitivity and lower specificity (80% sensitivity and 28% specificity) compared to the DUET referral tool (78% sensitivity and 42% specificity) (Table 4). Similar results were observed when the referral strategies were evaluated for their predictive performance in the subset of patients who did not have a known diagnosis of SpA; in predicting a diagnosis of SpA, the ASAS referral tool had a slightly higher sensitivity and lower specificity (75% sensitivity and 28% specificity) compared to the DUET referral tool (72% sensitivity and 43% specificity).

Of the 104 patients with SpA included in this analysis, 32 (30%) had been diagnosed as having SpA previously. Among these patients with a previous diagnosis of SpA, only 1 patient did not fulfill either of the 2 referral tools, whereas in 16 of the 72 patients with a new diagnosis of SpA, the diagnosis could not be correctly identified by either screening tool (Figure 2).

Of the 24 patients fulfilling the criteria of the ASAS but not the DUET referral tool, 5 were diagnosed as having axial SpA and 2 were diagnosed as having peripheral SpA, while 2 of the 10 patients meeting the criteria of the DUET but not the ASAS referral tool were diagnosed as having axial SpA and 2 were diagnosed as having peripheral SpA. Half of the patients who did not fulfill the criteria of either referral strategy (17 of 34 patients) were diagnosed as having axial SpA. Interestingly, all of the peripheral SpA patients fulfilled the criteria from at least 1 of the referral tools.

In this study, AAU patients who already had a known diagnosis of SpA did not differ from AAU patients who were newly diagnosed as having SpA, with regard to demographics such as age and sex and with regard to HLA–B27 status (positive versus negative) (Supplementary Table 3, http://onlinelibrary.wiley.com/doi/10.1002/art.42315). AAU patients with known SpA compared to AAU patients with newly diagnosed SpA more often had peripheral SpA (16% versus 3%), peripheral manifestations (69% versus 39%), and arthralgia (83% versus 36%). AAU patients with an established diagnosis of SpA compared to patients with newly diagnosed SpA had a longer duration of time since their first episode of uveitis (mean time since first uveitis episode 10.1 years versus 5.1 years) and had more AAU episodes over time (mean 11.6 episodes versus 6.0 episodes). Moreover, patients with known SpA had longer durations of back pain (mean 17.0 years versus 12.1 years), more often had radiographic axial SpA (82% versus 56% of axial SpA patients), and experienced reduced spinal mobility reflected by higher BASFI scores (mean 3.0 versus

Table 4. Performance of the Dublin Uveitis Evaluation Tool (DUET) versus an adaptation of the Assessment of SpondyloArthritis International Society (ASAS) referral tool in all AAU patients and in patients without a previously known diagnosis of SpA*

	All AAU patients (n = 187)		AAU patients without a known SpA diagnosis (n = 153)	
	ASAS	DUET	ASAS	DUET
Diagnosed with SpA, no./total no. of patients (%)	104/187 (55.6)		72/153 (47.1)	
Sensitivity	83/104 (79.8)	81/104 (77.9)	54/72 (75.0)	52/72 (72.2)
Specificity	23/83 (27.7)	35/83 (42.2)	23/81 (28.4)	35/81 (43.2)
PPV	83/143 (58.0)	81/129 (62.8)	54/112 (48.2)	52/98 (53.1)
NPV	23/44 (52.3)	35/58 (60.3)	23/41 (56.1)	35/55 (63.6)
Positive LR	1.1	1.3	1.0	1.3
Negative LR	0.7	0.5	0.9	0.6
Number needed to refer†	9.7	4.3	23.2	6.0

* PPV = positive predictive value; NPV = negative predictive value; LR = likelihood ratio (see Table 1 for other definitions).
† Number needed to refer defined as 1/(PPV–[1–NPV]).

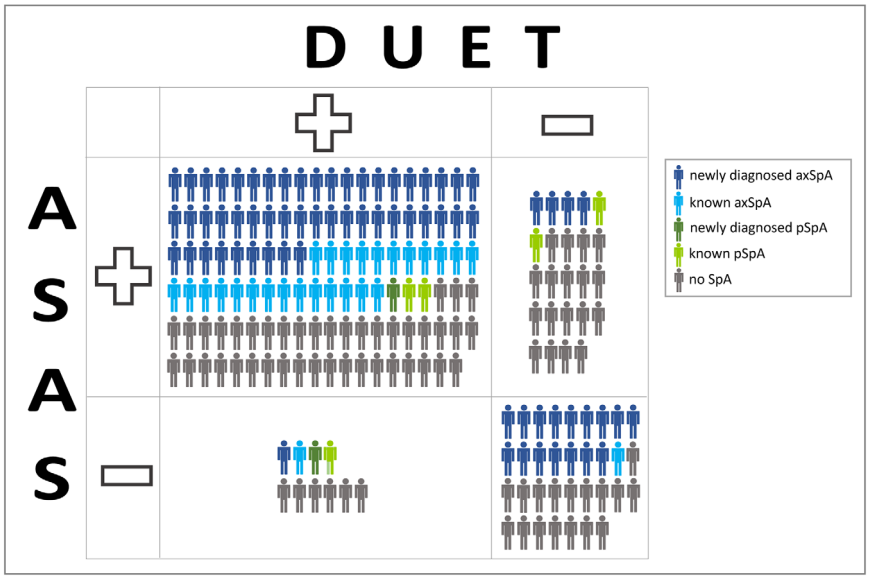

Figure 2. Performance of the Dublin Uveitis Evaluation Tool (DUET) and the Assessment of SpondyloArthritis international Society (ASAS) referral tool in correctly identifying acute anterior uveitis patients with a high probability of having axial spondyloarthritis (axSpA) or peripheral SpA (pSpA). Patients who fulfilled the criteria of the referral tool are grouped in boxes falling under a plus sign (+); patients who did not fulfill the criteria of the referral tool are grouped in boxes falling under a minus sign (–).

1.9). Although patients with previously diagnosed SpA compared to patients with newly diagnosed SpA had higher patient global assessment and physician global assessment scores (mean 5.3 versus 3.4 and 4.3 versus 3.1, respectively), other disease activity assessments (ASDAS, BASDAI) and inflammation parameters showed no difference between patients who had previously been diagnosed as having SpA and newly diagnosed SpA patients. While 22% of the patients with a known diagnosis of SpA were receiving treatment with a bDMARD at baseline, none of the patients who were diagnosed as having SpA as a result of the evaluations in this study were under bDMARD therapy.

DISCUSSION

We found a high prevalence of SpA in our cohort of patients with noninfectious AAU; 106 of 189 patients (56%) had concomitant SpA. Indeed, in 70% of patients, SpA had gone undiagnosed and was revealed during the study examination. SpA in AAU patients predominantly manifested as axial SpA. Two-thirds of the axial SpA patients presented with definitive sacroiliitis on radiography. The presence of SpA was independently associated with male sex, HLA–B27 positivity, psoriasis, and elevated CRP level.

This is the first study to screen unselected AAU patients for musculoskeletal manifestations using a standardized rheumatologic examination including MRI of the SI joint in all patients irrespective of back pain. This enabled us to reliably report the overall prevalence of SpA. When patients with a previously known SpA diagnosis were excluded from the analyses, the prevalence of SpA in our cohort decreased from 56% to 48%. The reported prevalence of SpA in AAU patients ranges widely from 20% to 78% (6–15), which may be primarily attributable to variations in the designs of the different studies (see Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.42315). Studies focusing on referral strategies have excluded patients with a prior SpA diagnosis (6–8, 12–15), thus underestimating the overall prevalence of SpA. Meanwhile, other studies have focused on HLA–B27–positive AAU patients (7,9,10) or patients with recurrent AAU (7,8); both of these features of AAU have been described as being associated with a higher prevalence of SpA (29,30). Other studies have been either retrospective analyses (9,11,13) or cross-sectional studies in which imaging was only performed when it was clinically indicated (MRI performed only in patients with chronic back pain beginning before age 45 years) (12). To our knowledge, in only 2 studies was MRI of the SI joint performed for all of the AAU patients included in the cohorts, including those without back pain: a study by Oliveira et al (8) and a study by Bubova et al (14) found that axial SpA had a prevalence of 40% and 41%, respectively; however, in the study by Oliveira et al only patients with recurrent AAU were included, and both studies focused on patients with no prior rheumatic disease diagnosis.

Not surprisingly, and consistent with previous findings (6,9,31), the presence of SpA in our cohort was independently associated with male sex, HLA–B27 positivity, psoriasis, and elevated CRP level, all of which are classic features of SpA. In contrast, IBP and the presence of peripheral manifestations (arthritis, dactylitis, enthesitis) lost their significant association with concomitant SpA in AAU patients in the multivariable analysis. Conflicting data exist on whether uveitis features such as recurrence or the occurrence of complications are higher in patients with

underlying SpA (6,9,10,31). In some studies, associations between underlying SpA in AAU patients and recurrent uveitis (6,10), fibrinous exudates, synechiae, and poorer visual outcome (31) have been described, which could not be reproduced in our cohort. Hypopyon and fibrin reactions were assessed as risk factors of HLA–B27–positive AAU in a meta-analysis (30). Interestingly, however, highly comparable prevalence of findings were reported in the most comprehensive study to date, which included more than 1,000 patients with HLA–B27–associated AAU (31).

Unilateral AAU (including recurrent episodes in which alternating eyes were involved) was numerically more frequent in AAU patients with SpA (91% versus 81%) but did not reach statistical significance. Simultaneous bilateral eye involvement was not associated with the presence of either IBD or psoriasis in our cohort, which might be because all but 1 patient with psoriasis and all of the IBD patients were HLA–B27–positive and had concomitant axial SpA. Although bilateral as well as posterior involvement of the eye and chronic uveitis were reported to occur more frequently in patients with IBD and psoriasis, patients with these extramusculoskeletal manifestations who also had concomitant axial SpA and/or were HLA–B27 positive were found to have predominantly unilateral AAU, as has previously been reported in patients with solely axial SpA (32,33). We found that there was a high prevalence of HLA–B27 positivity in our cohort of AAU patients (81%), which is consistent with the findings of a recent study in which analysis of the genetic backgrounds of AAU patients revealed an 81.8% prevalence of HLA–B27 positivity in 749 patients with ophthalmologist-diagnosed AAU (34).

Concomitant SpA in our cohort of unselected AAU patients was frequently unrecognized (70% of SpA patients), which emphasizes the need for effective referral strategies and close collaboration between ophthalmologists and rheumatologists. The more complex DUET referral strategy showed higher specificity for recognition of SpA in AAU patients than the ASAS referral tool, which had a slightly higher sensitivity. Taking into account only AAU patients without a prior diagnosis of SpA, a rheumatologist would have to see 2.1 patients fulfilling the criteria of the ASAS referral tool or 1.9 patients fulfilling the criteria of the DUET referral tool to diagnose 1 patient with SpA. However, with both referral strategies more than 20% of SpA patients would have been missed. This might be due to an unusual presentation of SpA in those patients as their back pain more frequently started after the age of 45 years and lasted fewer than 3 months, and thus ASAS classification criteria were less frequently fulfilled. This phenomenon was also described by Pato et al, who found that AAU patients with undiagnosed SpA had "atypical cases" of SpA, and that they experienced a shorter duration of symptoms together with less radiologic damage (35), which we also saw in our cohort. Moreover, 5 of the AAU patients newly diagnosed with axial SpA did not report any back pain but showed structural and active inflammatory lesions indicative of SpA on MRI. Although we admit that there is a risk of overdiagnosis when basing diagnosis mainly on imaging in patients without back pain, those 5 patients were HLA–B27–positive and showed an extramuskuloskeletal manifestation of SpA in the setting of AAU. Obviously, these patients have a subclinical course of their disease that may change over time. Furthermore, although these patients were asymptomatic during this study, they are at risk of developing functional limitations due to structural damage in the axial skeleton. Though diagnosing SpA in patients without musculoskeletal symptoms has no direct therapeutic consequence, it raises awareness and facilitates further rheumatologic care if the patient develops symptoms in the future.

Another explanation for differences in the performance of the DUET referral tool in our study as compared to the original work by Haroon et al (6) (72% sensitivity and 43% specificity in our cohort versus 96% sensitivity and 97% specificity in the DUET cohort) could be the different definitions of SpA that were used in each study. While our study relied on the diagnosis of SpA by experienced rheumatologists, patients in the DUET cohort were diagnosed according to the classification criteria of the ASAS and the Classification of Psoriatic Arthritis Study Group (6). Classification criteria were initially created to define a homogenous research group of patients with an already established diagnosis and not to primarily diagnose patients (36). Using classification criteria as diagnostic tools results in misdiagnosis, as the sensitivity of the ASAS classification criteria was reported to be 79.5% with a specificity of 83.3% (28).

Given the high prevalence of undiagnosed SpA in AAU patients, it can be recommended that all AAU patients with musculoskeletal symptoms (back or joint pain) or even all patients with AAU be referred for further rheumatologic examination. With this strategy, ~2 AAU patients (PPV of >50%) have to be evaluated for a rheumatologist to make 1 diagnosis of SpA. In this patient population, such a strategy would be better than referral strategies for patients with chronic back pain, which usually have a PPV of 30–45% for the diagnosis of SpA (19). As two-thirds of the AAU patients with axial SpA in this study showed definitive sacroiliitis on radiography, it seems reasonable to first perform radiography of the SI joints in AAU patients with back pain and use MRI as a second step only in patients without definitive sacroiliitis, which follows the EULAR recommendations (37).

The limitations of this study include that MRI was only routinely performed on SI joints. Thus, active and/or chronic changes typical of axial SpA occurring solely in the spine could have remained unrecognized. However, the evaluation of spine and SI joint MRI in combination is known to add only little incremental value for diagnosing axial SpA when compared to the evaluation of SI joint MRI alone, according to the current literature (38). Moreover, in our study, rheumatologists could order additional spinal MRI when indicated and had access to already performed spinal MRIs prior to study inclusion (15 patients with spinal MRI). As AAU patients were included in this study irrespective of their

current treatment, another limitation could be that patients receiving treatment with bDMARDs at the time of inclusion were not correctly identified as having SpA, as bDMARDs are also an effective treatment for musculoskeletal symptoms. The number of those patients, however, was low (n = 8 [4%]), and structural changes indicative of axial SpA could still have been recognized. Moreover, we had to exclude 15 patients (7.4%) with incomplete rheumatologic assessment, which might have caused a selection bias. The excluded patients reported current and chronic back pain less frequently, but they reported arthralgia requiring medical care more frequently, received treatment with NSAIDs less often, and were less likely to be HLA–B27 positive compared to the included patients (Supplementary Table 1, http://onlinelibrary.wiley.com/doi/10.1002/art.42315).

To conclude, in this study we found a high prevalence of both overall and previously undiagnosed SpA in AAU patients. SpA was equally frequent in patients presenting with their first episode of AAU as in patients with recurrent AAU and not associated with any particular ophthalmologic feature. Based on these findings, it can be recommended that all patients with AAU who report experiencing musculoskeletal symptoms should be referred to a rheumatologist for further evaluation. Rheumatologists should consider that a diagnosis of SpA in AAU patients might present atypically, with no or mild back pain starting after the age of 45 years and lasting less fewer than 3 months.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Rademacher had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rademacher, Pleyer, Poddubnyy.

Acquisition of data. Rademacher, Müllner, Diekhoff, Haibel, Igel, Pohlmann, Proft, Protopopov, Rodriguez, Torgutalp, Pleyer, Poddubnyy.

Analysis and interpretation of data. Rademacher, Müllner, Pleyer, Poddubnyy.

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ROLE OF THE STUDY SPONSOR

AbbVie had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by AbbVie.

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