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BRIEF REPORT

Impact of Uveitis on the Phenotype of Patients With Recent Inflammatory Back Pain: Data From a Prospective Multicenter French Cohort

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Objective. **To determine the prevalence of uveitis in patients with recent inflammatory back pain (IBP) suggestive of spondylarthritis (SpA), and to investigate the impact of uveitis on the overall features of these patients.**

Methods. **The Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR; Outcome of Recent Undifferentiated Spondylarthropathies) cohort is a prospective multicenter French cohort of 708 patients with early IBP suggestive of SpA. Uveitis was defined by an ophthalmologic episode diagnosed as uveitis by an ophthalmologist, or history of a medical diagnosis of uveitis given to the patient. Data on the baseline demographic characteristics, functional status and quality of life, imaging features, bone mineral density (BMD), and blood tests were compared in patients with and without uveitis. Factors associated with the presence of uveitis were identified both by univariate and multivariate analysis (logistic regression).**

Results. **The prevalence of uveitis at inclusion in the DESIR cohort was 8.5%. Uveitis occurred after the first symptoms of IBP in 45% of patients. The presence of uveitis was significantly associated (univariate) with pain in the cervical spine, infection preceding inflammatory disease, a previous diagnosis of inflammatory bowel disease (IBD), the Short Form 36 (SF-36; mental and physical health and social relationship subscales), Achilles enthesitis, elevated leukocyte count, and radiologic hip involvement, but not with fulfillment of classification criteria, HLA–B27, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, Ankylosing Spondylitis Disease Activity Score, and BMD. Stepwise multivariate analysis found an association between uveitis and pain in the cervical spine, infection preceding inflammatory disease, a previous diagnosis of IBD, and the physical health limitation of the SF-36 ($P < 0.05$).**

Conclusion. **In recent IBP suggestive of SpA, uveitis is associated with IBD and infection. This might suggest a role of environmental factors in the incidence of uveitis in SpA.**

Introduction

Anterior uveitis or iridocyclitis is the most frequent extraarticular feature in spondylarthritis (SpA), and one element included in the various sets of classification criteria currently available for SpA (1). The prevalence of SpA in patients with uveitis has been evaluated in several studies; in a prospective study of 433 patients with different types of uveitis, SpA was diagnosed according to the European Spondylarthropathy Study Group (ESSG) classification criteria in 44 patients (10%), of whom 19 had ankylosing

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Significance & Innovations

- In early inflammatory back pain suggestive of spondylarthritis (SpA), uveitis (history or current symptoms) is present in 8.5% of the cases, and is significantly associated with pain in the cervical spine, infection preceding inflammatory disease, and a previous diagnosis of inflammatory bowel disease.
- This may suggest a common role for environmental factors in the incidence of uveitis and SpA.

spondylitis (AS) (2). One hundred seventy-five consecutive cases with HLA–B27–associated uveitis were systematically referred to rheumatologists. AS was diagnosed in 81 patients (46%) (3). The onset of extraocular symptoms occurred at a younger age than the first attack of uveitis, and patients with extraocular disease had a greater total number of attacks of uveitis (3).

A retrospective study of 350 cases of SpA (207 with AS) found 30 AS patients (14.5%) with 55 episodes of acute anterior uveitis (4); anterior uveitis was associated with the juvenile onset of the disease and involvement of the entheses of the lower extremities.

A systematic literature review based on 1,989 patients with SpA (5) revealed a mean prevalence of uveitis of 32.7%; the prevalence increased with disease duration and was higher in HLA–B27–positive patients, with an odds ratio (OR) of 4.2. Uveitis was acute in 88%, anterior in 90%, and unilateral in 87%, with recurrence in 50%. These data emphasize the close relationship between SpA and uveitis. Inflammatory back pain (IBP) is the main presenting symptom and entry for classification of SpA. There are no data about uveitis in recent IBP.

The main objective of this study was to determine the prevalence of uveitis and its characteristics in patients with recent IBP. The secondary objectives were to evaluate the impact of uveitis on clinical, laboratory, and imaging features (standard radiographs, magnetic resonance imaging [MRI] of the entire spine, and ultrasound); bone mineral density (BMD) and body composition features (fat mass and lean mass); and fulfillment of classification criteria.

Methods

This was a cross-sectional study evaluating all patients enrolled in the Devenir des Spondylarthropathies Indifférenciées Récentes (DESIR; Outcome of Recent Undifferentiated Spondylarthropathies) cohort and for whom data were available at baseline. The DESIR cohort is a prospective multicenter French cohort of patients with early IBP (classified according to either the criteria by Calin et al [6] or the Berlin criteria [7], taking into account for the latter 2 of 4 items) of a duration of more than 3 months and less than 3 years, with symptoms suggestive of SpA according to the local investigator's assessment (score of ≥5 on a 0–10 numerical rating scale, where 0 = not suggestive and 10 = very suggestive of SpA), and planned to be followed up to at least 5 years. The method of construction of the cohort, as well as the main characteristics of the patients at baseline, have been reported previously (8). This cohort included 708 patients (mean age 33.8 years, 53.8% women, and 57.3% HLA–B27 positive). The presence of uveitis was assessed by the investigators for all patients at baseline. Uveitis was defined by an ophthalmologic episode diagnosed as uveitis by an ophthalmologist, or history of a medical diagnosis of uveitis given to the patient. The baseline characteristics included age, ethnicity, date at onset of IBP and peripheral arthritis, nature of IBP, presence of SpA features, relevant family history, and medication, including the use of nonsteroidal antiinflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs). The duration of axial symptoms was defined as the time difference between the first axial symptom and the initial interview. A physical examination was also performed to determine the Ritchie Articular Index (53 joints) and swollen joint count (28 joints), spinal mobility as measured by the Bath Ankylosing Spondylitis Metrology Index, chest expansion, and enthesitis index. Extraarticular features were also evaluated, particularly psoriasis and inflammatory bowel disease (IBD; presence or history of a medical diagnosis).

Patients were asked to complete the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Global Index, Health Assessment Questionnaire (HAQ), Short Form 36 (SF-36), and Ankylosing Spondylitis Quality of Life questionnaire.

Blood tests were performed in the regional rheumatology centers. These included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and HLA–B27 antigen, and usual biologic parameters. The Ankylosing Spondylitis Disease Activity Score (ASDAS) (9) was calculated using the CRP level.

All imaging modalities (radiographs and MRIs) were evaluated by the local radiologist or rheumatologist. Radiographs of the sacroiliac and hip joints were graded according to the following grading scale: 0 = normal, 1 = doubtful (grade 1), 2 = obvious (grade 2 or 3), and 3 = fusion. Lateral radiographs of the cervical and lumbar spine were used to calculate the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) (10).

T1-weighted fast spin-echo and STIR 1–1.5T MRIs of the spine and the sacroiliac joints were performed to assess inflammatory and structural lesions. The MRIs were classified by the local radiologist or rheumatologist as having definite, doubtful, or absent inflammatory or structural lesions at the spinal and sacroiliac levels.

Data on the baseline demographic characteristics, functional status and quality of life, imaging features (standard radiographs, MRI, ultrasound), BMD, and blood tests were compared in patients with and without uveitis. These data allowed testing of each patient for the fulfillment of ESSG, Amor, and Assessment of SpondyloArthritis international Society (ASAS) classification criteria (1). Both the date of the first symptom of IBP and the symptoms of uveitis were recorded, as well as the date of the visit. Factors associated with the presence of uveitis were identified both by univariate and then multivariate analysis (logistic regression

Table 1. Comparison of baseline characteristics between patients with and without a history of uveitis*

	Uveitis presence (n = 60)	Uveitis absence (n = 648)	*P*
Male sex, %	41.7	46.7	0.45
Age, mean ± SD years	34.8 ± 8.6	33.7 ± 8.6	0.36
Age at onset of IBP, mean ± SD years	32.9 ± 8.7	32.1 ± 8.7	0.54
Family history of ankylosing spondylitis, %	25.0	19.1	0.41
Family history of uveitis, %	10.0	4.0	0.11
Presence of peripheral arthritis, %	56.7	57.1	0.94
Presence of enthesitis, %	48.3	49.1	0.91
Chest wall pain, %	38.3	45.2	0.30
Dactylitis, %	15.0	12.8	0.63
Location of axial involvement since the beginning, %			
Cervical spine	51.7	37.5	0.03†
Thoracic spine	55.0	57.3	0.74
Lumbar spine	83.3	91.0	0.052
Gluteal area	70.0	75.0	0.39
Efficacy of NSAIDs, %	76.3	80.4	0.44
Extraarticular features, %			
Psoriasis	16.7	15.7	0.85
Events in the 3 months before the first inflammatory symptom, %			
Infection	13.3	3.4	0.002†
Diagnosis before inclusion, %	86.7	73.3	0.024†
Ankylosing spondylitis	45.0	41.8	0.63
Psoriatic arthritis	0	4	0.11
IBD-associated SpA	8.3	2.5	0.026†
Undifferentiated SpA	31.7	23.1	0.13
Duration of IBP symptoms at inclusion, no. of days	348	238	0.01†
Fulfillment of classification criteria, %			
ASAS (axial)	76.7	66.2	0.09
ESSG	83.3	77.0	0.26
Amor	85.0	76.7	0.14
Clinical data			
BMI, mean ± SD kg/m^2	23.9 ± 3.9	23.9 ± 4.7	0.90
BASMI, mean ± SD score	2.28 ± 0.82	2.18 ± 0.92	0.30
Achilles enthesitis, %	18.5	22.5	0.04†
Laboratory tests			
HLA–B27 positive, %	63.3	57.1	0.13
ESR, mean ± SD mm/hour	11.82 ± 13.04	14.01 ± 15.05	0.51
CRP level, mean ± SD mg/liter	9.17 ± 13.24	8.98 ± 14.59	0.13
Hemoglobin, mean gm/dl	13.55	16.28	0.39
White blood cell count, mean ± SD mm^3	13,264 ± 2,908	8,412 ± 2,497	0.019†
Activity, QOL			
PASS, %	44.1	41.1	0.66
BAS-G, mean ± SD (range 0–10)	4.71 ± 2.36	5.12 ± 2.58	0.24
BASDAI, mean ± SD (range 0–100)	42.8 ± 20.5	44.8 ± 19.9	0.46
ASDAS-CRP level, mean ± SD score	2.57 ± 1.0	2.50 ± 1.0	0.59
BASFI, mean ± SD (range 0–100)	26.09 ± 21.62	30.87 ± 22.84	0.13
HAQ, mean ± SD	0.55 ± 0.45	0.57 ± 0.45	0.53
ASQoL, mean ± SD	8.28 ± 5.33	9.35 ± 4.90	0.11
SF-36 physical health subscale, mean ± SD	0.73 ± 1.22	1.10 ± 1.16	0.02†
SF-36 social relationship subscale, mean ± SD	0.85 ± 1.21	1.14 ± 1.21	0.048†
SF-36 mental health subscale, mean ± SD	0.74 ± 1.0	1.08 ± 1.1	0.017†
Imaging			
Radiograph sacroiliitis, %‡	58.9	47.9	0.12
Radiograph hip involvement, %‡	10.8	4.9	0.04†
mSASSS, mean ± SD	1.61 ± 4.76	1.01 ± 2.67	0.92
MRI abnormalities, %			
Inflammatory lesion (sacroiliac or spine)	62.5	55.8	0.46
Chronic lesion (sacroiliac or spine)	55.4	40.6	0.10
Enthesis ultrasound (n = 399), %			
At least 1 abnormal finding	41.7	31	0.09
Power Doppler positive	8.8	6.0	0.46

* IBP = inflammatory back pain; NSAIDs = nonsteroidal antiinflammatory drugs; IBD = inflammatory bowel disease; SpA = spondylarthritis; ASAS = Assessment of SpondyloArthritis international Society; ESSG = European Spondylarthropathy Study Group; BMI = body mass index; BASMI = Bath Ankylosing Spondylitis Metrology Index; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; QOL = quality of life; PASS = Patient Acceptable Stable State; BAS-G = Bath Ankylosing Spondylitis Global Index; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; ASDAS-CRP = Ankylosing Spondylitis Disease Activity Score (CRP based); BASFI = Bath Ankylosing Spondylitis Functional Index; HAQ = Health Assessment Questionnaire; ASQoL = Ankylosing Spondylitis Quality of Life questionnaire; SF-36 = Short Form 36; mSASSS = modified Stoke Ankylosing Spondylitis Spinal Score; MRI = magnetic resonance imaging.
† Significant at $P < 0.05$.
‡ Score ≥1 (see Methods for details).

Table 2. Stepwise multivariate analysis*

	Uveitis (n = 60)	No uveitis (n = 648)	Adjusted OR (95% CI)	*P*
Pain in the cervical spine, no. (%)	31 (51.7)	243 (37.5)	2.03 (1.14–3.64)	0.017
Infection preceding inflammatory disease, no. (%)	8 (13.3)	22 (3.4)	5.45 (2.20–14.49)	0.0002
Previous diagnosis of inflammatory bowel disease, no. (%)	6 (10)	20 (3.1)	3.76 (1.37–10.31)	0.01
Physical health limitation of the SF-36, mean ± SD	56.7 ± 41.4	44.0 ± 39.1		0.0017

* OR = odds ratio; 95% CI = 95% confidence interval; SF-36 = Short Form 36.

with the variables significant in univariate analysis). *P* values less than 0.05 were considered significant. Data were extracted from the M0 DESIR database locked on June 30, 2010.

The DESIR study was approved by the French Departmental Directorate of Health and Social Affairs (Directeur Départemental des Affaires Sanitaires et Sociales) and the approval of the appropriate local ethical committees was obtained. The study was conducted in accordance with the Declaration of Helsinki and the Guidance for Good Clinical Practice (French version), November 30, 2006. Participants gave their written informed consent.

Results

Sixty cases of uveitis were reported at baseline, and the prevalence of uveitis in the DESIR cohort was 8.5% (n = 60 of 708 patients with recent IBP; 95% confidence interval [95% CI] 6.58–10.83). Uveitis occurred after the first symptoms of IBP in 45%, before in 37%, and simultaneously (±1 month) in 18% of the cases. Uveitis was remitting in 33 cases, relapsing in 21 cases, and continuous in 6 cases. In univariate analysis (Table 1), the presence of uveitis was significantly associated with pain in the cervical spine, infection preceding (less than 3 months) inflammatory disease, a previous diagnosis of IBD, some dimensions of the SF-36 (mental and physical health and social relationship subscales), Achilles enthesitis, elevated leukocyte count, serum creatinine levels, and radiologic hip involvement. Uveitis was not associated with fulfillment of classification criteria, HLA–B27, BASDAI, BASFI, and ASDAS. Uveitis was not associated with BMD and body composition (n = 341), metabolic biologic syndrome (glycemia, lipids), concomitant treatment in the last 6 months (NSAIDs, steroids, DMARDs), or comorbidities, especially cardiovascular disease, diabetes mellitus, and smoking (data not shown). A stepwise multivariate analysis found an association between uveitis and pain in the cervical spine, infection preceding inflammatory disease, previous diagnosis of IBD-associated SpA, and the physical health limitation of the SF-36 (Table 2).

Infections preceding less than 3 months of onset of inflammatory signs were recorded by interview in 13.3% of patients (8 of 60) with uveitis and 3.4% without uveitis (22 of 647). Documented information was available in some patients: 1 with chlamydia, 2 with streptococcus, and 3 with herpesvirus in the uveitis group, and 3 with chlamydia, 1 with salmonella, 1 with Epstein-Barr virus, 1 with streptococcus, and 2 with herpesvirus in the nonuveitis group, with some data missing.

Discussion

In this large cohort of early IBP suggestive of SpA, we found a prevalence of uveitis of 8.5%. Most of these patients fulfilled, at inclusion, the ASAS classification criteria for axial SpA, with (77%) or without (66%) uveitis. As expected, more patients fulfilled these criteria when uveitis was present, but without reaching statistical significance. This prevalence was evaluated at entry into the cohort (mean duration of IBP symptoms of less than 12 months), and was smaller than some series of advanced cases of AS in the literature (5). This should be confirmed in the subsequent followup of the DESIR cohort planned for 10 years, as it was demonstrated that uveitis prevalence increases with disease duration in SpA (5).

We found no differences in age at onset of IBP between patients with and without uveitis, whereas in the study by Sampaio-Barros et al, anterior uveitis was associated with the juvenile onset of the disease and with the enthesopathic involvement of the lower extremities in patients with AS (4). However, Rudwaleit et al (11) found no statistical difference in uveitis prevalence between early and late SpA (19.3% versus 22.4%) or between nonradiographic and radiographic SpA (12.4% versus 19.3%) patients from the German Spondyloarthropathy Inception Cohort (GESPIC). This prevalence was somewhat higher than in our cohort, but the definition of "early" was different (less than 5 years in the GESPIC versus less than 3 years in the DESIR).

In univariate analysis, uveitis was associated with Achilles enthesitis (but less frequent in cases of uveitis) and a trend for at least one abnormality at ultrasound examination to be more frequent in cases of uveitis in DESIR. Evaluation of uveitis in 350 patients with SpA revealed a frequent association with enthesitis (4). Uveitis was also associated with radiographic hip involvement, with less normal radiographs of the hip in the population with uveitis. Hip involvement is a classic prognosis factor in AS, but we found no other imaging difference (mSASSS, inflammatory or chronic MRI) associated with uveitis in DESIR.

We found no other particular rheumatologic finding associated with uveitis. Specifically, no association with peripheral arthritis was obvious, whereas in patients with AS, peripheral involvement was more often associated with uveitis (36% uveitis in patients with peripheral arthritis versus 20% without peripheral arthritis [$P = 0.005$] among 271 patients with AS defined by the modified New York criteria) (12). No particular comorbidities (no meta-

bolic syndrome, no difference in smoking) were associated with uveitis in DESIR.

No difference in HLA–B27 positivity between patients with or without a history of uveitis was noted. This may represent, in first analysis, a discrepancy with other results from the same cohort (13); however, in that study, analysis was done only in patients fulfilling classification criteria, and uveitis was evaluated as the dependant variable (with adjustment to other variables such as sex, ethnicity, familial history of SpA, age, duration of IBP, CRP level, ESR, and current NSAID use). In multivariate analysis, uveitis was found to be negatively associated with white race (OR 0.33, 95% CI 0.12–0.96; $P = 0.04$) and positively associated with duration of IBP (OR 1.48, 95% CI 1.04–2.13; $P = 0.03$) and HLA–B27 positivity (OR 2.63, 95% CI 1.28–5.39; $P = 0.01$).

No difference in biologic measures of inflammation (ESR, CRP) was found in cases of uveitis, but an increased white blood cell count was found in patients with uveitis in univariate analysis, and this may be related to an infectious background.

No increase in disability (HAQ, BASFI) or in disease activity (BASDAI, ASDAS) was associated with uveitis, as was no difference in the use of concomitant treatment. Taken together, these data (except for coxitis) did not support the hypothesis of increased activity, severity, or functional impairment in cases of IBP when associated with uveitis. The long term of the followup planned in the DESIR cohort will allow evaluation of the prognosis value of uveitis on the subsequent evolution (rheumatologic and extrarheumatologic).

Finally, in multivariate analysis, uveitis was associated with physical health limitation in the SF-36 (that may be a consequence of extraarticular involvement), cervical spine pain, previous diagnosis of IBD-associated SpA, and history of infection in the 3 months before the first onset of inflammatory symptoms. Infection may trigger both uveitis and SpA, and therefore may be a common link between the 2 conditions.

An association between uveitis and Crohn's disease has been previously reported (14), with uveitis occurring in 5% of patients with IBD (15); on the other hand, the association between IBD and SpA is well known, so the association between uveitis and a previous diagnosis of IBD-related SpA is not surprising. Moreover, IBD may favor introduction of bacterial antigens, a potential mechanism for SpA.

In recent IBP suggestive of SpA, uveitis was associated with some particular rheumatologic and extrarheumatologic features. Our data, and in particular the association with IBD and preceding infection, might suggest a role of environmental factors in the incidence of uveitis in SpA.

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. Wendling 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. Wendling, Prati, Demattei, Daures, Dougados.
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ROLE OF THE STUDY SPONSOR

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