TITLE:

High prevalence of previously undiagnosed axial spondyloarthritis in patients referred with anterior uveitis and chronic back pain – the SpEYE study.

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SHORT RUNNING HEAD

The SpEYE study

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ABSTRACT

Background

To reduce the diagnostic delay in axial spondyloarthritis (axSpA), guidelines recommend to refer patients with acute anterior uveitis (AAU) and chronic back pain (CBP) to a rheumatologist. This observational study evaluated the prevalence of previously unrecognized axSpA in AAU patients with CBP in daily practice, referred by ophthalmologists who had received instructions to increase awareness.

Methods

All AAU patients referred with CBP (≥3 months, started <45 years of age), from five Ophthalmology clinics underwent rheumatologic assessment, including pelvic X-rays. Patients with previously diagnosed rheumatic disease and established other cause of AAU 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 years, median CBP duration 10 years). 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) were suspicious of axSpA and 37% (n=30) did not have axSpA. AxSpA was diagnosed more often in men (33% of the men versus 13% of women).

Conclusion

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

INTRODUCTION:

The average diagnostic delay in axSpA is about 6-8 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 extra-articular manifestation in axSpA, with a lifetime risk of up to 50%.[3-8] 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%).[8-11] In AAU patients, axSpA develops in up to 50% of the HLA-B27 positive-, and up to 20% of the HLA-B27 negative patients.[12-15] AAU is slightly more prevalent in radiographic (r-)axSpA, than in non-radiographic (nr-)axSpA.[16] So far, no relevant gender differences in prevalence of AAU in axSpA have been observed.[7,17-19] However, Braakenburg demonstrated that male axSpA patients 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 SpondyloaArthritis international society (ASAS) for the early referral of patients with a suspicion of axSpA contain criteria for CBP (duration >3 months, onset <45 years), and a list of SpA-features, including AAU.[21] The combination of CBP and one or more of these features should prompt a referral to 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, the recognition of IBP is challenging.[22,23] Therefore, referral guidelines aimed at non-rheumatologists 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 referral of AAU patients to the rheumatologist are lacking. The Dutch Uveitis guidelines recommend rheumatological evaluation when AAU is accompanied by back pain.[26] Two recent 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 AAU patients 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 (Sp-EYE) study was initiated to study the effect of an initiative in the Amsterdam region to encourage ophthalmologists to refer all patients with at least one 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 for three diagnostic groups (definite, suspicion of axSpA, no axSpA, respectively).

MATERIAL AND METHODS

1. Study design and population

This manuscript describes the baseline results of a prospective cohort study of patients who were referred to the rheumatologist with AAU and CBP. Patients were referred from five regional Ophthalmology centres (academic and non-academic) to the rheumatologist (Rheumatology department Amsterdam University Medical Centre, location VUmc), between April 2017 and January 2020. To increase awareness, Ophthalmology centres were visited and informed through a presentation and brief written information (e-mail and hand-out) at initiation, with yearly repeats. The study protocol was approved by the Medical Ethics Committee of the Amsterdam UMC-VUmc (approval number 2017-037). All study participants gave written informed consent and the study was performed according to the Helsinki Declaration.

2. Referral criteria

Referral criteria were age ≥18 years, a history of ≥1 acute anterior uveitis (AAU) and CBP (currently or previously; with at least 3 months duration, started before the age of 45 years). Patients with a previous diagnosis of AxSpA, juvenile arthritis, another cause of AAU (such as infection) or another auto-immune disease were excluded. However, patients with psoriasis, reactive arthritis or inflammatory bowel disease could be included.

3. Diagnosis of axial spondyloarthritis

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, Erythrocyte Sedimentation Rate) and pelvis radiography (judged by a musculoskeletal radiologist and a rheumatologist). 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' axial SpA (no follow up needed). The 'suspicion of axSpA' group consists of patients in whom rheumatologists cannot 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 two years (longitudinal phase of this study, of which the results will be published later). In patients with a definite- or suspicion- clinical AxSpA diagnosis, fulfilment of the ASAS classification criteria , radiographic or non-radiographic axSpA, was assessed as well.[28]

4. Study parameters

At baseline the following parameters were collected.

4.1 Patient characteristics

Demographics, Body Mass Index, Non-Steroidal Anti-inflammatory Drugs (NSAID's), AAU flares (total number, and year of first and subsequent AAU)

4.2 Back pain

*Y*ear of onset, ASAS Inflammatory Back Pain characteristics (IBP; start <40 years of age, gradual onset, improvement with exercise, no improvement when resting, pain at night which improves upon getting up; IBP if fulfilling ≥4 of the 5 characteristics).[29]

4.3 Presence of ASAS SpA features

ASAS IBP, psoriasis, (reactive) arthritis, inflammatory bowel disease, enthesitis, SpA family history, response of CBP to NSAIDs, HLA-B27 and elevated C-reactive protein (>7 mg/L).[28]

4.4 Physical signs of spondyloarthritis

Bath Ankylosing Spondylitis Metrology Index (BASMI), 44-swollen joint count and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES).[30,31]

4.5 Radiographic changes

Sacroiliitis on the baseline X-ray of the pelvis according to the modified New York criteria.[28]

4.6 Patient reported outcome measures (questionnaires)

Bath AS Disease Activity Index (BASDAI), AS Disease Activity Score CRP (ASDAS-CRP) and Bath AS Functional Index (BASFI).[32-34]

5. Evaluation of the execution of the referral strategy

To evaluate to what extent the referral strategy was executed in practice, a small sub-study was performed in one of the participating centres 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 patients files of all AAU patients 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 (e.g. infection, previously diagnosed rheumatic disease, eye syndrome) were excluded. Outcome parameters of interest were: whether patients were referred to the rheumatologist or whether CBP was ruled out.

6. Statistical analyses

Data analysis was performed with SPSS version 26.0. Data are presented as mean (with standard deviation, SD), number (with percentage), percentage only, or median (inner quartile range, IQR) for parameters without a normal distribution. Explorative analyses were performed on differences between definite-, suspicion- and no-axSpA, in demographics, SpA characteristics and disease activity, with logistic regression (dichotomous variables) and one-way analysis of variance (ANOVA; for continuous variables). For parameters that differed significantly among groups, comparison was performed for definite- versus, respectively, suspicion- and no-axSpA. In addition, three 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 (Figure 1). Twenty patients did not fulfil the referral criteria (11 men, age 41 years SD 14, 5 patients 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 more than one AAU episode (including the AAU that led to referral), alternating between eyes in the majority (n=27), and with median 4 years since the first attack.

At baseline, 86% (n=70) of the patients was 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 developed the first CBP complaints 10 years before referral. At referral, 19% (n=15) of the patients already used an NSAID for their CBP, on their own initiative.

1. Clinical diagnosis of axial spondyloarthritis

A total of 19 patients were diagnosed as “definite axSpA” (23%; Table 1); of whom ten as radiographic- and nine as non-radiographic axSpA (see Supplementary 1 and 2 for details on the, respectively, nr-axSpA patients and the one HLA-B27 negative patient). Further, 32 (40%) patients with mild symptoms were diagnosed as ‘suspicion of axSpA’ (details in Supplementary table 3). An MRI of the SI-joints was made in 4/33 “suspicion” patients, which was negative in all cases. Accordingly, one patient was considered to have ‘no-axSpA’, whereas the other three patients still remained in follow-up (‘suspicion’) due to progression of symptoms. Thirty patients (37%) did not have axSpA, of whom one had sarcoidosis.

Treatment with NSAIDs was initiated in all 19 definite-axSpA patients (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 suspicion patients, of whom the majority fulfilled the criteria for nr-axSpA (Table 1).

1.1 Radiographic changes

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

1.2 Characteristics of patients with a definite axSpA diagnosis

Explorative analyses revealed that patients with definite-, suspicion- and no-axSpA only differed in a few characteristics (Table 1, Figure 2). Patients with definite-axSpA significantly more often had IBP (17/19) and were HLA-B27 positive (18/19), compared to patients with no-axSpA (IBP: 8/30, p=0.01; HLA-B27: 9/30, p=0.001). Compared to suspicion-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 (SD1)), and a worse spinal mobility (BASMI: 3.1 (SD1.4)), compared to both, the suspicion- (SpA-features: 3 (SD1), p=0.01; BASMI: 1.5 (SD0.9), p=0.001) and no-axSpA group (SpA-features: 2 (SD1), p<0.001; BASMI: 1.8 (SD1.1), p=0.001).

2. Onset of back pain in relation to anterior uveitis

Of all 81 patients, 34 (42%) were referred after their first AAU; and had suffered from CBP for 15 years (median, 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 axSpA patients with >1 AAU (n=13), and to 83% and 88% of the patients with respectively suspicion-axSpA (n=18) and no-axSpA (n=16) and >1 AAU.

3. Gender differences

In total, 42 men (median age 42 years, IQR 16) and 39 women (median age 40 years, IQR 15) were included. A positive history of >1 previous AAU flares was slightly more common in men (28/42, versus 19/39 in women, p=0.10; both a 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%, versus 13% in women; p=0.03), with the radiographic type in 7/14 of the diagnoses in men, and 3/5 of the diagnoses in women.

4. Performance of the referral strategy in a subsample of AAU patients

To evaluate to what extent ophthalmologists applied the referral strategy, a small sub-study was performed in one of the participating Ophthalmology centres. In the Amsterdam UMC, between January 2017 and June 2019, 130 adults with AAU visited the Ophthalmologhy 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 ‘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 long-standing, with a mean back pain duration of 10 years. This underscores the importance of implementing the existing referral advices as described in both the Dutch Ophthalmological 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 et al reported a prevalence of 13% newly diagnosed spondyloarthritis in consecutive patients with uveitis.[35] In the 2015 DUET study 42% of 173 AAU patients from the University Ophthalmology centre fulfilled the ASAS (classification) criteria for axSpA (65% radiographic), and 2% for peripheral SpA.[27] The multicentre 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 all patients who had presented with AAU were approached to ask for a history of CBP.[25] Of the 77 respondents with self-reported CBP, 32% fulfilled the ASAS axSpA criteria, and 23% were found to have axSpA. Our prevalence of clinical axSpA diagnoses is the same as Sykes, but lower than SENTINEL, which used different inclusion criteria. DUET only reported the prevalence of positive ASAS criteria of the entire population, which was lower (42%) than in the current study (57%), probably due to selection of patients with CBP in our study.

In this evaluation, the diagnosis was based on clinical evaluation and not primarily on fulfilment of the classification criteria.. We introduced the term ‘suspicious-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 two year follow up will inform us on the proportion of patients going on to develop full flown 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 AAU patients for further evaluation.[26] In addition, the referral algorithm proposed by the aforementioned DUET 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 are 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, 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-axSpA), radiographic sacro-iliac 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 that 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 group who was suspicious for axSpA will potentially show additional axSpA diagnoses.

A strength of this study is that it focused on clinical diagnosis of axSpA, the gold standard, rather than 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 'axSpA-positive', based on the ASAS criteria, and this would also apply to 31% of the 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 "check boxes".[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 even yields a higher prevalence of axSpA in the future.

The major limitation of this study is the lack of a baseline MRI, which might have yield 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 evaluation of Axial Spondyloarthritis , which recommends to perform an MRI only in case of doubt on the clinical diagnosis in patients with an inconclusive pelvic radiograph, given its limitations in sensitivity and specificity (even in active axSpA).[41-44] In the follow up phase of this study, MRI is performed on clinical indication. Second, diagnosing axSpA can be very challenging, even more if determined at a single time point. This is also demonstrated by the number of possible-axSpA patients in this study. Therefore, for this 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 AAU patients (who were not referred). Fourth, the comparison of the clinical characteristics of three diagnostic groups was explorative and not meant to be conclusive. Fifth, this study only focused 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 and DUET study. 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, eventually is essential to improve the diagnostic delay in all axSpA patients.

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 number of axSpA diagnoses in this group.

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FIGURE LEGENDS

FIGURE 1. STUDY FLOW CHART of patients referred from the ophthalmologist to the rheumatologist. AAU, acute anterior uveitis; axSpA, axial spondyloarthritis. *Among the excluded patients, five were HLA-B27 positive, one had radiological signs of ileitis condensans, and none were clinically diagnosed with axSpA

FIGURE 2. PATIENT CHARACTERISTICS PER DIAGNOSTIC GROUP. The prevalences in the overall population (n=81) were, respectively: 52% men, 58% >1 previous AAU, 53% inflammatory back pain, 56% HLA-B27 positive, 21% elevated CRP, 32% any SI joint abnormality and 14% radiographic sacroiliitis. AAU, acute anterior uveitis; axSpA, axial spondyloarthritis; CRP, C-reactive protein; SI, sacroiliac.
*any radiographic abnormalities according to the modified New York criteria (≥grade I unilaterally). ** Sacroiliitis according to the modified New York criteria.

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

	Overall	Clinical diagnosis			
		Definite axSpA	Suspicion of axSpA	No axSpA	*Differences between diagnostic groups*
	(n=81)	(n=19)	(n=32)	(n=30)	*p-value**
Age, median	41 (25)	34 (23)	38 (18)	42 (14)	*0.15*
Gender, men	42 (52)	14 (74)	15 (47)	13 (43)	*0.09*
Ethnicity[1], Caucasian	58 (72)	14 (79)	24 (75)	20 (67)	*0.23*
Body mass index, median	25 (5)	24 (5)	25 (5)	25 (7)	*0.25*
Fulfilling ASAS classification criteria [2]	46 (57)	19 (100)	18 (56)	9 (30)	
Radiographic axSpA (ASAS)	11 (24)	10 (53)	1 (3)	0 (0)	
Non-radiographic axSpA (ASAS)	35 (76)	9[5] (47)	17[6] (53)	9 (30)	
Anterior uveitis, >1 flare in total	47 (58)	13 (68)	18 (56)	16 (55)	*0.57*
Years since first AAU, median	4 (7)	5 (18)	5 (8)	2 (6)	
Number of previous flares, median	3 (2)	3 (5)	3 (5)	3 (1)	
Back pain before first AAU	60 (74)	13 (68)	24 (73)	23 (79)	
Back pain					
Currently back pain	70 (86)	17 (90)	26 (81)	27 (90)	*0.56*
Age at onset, years, mean	27 (10)	26 (10)	26 (10)	27 (11)	*0.87*
Years since onset, median	10 (19)	10 (22)	8 (19)	14 (21)	*0.33*
Inflammatory back pain[3], ever	45 (56)	17 (89)	20 (63)	8 (29)	***<0.002***
ASAS SpA features [4], mean number	3 (1)	4 (1)	3 (1)	2 (1)	***<0.001***
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	13 (12)	18 (21)	14 (11)	11 (11)	
Other SpA features					
Morning stiffness >30 minutes	34 (42)	8 (42)	17 (53)	9 (30)	*0.19*
Alternating buttock pain	28 (35)	10 (53)	12 (38)	6 (21)	*0.07*

Artralgia 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 parameters					
BASMI linear score, mean	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	3 (1-5)	3 (1)	3 (4)	3 (3)	
Arthritis currently (44 joint count >0)	3 (4)	0 (0)	2 (6)	1 (3)	*0.87*
Patient global disease activity, mean NRS	4 (3)	4 (2)	4 (3)	4 (4)	*0.41*
Back pain at night, median NRS	3 (0-6)	3 (6)	2 (6)	3 (6)	*0.54*
BASDAI score, median	2.7 (2)	3.3 (2.6)	2.6 (2. 8)	2.7 (36)	*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	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	1 (3)	1 (4)	1 (2)	1 (2)	*0.66*

Legend: Numbers are mostly depicted as number of patients (%), unless stated otherwise (mean (±SD) or median (IQR). *p-value of <0.002 was regarded statisticall significant, after Bonferroni correction for multiple testing. 1. Caucasian 72%, African 6%, Hindustan 5%, Turkish 5%, Moroccan 4%, Asian 1%, Latin American 3%, mixed ethnicity 4%; 2. Patients fulfilling the ASAS classification criteria for axSpA (radiographic or non-radiographic)(22); 3. IBP according to the ASAS IBP criteria(23); 4. No patient had a history of dactylitis or inflammatory bowel disease; 5. An MRI was made in 1/9 nr-axSpA patients, demonstrating sacroiliitis. The others were diagnosed based on a compatible clinical clinical picture. 6. An MRI was made in 4/33 suspicious patients, and was negative in alle cases.

AAU, acute anterior uveitis; ASAS, Assessment of Spondyloarthritis international Society; axSpA, axial spondyloarthritis; ASDAS, AS 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; HLA-B27, Human Leukocyte Antigen B27; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; NRS, numeric rating scale; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2. Radiographic changes of the sacroiliac joints

	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**	*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***	*3 (27)*	*2 (20)*	*1 (100)* [A]	-
Grade 3 bilateral	*3 (27)*	*3 (30)*	-	-
*Grade 4 unilateral****	*3 (27)*	*3 (30)*	-	-

Legend: Radiographic changes of the sacroiliac joints, according to the modified New York criteria.(22) Numbers are depicted as number of patients (%). *with grade 1 on the other side; **with grade 2 on the other side; ***with grade 3 on the other side. AxSpA, axial spondyloarthritis. A: 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). AS = ankylosing spondylitis (radiographic axial SpA)

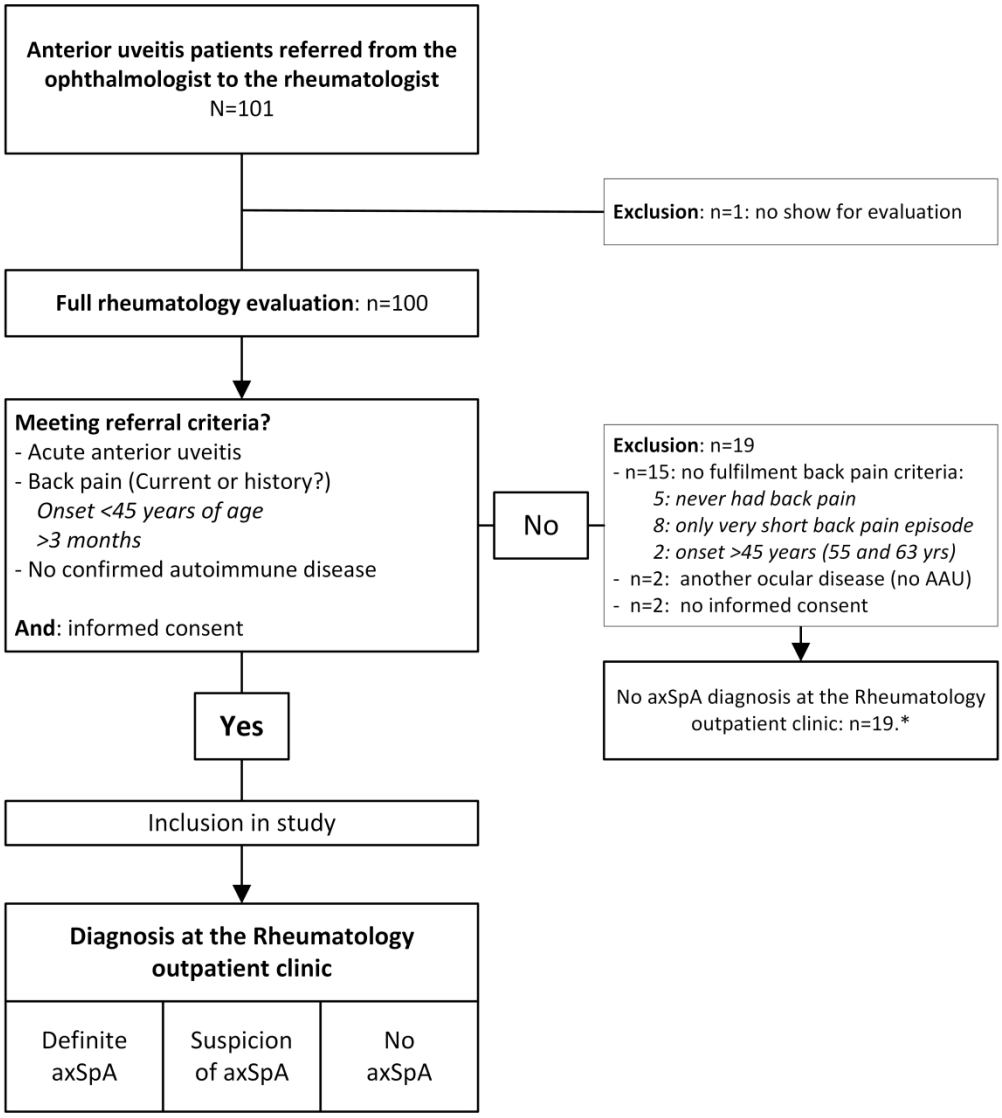

FIGURE 1. STUDY FLOW CHART of patients referred from the ophthalmologist to the rheumatologist. AAU, acute anterior uveitis; axSpA, axial spondyloarthritis. *Among the excluded patients, five were HLA-B27 positive, one had radiological signs of ileitis condensans, and none were clinically diagnosed with axSpA.

158x175mm (600 x 600 DPI)

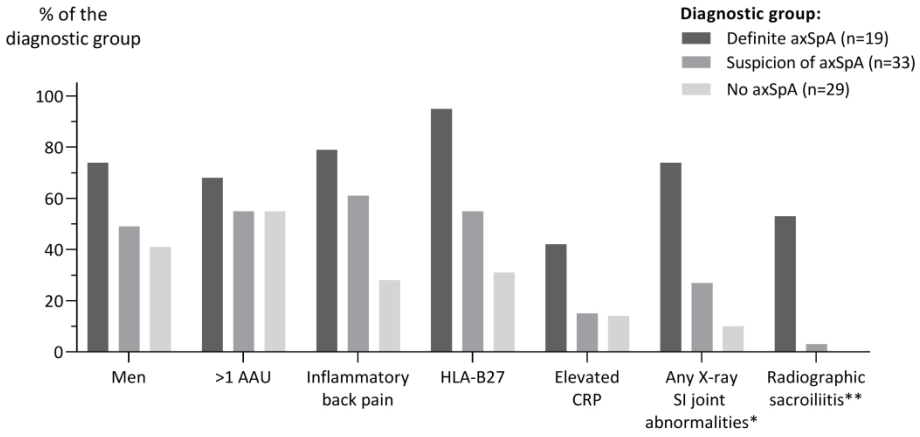

FIGURE 2. PATIENT CHARACTERISTICS. Figure 2 depicts, per diagnostic group (definite, suspicion, no-axSpA) the prevalence of certain characteristics. The prevalences in the overall population (n=81) were, respectively: 52% men, 58% >1 previous AAU, 53% inflammatory back pain, 56% HLA-B27 positive, 21% elevated CRP, 32% any SI joint abnormality and 14% radiographic sacroiliitis. AAU, acute anterior uveitis; axSpA, axial spondyloarthritis; CRP, C-reactive protein; SI, sacroiliac.
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137x72mm (600 x 600 DPI)