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High Prevalence of Previously Undiagnosed Axial Spondyloarthritis in Patients Referred With Anterior Uveitis and Chronic Back Pain: The SpEYE Study

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ABSTRACT. ***Objective.*** To reduce the diagnostic delay in axial spondyloarthritis (axSpA), guidelines recommend referring patients with acute anterior uveitis (AAU) and chronic back pain (CBP) to a rheumatologist. This observational study in daily practice evaluated the prevalence of previously unrecognized axSpA in patients with AAU who were referred by ophthalmologists because of concurrent CBP.

Methods. All patients with AAU referred with CBP (≥ 3 months, age of onset < 45 yrs) from 5 ophthalmology clinics underwent rheumatologic assessment, including pelvic radiographs. Patients with previously diagnosed rheumatic disease and AAU due to other causes were excluded. The primary endpoint was a clinical axSpA diagnosis by the rheumatologist.

Results. Eighty-one patients fulfilled the referral criteria (52% male, 56% HLA-B27 positive, median age 41 yrs, median CBP duration 10 yrs). In total, 58% (n = 47) had recurring AAU, of whom 87% already had CBP during previous AAU attacks. After assessment, 23% (n = 19) of patients were clinically diagnosed with definite axSpA (10/19 radiographic), 40% (n = 32) with suspicion of axSpA, and 37% (n = 30) with no axSpA. AxSpA was diagnosed more often in men (33% of the men vs 13% of the women).

Conclusion. A high prevalence of axSpA was found in patients with AAU referred because of CBP. There was substantial diagnostic delay in the majority of patients with recurring AAU, as many already had CBP during previous AAU flares. In AAU, screening for CBP and prompt referral has a high diagnostic yield and should consistently be promoted among ophthalmologists.

Key Indexing Terms: anterior uveitis, back pain, ophthalmologists, spondylarthropathies

The average diagnostic delay in axial spondyloarthritis (axSpA) is about 6 to 8 years, during which patients often suffer a prolonged period of pain, functional decline, risk of work loss, and radiographic changes.[1] A longer delay is associated with worse disease outcomes and lower treatment efficacy.[2] Acute anterior uveitis (AAU) is relatively rare in the general population and strongly associated with HLA-B27 and axSpA. Timely referral of patients with AAU and chronic back pain (CBP) could reduce the diagnostic delay in axSpA.

AAU is the most prevalent extraarticular manifestation in axSpA, with a lifetime risk of up to 50%.[3,4,5,6,7,8] Conversely, in AAU, axSpA is the most common associated systemic disease, with both diseases sharing the same genetic predisposition, the HLA-B27 antigen (overall prevalence in the Dutch population is 8–9%).[8,9,10,11] In those with AAU, axSpA develops in up to 50% of the HLA-B27–positive patients, and up to 20% of the HLA-B27–negative patients.[12,13,14,15] AAU is slightly more prevalent in radiographic (r-) axSpA than in nonradiographic (nr-) axSpA.[16] So far, no relevant sex differences in prevalence of AAU in axSpA have been observed.[7,17,18,19] However, Braakenburg demonstrated that male patients with axSpA were more frequently diagnosed with axSpA before their first AAU attack, whereas the diagnosis in women was significantly more often made after the first AAU.[20] This suggests that screening patients with AAU might be especially important for women.

The 2015 recommendations of the Assessment of SpondyloArthritis international Society (ASAS) for the early referral of patients with a suspicion of axSpA contain criteria for CBP (duration ≥ 3 months, age of onset < 45 yrs), and a list of SpA manifestations including AAU.[21] The combination of CBP and ≥ 1 of these features should prompt a referral to

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the rheumatologist. Inflammatory back pain (IBP), characterized by morning stiffness, nightly pain, and improvement with movement, is more specific for axSpA than CBP.[21] However, recognizing IBP is challenging.[22,23] Therefore, referral guidelines aimed at nonrheumatologists focus on CBP.

AAU can be the first presenting symptom of axSpA but is often preceded by CBP.[14,24,25] Unfortunately, international ophthalmology guidelines on the referral of patients with AAU to the rheumatologist are lacking. The Dutch uveitis guidelines recommend rheumatological evaluation when AAU is accompanied by back pain.[26] Two previous studies have reported a high chance of detecting axSpA in patients presenting with AAU without a previously diagnosed rheumatic disease.[13,27] However, screening of all patients with AAU is not common practice due to high patient numbers. Therefore, a more specific strategy as suggested by the ASAS is probably more efficient. However, the performance of this screening strategy in daily practice has not yet been described.

The Spondyloarthritis-Eye (SpEYE) study was initiated to study the effect of an initiative in the Amsterdam region to encourage ophthalmologists to refer all patients with ≥ 1 attack of AAU and CBP to the rheumatology outpatient clinic. The primary aim was to estimate the proportion of new axSpA diagnoses in this group. Secondarily, in an exploratory analysis, the clinical characteristics, in particular gender, were evaluated in 3 diagnostic groups (definite, suspicion of axSpA, no axSpA).

METHODS

Study design and population. Here we describe the baseline results of a prospective cohort study of patients who were referred to the rheumatologist with AAU and CBP. Patients were referred from 5 regional ophthalmology centers (academic and nonacademic) to the rheumatologist (Rheumatology Department, Amsterdam University Medical Centre [UMC], location VUmc) between April 2017 and January 2020. To increase awareness, ophthalmology centers were visited and informed through a presentation and brief written materials (email and handout) at study initiation, with yearly repeats. The study protocol was approved by the Medical Ethics Committee of the Amsterdam UMC-VUmc (approval no. 2017-037). All study participants gave written informed consent, and the study was performed according to the Declaration of Helsinki.

Referral criteria. Referral criteria were age ≥ 18 years, a history of ≥ 1 AAU, and CBP (current or previous; with ≥ 3 months' duration, started before the age of 45 yrs). Patients with a previous diagnosis of axSpA, juvenile arthritis, another cause of AAU (such as infection), or another autoimmune disease were excluded. However, patients with psoriasis (PsO), reactive arthritis, or inflammatory bowel disease (IBD) could be included.

Diagnosis of axSpA. All referred patients underwent rheumatologic assessment, including those who did not meet the referral criteria. Potential differential diagnoses were considered as well. At baseline, the clinical diagnosis was made by an experienced rheumatologist (IvdHB, for all patients), based on clinical evaluation, laboratory examination (HLA-B27, C-reactive protein [CRP], erythrocyte sedimentation rate), and pelvis radiography (judged by a musculoskeletal radiologist and a rheumatologist). Magnetic resonance imaging (MRI) of the sacroiliac (SI) joints was performed on clinical indication during follow-up, which is in accordance with the common daily practice in the Netherlands. The diagnosis was reported as "definite axSpA," "suspicion of axSpA" or "no axSpA" (no follow-up needed). The suspicion of axSpA group consisted of patients in whom rheumatologists could not yet draw a definite conclusion due to the mild, inconsistent, or atypical components, or a potential differential diagnosis. These patients are followed for at least 2 years (longitudinal phase of this study, of which the results will be published later). In patients with a clinical diagnosis of definite or suspicion of axSpA, the fulfillment of the ASAS classification criteria for r-axSpA or nr-axSpA was assessed as well.[28]

Study parameters. At baseline, the following variables were collected:

1. Patient characteristics: demographics, BMI, nonsteroidal antiinflammatory drugs (NSAIDs), AAU flares (total number, and year of first and subsequent AAU).
2. Back pain: year of onset, ASAS IBP characteristics (age of onset < 40 yrs, gradual onset, improvement with exercise, no improvement when resting, pain at night that improves upon getting up; IBP if fulfilling ≥ 4 of the 5 characteristics).[29]
3. Presence of ASAS SpA features: ASAS IBP, PsO, (reactive) arthritis, IBD, enthesitis, SpA family history, response of CBP to NSAIDs, HLA-B27, and elevated CRP (> 7 mg/L).[28]
4. Physical signs of SpA: Bath Ankylosing Spondylitis Metrology Index (BASMI), 44-joint swollen joint count, and Maastricht Ankylosing Spondylitis Enthesitis Score.[30,31]
5. Radiographic changes: sacroiliitis on the baseline radiograph of the pelvis according to the modified New York (mNY) criteria.[28]
6. Patient-reported outcome measures (questionnaires): Bath Ankylosing Spondylitis Disease Activity Index, Ankylosing Spondylitis Disease Activity Score with CRP, and Bath Ankylosing Spondylitis Functional Index.[32,33,34]

Evaluation of the execution of the referral strategy. To evaluate to what extent the referral strategy was executed in practice, a small substudy was performed in one of the participating centers to answer the question, "How many of the patients who attended the ophthalmology department with AAU, and were eligible for screening for axSpA (no known cause of AAU), were in fact screened for CBP?" The medical records of all patients with AAU who attended the ophthalmology outpatient clinic of the Amsterdam UMC, between January 2017 and June 2019 were retrospectively evaluated. Patients were collected from the hospital charts based on the diagnosis codes "anterior uveitis," "acute anterior uveitis," "chronic anterior uveitis," and "idiopathic anterior uveitis." Patients with a known cause of AAU (eg, infection, previously diagnosed rheumatic disease, eye syndrome) were excluded. Outcome variables of interest were whether patients were referred to the rheumatologist or whether CBP was ruled out.

Statistical analyses. Data analysis was performed with IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp). Data are presented as mean (SD), number (with percentage), percentage only, or median (IQR) for variables without a normal distribution. Explorative analyses were performed on differences between definite, suspicion of axSpA, and no axSpA, in demographics, SpA characteristics, and disease activity, with logistic regression (dichotomous variables) and ANOVA (for continuous variables). For variables that differed significantly among groups, comparison was performed for definite vs, respectively, suspicion of axSpA and no axSpA. In addition, 3 potential gender differences were evaluated. Bonferroni correction for multiple testing (33 tests) was applied, resulting into a level of significance of $P < 0.002$.

RESULTS

Between April 2017 and January 2020, 101 patients were referred by the ophthalmologists to the rheumatologist. Twenty patients did not fulfill the referral criteria (11 men, age 41 yrs [SD 14], 5 HLA-B27 positive; Figure 1).

Of the 81 included patients, 52% (n = 42) were male with a median age of 41 years (IQR 15, Table 1). Overall, 56% (n = 45) of patients were HLA-B27 positive, and at referral, most patients (85%, n = 69) had unilateral AAU. Fifty-eight percent (n = 47) had suffered ≥ 1 AAU episode (including the AAU that led to

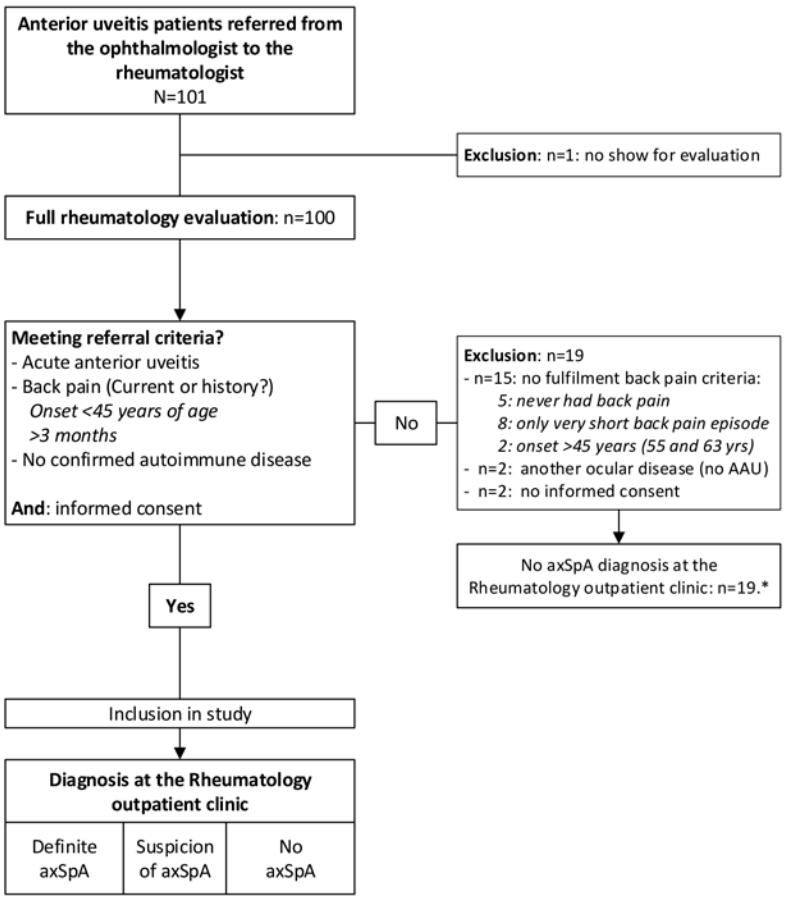

Figure 1. Study flow chart of patients referred from the ophthalmologist to the rheumatologist. * Among the excluded patients, 5 were HLA-B27 positive, 1 had radiological signs of ileitis condensans, and none were clinically diagnosed with axSpA. AAU: acute anterior uveitis; axSpA: axial spondyloarthritis.

referral), alternating between eyes in the majority (n = 27), and with median of 4 years since the first attack.

At baseline, 86% (n = 70) of the patients were currently experiencing back pain (overall severity median 3 [IQR 4]; among patients with current back pain: 4 [IQR 5]). Fifty-six percent (n = 45) of all patients had a history of IBP. Patients on average had their first CBP complaint 10 years before referral. At referral, 19% (n = 15) of the patients already used an NSAID for their CBP on their own initiative, without a prescription.

Clinical diagnosis of axSpA. A total of 19 patients were diagnosed with definite axSpA (23%; Table 1); of whom 10 had r-axSpA and 9 had nr-axSpA (see Supplementary Data 1 and 2 for details on the patients with nr-axSpA and the 1 HLA-B27–negative patient, respectively; available from the authors on request). Further, 32 (40%) patients with mild symptoms were diagnosed with suspicion of axSpA (Supplementary Data 3). An MRI of the SI joints was done in 4/33 patients with suspicion of axSpA; this was negative in all cases. Accordingly, 1 patient was considered to have no axSpA, whereas the other 3 patients remained in follow-up (suspicion of axSpA) due to progression of symptoms. Thirty patients (37%) did not have axSpA; of these, 1 patient had sarcoidosis.

Treatment with NSAIDs was initiated in all 19 patients with definite axSpA (15 daily use) and in 22 of the 32 patients with a suspicion of axSpA (13 daily use).

In addition to the clinical diagnosis, all patients with definite axSpA or suspicion of axSpA were checked for the ASAS classification criteria. All patients with definite axSpA fulfilled the ASAS classification criteria (53%, 10/19 patients, for r-axSpA), compared to 56% (18/32 patients) of the patients with suspicion of axSpA, of whom the majority fulfilled the criteria for nr-axSpA (Table 1).

Radiographic changes. Radiographic changes of the SI joints were present in 32% of the patients (n = 26), ranging from mild abnormalities to full ankylosis (Table 2). Radiologic sacroiliitis according to the mNY criteria[28] was detected in 11 patients, of whom 1 (female, 38 yrs, HLA-B27–positive) had only minor symptoms (short episodes of very mild back pain, no IBP, excellent spinal mobility), resulting in a diagnosis of suspicion of axSpA.

Characteristics of patients with a definite axSpA diagnosis. Explorative analyses revealed that patients with definite, suspicion, and no axSpA differed only in a few characteristics (Table 1, Figure 2). Patients with definite axSpA had IBP significantly more often (17/19) and were HLA-B27 positive (18/19),

Table 1. Patient characteristics at referral, subdivided for the clinical diagnoses.

	Overall	Clinical Diagnosis			
		Definite AxSpA	Suspicion of AxSpA	No AxSpa	*P**
	n = 81	n = 19	n = 32	n = 30	
Age, yrs, median (IQR)	41 (25)	34 (23)	38 (18)	42 (14)	0.15
Gender, men	42 (52)	14 (74)	15 (47)	13 (43)	0.09
Ethnicity[a], White	58 (72)	14 (79)	24 (75)	20 (67)	0.23
BMI, median (IQR)	25 (5)	24 (5)	25 (5)	25 (7)	0.25
Fulfilling ASAS classification criteria[b]	46 (57)	19 (100)	18 (56)	9 (30)	
r-axSpA	11 (24)	10 (53)	1 (3)	0 (0)	
nr-axSpA	35 (76)	9[c] (47)	17[d] (53)	9 (30)	
Anterior uveitis, > 1 flare in total	47 (58)	13 (68)	18 (56)	16 (55)	0.57
Years since first AAU, median (IQR)	4 (7)	5 (18)	5 (8)	2 (6)	
No. of previous flares, median (IQR)	3 (2)	3 (5)	3 (5)	3 (1)	
Back pain before first AAU	60 (74)	13 (68)	24 (73)	23 (79)	
Back pain					
Current back pain	70 (86)	17 (90)	26 (81)	27 (90)	0.56
Age at onset, yrs, mean (SD)	27 (10)	26 (10)	26 (10)	27 (11)	0.87
Years since onset, median (IQR)	10 (19)	10 (22)	8 (19)	14 (21)	0.33
IBP[e], ever	45 (56)	17 (89)	20 (63)	8 (29)	**< 0.002**
ASAS SpA features[f], n, mean (SD)	3 (1)	4 (1)	3 (1)	2 (1)	**0.01**
HLA-B27 positive	45 (56)	18 (95)	18 (56)	9 (31)	**0.001**
Arthritis history	4 (5)	2 (11)	2 (6)	0 (0)	0.86
Enthesitis history	6 (7)	2 (11)	3 (9)	1 (3)	0.59
Psoriasis history	7 (9)	3 (16)	2 (6)	2 (7)	0.47
Good response to NSAIDs	30 (37)	13 (68)	11 (34)	6 (20)	0.005
Family history of SpA	9 (11)	3 (16)	4 (13)	2 (7)	0.60
Elevated CRP (> 7 mg/L)	17 (21)	8 (42)	5 (16)	4 (13)	0.006
CRP level, mg/L, median (IQR)	13 (12)	18 (21)	14 (11)	11 (11)	
Other SpA features					
Morning stiffness > 30 min	34 (42)	8 (42)	17 (53)	9 (30)	0.19
Alternating buttock pain	28 (35)	10 (53)	12 (38)	6 (21)	0.07
Arthralgia without arthritis	19 (24)	1 (5)	10 (31)	8 (27)	0.16
Sternal pain	12 (15)	4 (21)	6 (19)	2 (7)	0.31
Disease variables					
BASMI linear score, mean (SD)	1.9 (1.2)	3.0 (1.4)	1.5 (0.9)	1.8 (1.0)	**< 0.001**
Enthesitis (MASES) score ≥ 1	22 (27)	2 (11)	10 (30)	11 (40)	0.19
MASES score, median (IQR)	3 (4)	3 (1)	3 (4)	3 (3)	
Current arthritis (44-joint count > 0)	3 (4)	0 (0)	2 (6)	1 (3)	0.87
Patient global disease activity, NRS, mean (SD)	4 (3)	4 (2)	4 (3)	4 (4)	0.41
Back pain at night, NRS, median (IQR)	3 (5)	3 (6)	2 (6)	3 (6)	0.54
BASDAI score, median (IQR)	2.7 (2)	3.3 (2.6)	2.6 (2.8)	2.7 (3.6)	0.88
Back pain (BASDAI 2), median NRS	3.0 (4.0)	3.5 (3.0)	3.0 (3.5)	4.0 (6.0)	0.98
ASDAS score, mean (SD)	2.0 (0.9)	2.3 (1.0)	2.0 (0.8)	1.9 (1.0)	0.33
High disease activity (≥ 2.1)	34 (42)	9 (47)	13 (41)	11 (38)	
BASFI score, median (IQR)	1 (3)	1 (4)	1 (2)	1 (2)	0.66

Values are expressed as n (%), unless stated otherwise. * *P* values show differences between diagnostic groups. *P* < 0.002 was regarded as statistically significant, after Bonferroni correction for multiple testing. [a] White 72%, African 6%, Hindustan 5%, Turkish 5%, Moroccan 4%, Asian 1%, Latin American 3%, mixed ethnicity 4%. [b] Patients fulfilling the ASAS classification criteria for axSpA (r-axSpA or nr-axSpA).[22] [c] An MRI was made in 1/9 nr-axSpA patients, demonstrating sacroiliitis. The others were diagnosed based on a compatible clinical picture. [d] An MRI was made in 4/33 patients with suspicion of axSpA, and was negative in all cases. [e] IBP according to the ASAS IBP criteria.[23] [f] No patient had a history of dactylitis or inflammatory bowel disease. AAU: acute anterior uveitis; ASAS: Assessment of Spondyloarthritis international Society; axSpA: axial spondyloarthritis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; IBP: inflammatory back pain; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; nr-axSpA: nonradiographic axSpA; NRS: numerical rating scale; NSAID: nonsteroidal antiinflammatory drug; r-axSpA: radiographic axSpA.

compared to patients with no axSpA (IBP: 8/30, $P = 0.01$; HLA-B27: 9/30, $P = 0.001$). Compared to suspicion of axSpA, only HLA-B27 was more prevalent (IBP: 20/32, $P = 0.41$; HLA-B27: 18/32, $P = 0.005$). Patients with definite axSpA had a higher number of ASAS SpA features (4 [SD 1]), and worse spinal mobility (BASMI: 3.0 [SD 1.4]), compared to both the

suspicion of axSpA (SpA features: 3 [SD 1], $P = 0.01$; BASMI: 1.5 [SD 0.9], $P < 0.001$) and no axSpA groups (SpA features: 2 [SD 1], $P < 0.001$; BASMI: 1.8 [SD 1.1], $P < 0.001$).

Onset of back pain in relation to anterior uveitis. Of all 81 patients, 34 (42%) were referred after their first AAU, and had CBP for a median of 15 years (IQR 20). The remaining 47 (58%) patients had > 1 previous AAU (median 3 AAU flares, IQR 2, 62% HLA-B27 positive). Importantly, of these patients, 41 (87%) either already had CBP before their first AAU (n = 30) or developed CBP in between the first and penultimate AAU (n = 11). This applied to 92% of the definite axSpA patients with > 1 AAU (n = 13), and to 83% and 88% of the patients with suspicion of axSpA (n = 18) and no axSpA (n = 16), respectively, with > 1 AAU.

Gender differences. In total, 42 men (median age 42 yrs [IQR 16]) and 39 women (median age 40 yrs [IQR 15]) were included. A history of > 1 previous AAU flares was slightly more common in men (28/42, vs 19/39 in women, $P = 0.10$; both with median of 3 attacks). Overall, in 96% of these men and 83% of women ($P = 0.13$), CBP had already developed before the first or penultimate AAU.

After clinical evaluation, men were more likely to be diagnosed with axSpA (33%, vs 13% in women; $P = 0.03$), with radiographic axSpA in 7/14 of the diagnoses in men, and 3/5 of the diagnoses in women.

Performance of the referral strategy in a subsample of patients with AAU. To evaluate to what extent ophthalmologists applied the referral strategy, a small substudy was performed in one of the participating ophthalmology centers. In the Amsterdam UMC, between January 2017 and June 2019, 130 adults with AAU visited the ophthalmology outpatient clinic. Seventy-four patients had a known cause of AAU: 51 patients with an underlying systemic disease (27 axSpA, 7 sarcoidosis, 4 psoriatic arthritis, 13 other) and 23 patients with a specific uveitis diagnosis, not associated with SpA.

Consequently, 58 patients could be regarded as eligible for CBP screening. Of these, 22 (38%) were referred to the rheumatologist, and for 19 patients (33%) CBP was reported as absent. In the remaining 17 patients (29%), either an incomplete uveitis screening was performed (n = 5, without asking for CBP) or it was not described in the patient file whether CBP was ruled out. Therefore, the referral strategy was inadequately applied in 29% of patients.

DISCUSSION

In this evaluation, 23% of patients referred with AAU and a history of CBP were found to have a clinical diagnosis of axSpA requiring treatment. In these patients, the disease was previously undiagnosed and longstanding, with a mean CBP duration of 10 years. This underscores the importance of implementing the existing referral advice as described in both the Dutch Ophthalmological Society and ASAS recommendations. In addition, 40% of the patients had a suspicion of axSpA, requiring follow-up.

To our knowledge, this is the first evaluation of the strategy of screening AAU patients with a history of CBP in daily clinical practice, although its importance has already been acknowledged decades ago. In 1989, Rosenbaum reported a prevalence of 13% newly diagnosed SpA in consecutive patients with uveitis.[35] In the 2015 DUET study, 42% of 173 patients with AAU from the University of Dublin (Royal Victoria Eye and Ear Hospital) fulfilled the ASAS classification criteria for axSpA (65% radiographic), and 2% for peripheral SpA.[27] The multicenter SENTINEL project studied 798 patients with a single AAU and HLA-B27 positivity, or recurring HLA-B27–negative AAU[13]: 50% fulfilled the ASAS axSpA criteria (60% radiographic), 41% were found to have clinical axSpA, and 12% peripheral SpA. In a study by Sykes et al, all patients who had presented with AAU were approached for a history of CBP.[25] Of the 77 respondents with self-reported CBP, 32% fulfilled the

Table 2. Radiographic changes of the sacroiliac joints, according to the modified New York criteria.[22]

	Overall	Clinical Diagnosis		
		Definite AxSpA	Suspicion of AxSpA	No AxSpA
	n = 81	n = 19	n = 32	n = 30
Sacroiliac joint changes	**26 (32)**	**14 (74)**	**9 (28)**	**3 (10)**
Mild changes	**15 (58)**	**4 (29)**	**8 (89)**	**3 (100)**
Grade 1 unilateral	7 (47)	1 (25)	4 (44)	2 (66)
Grade 1 bilateral	4 (27)	2 (50)	2 (22)	–
Grade 2 unilateral[a]	4 (27)	1 (25)	2 (22)	1 (33)
Severe sacroiliitis (AS)	**11 (42)**	**10 (71)**	**1 (11)**	**0 (0)**
Grade 2 bilateral	2 (18)	2 (20)	–	–
Grade 3 unilateral[b]	3 (27)	2 (20)	1 (100)[c]	–
Grade 3 bilateral	3 (27)	3 (30)	–	–
Grade 4 unilateral[d]	3 (27)	3 (30)	–	–

Values are expressed as n (%). Numbers and percentages in subgroups are derived from values in bold. [a] With grade 1 on the other side. [b] With grade 2 on the other side. [c] Female patient of 38 years, HLA-B27 positive, and history of achillodynia, who, at baseline, only had mild symptoms, insufficient to make a definite axSpA diagnosis (short episodes of very mild back pain, no IBP, excellent spinal mobility). [d] With grade 3 on the other side. AS: ankylosing spondylitis (radiographic axSpA); axSpA: axial spondyloarthritis; IBP: inflammatory back pain.

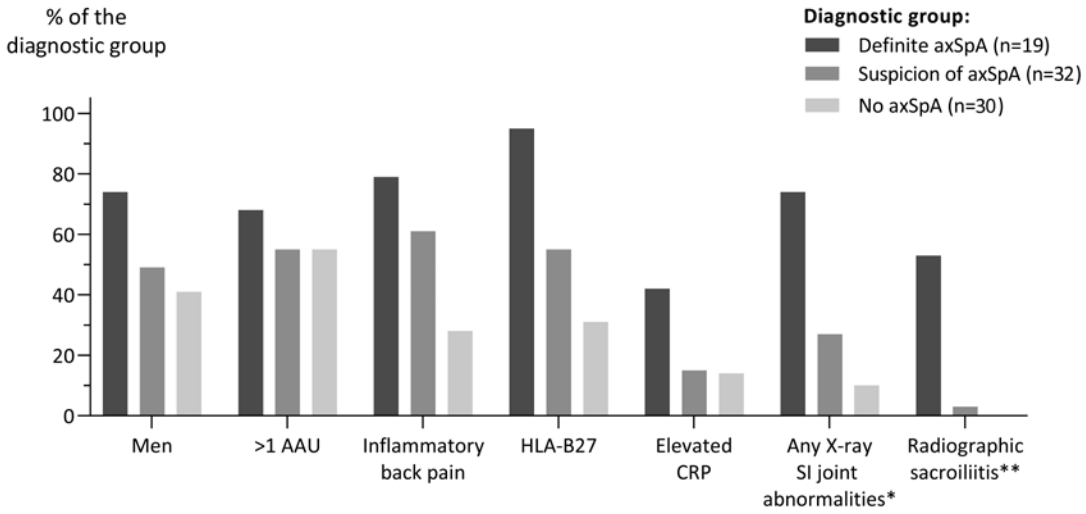

Figure 2. Patient characteristics per diagnostic group. The prevalence in the overall population (n = 81) was 52% men, 58% > 1 previous AAU, 53% inflammatory back pain, 56% HLA-B27 positive, 21% elevated CRP (> 7 mg/L), 32% any SI joint abnormality, and 14% radiographic sacroiliitis. * Any radiographic abnormalities according to the mNY criteria (≥ grade I unilaterally). ** Sacroiliitis according to the mNY criteria. AAU: acute anterior uveitis; axSpA: axial spondyloarthritis; CRP: C-reactive protein; mNY: modified New York; SI: sacroiliac.

ASAS axSpA criteria and 23% were found to have axSpA. Our prevalence of clinical axSpA diagnoses is the same as Sykes et al[25] but lower than SENTINEL,[13] which used different inclusion criteria. DUET reported only the prevalence of positive ASAS criteria of the entire population,[27] which was lower (42%) than in the current study (57%), probably due to selection of patients with CBP in our study.

In the present study, the diagnosis was based on clinical evaluation and not primarily on fulfillment of the classification criteria. We introduced the term *suspicion of axSpA* to describe patients with symptoms that raise a high suspicion of developing axSpA in the (near) future and require follow-up. As our referral strategy explicitly aimed to detect axSpA in an early phase, the high prevalence (40%) of this type of patients found in this study is not surprising. The evaluation of the diagnoses after the 2-year follow-up will inform us on the proportion of patients going on to develop full-blown axSpA and will be published soon.

Potentially, at least 10% of the patients with a new axSpA diagnosis could present with AAU, emphasizing the importance of targeting ophthalmologists.[15] For many years, HLA-B27 positivity has played an important role in the decision to refer patients with AAU for further evaluation.[26] In addition, the referral algorithm proposed by the DUET study included a combination of CBP and HLA-B27, with a high sensitivity and specificity for fulfilling the ASAS axSpA criteria.[27] However, this strategy might be suboptimal, as only 80% of the axSpA patients were HLA-B27 positive. Also, in daily clinical practice, asking for CBP alone might be more feasible than expensive HLA testing.

The majority of the patients had a long duration of CBP before diagnosis, a testimony to the insidious nature of axSpA. In a study of 136 axSpA patients with AAU, 82% initiated with back or joint complaints many years before their first AAU, but only 35% had been diagnosed with SpA before that first AAU.[14] In our study, at referral, 58% of patients had experienced several AAU attacks, with CBP preceding those earlier AAUs in 87%. The insidious course of axSpA is also underscored by our finding that even in patients with mild or atypical clinical characteristics (suspicion of axSpA), radiographic SI changes were present (27%). This underlines the importance of alertness among ophthalmologists, and a low threshold for referral to the rheumatologist.

There appears no gender difference in the prevalence of AAU in the general population, nor for AAU in axSpA, although some studies suggest a male predominance.[36] Up to 60% of patients develop overt axSpA after the first AAU attack and a previous study reported an increase of new axSpA diagnoses after the onset of AAU in women.[20,37,38] This was not confirmed by our data, which showed a higher number of new diagnoses of axSpA in men. However, our sample size is too small to draw conclusions, and the lack of baseline MRI might have resulted in an underestimation of the axSpA prevalence in women, as women are known to show less radiographic progression.[39,40] Longitudinal follow-up of the suspicion of axSpA group will potentially show additional axSpA diagnoses.

A strength of this study is the focus on the clinical diagnosis of axSpA—the gold standard—rather than the fulfillment of the ASAS axSpA classification criteria, which was done in other studies.[27] Classification criteria are meant to create homogeneous groups among patients who are already diagnosed with the disease. These criteria should therefore not be used as a diagnostic tool and might result in an overestimation of the axSpA prevalence, especially in AAU populations. In our study population, 57% would be scored as "axSpA positive" based on the ASAS criteria, and this would also apply to 31% of the 30 patients with no clinical diagnosis (no axSpA). This contrast between the clinical diagnosis and classification criteria was also found in other studies.[13,25] This emphasizes the importance of a clinical diagnosis, and not to use the classification criteria as

"checkboxes."[41] However, the fact that many of the patients who were not (yet) diagnosed with axSpA had several SpA features might mean that this group will yield an even higher prevalence of axSpA in the future.

The major limitation of this study is the lack of a baseline MRI, which might have resulted in a few additional diagnoses of nr-axSpA in the suspicion of axSpA group. This study was performed in accordance with the Dutch clinical guidelines for the evaluation of axSpA, which recommends performing an MRI only in case of doubt in the clinical diagnosis in patients with an inconclusive pelvic radiograph, given limitations of MRI in sensitivity and specificity (even in active axSpA).[41,42,43,44] In the follow-up phase of this study, MRI is performed on clinical indication. Second, diagnosing axSpA can be very challenging, even more so if determined at a single timepoint. This is also demonstrated by the number of patients with possible axSpA in this study. Therefore, for the present study, the possibility of misclassification should be taken into account. The longitudinal part of this study will enhance the precision of the diagnostic value of our referral strategy. Third, evaluation of the use of this referral strategy showed inadequate screening in 29% of the patients with AAU (who were not referred). Fourth, the comparison of the clinical characteristics of the 3 diagnostic groups was explorative and not meant to be conclusive. Fifth, this study focused only on axSpA, whereas AAU occurs in peripheral SpA as well. However, the peripheral manifestations are less likely to correlate with AAU, based on the SENTINEL[13] and DUET[27] studies. Sixth, the current strategy specifically targets ophthalmologists. However, it is important to acknowledge that a more general awareness, also among general practitioners and other (para) medics, is essential to improve the diagnostic delay in all patients with axSpA.

In summary, in this first study in routine clinical practice, the ASAS strategy to refer AAU patients with CBP proved to have a high diagnostic yield for axSpA and should be consistently promoted among ophthalmologists and rheumatologists. Our study revealed a high number of previously missed axSpA diagnoses in patients with AAU despite a long history of back pain. We will continue to follow this cohort to provide insight into the disease course of axSpA in patients with AAU and the future number of new patients with axSpA among the patients who have now been classified as suspicion of axSpA.

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