Juvenile Spondyloarthritis: focus on uveitis.

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Short Report

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Abstract

Background Juvenile spondyloarthritis (JSpA) represents a group of inflammatory arthritides with several distinctive features (enthesitis, involvement of spine and sacroiliac joint, HLA-B27 association and development of uveitis). There are limited data on the course of uveitis in children with JSpA. This study aims to estimate the prevalence of uveitis and to look at the presence of HLA-B27 in relation to uveitis occurrence and ocular symptoms in a cohort of JSpA patients.

Findings This is a cross sectional/retrospective study involving patients with JSpA followed in a tertiary referral hospital. Two hundred twenty-three patients were enrolled in the study. The prevalent diagnosis was enthesitis-related arthritis (ERA) (62%) followed by juvenile psoriatic arthritis (PsA), undifferentiated arthritis (UA), and the arthropathies associated with inflammatory bowel disease (IBD-A) (18%, 13%, 12%, respectively). Uveitis was reported in twenty-four patients (11%) of the JSpA cohort (JSpA-U). ERA patients had the highest uveitis prevalence (ERA-U) (13%) with similar prevalences in UA, PsA (7%) and in IBD-A (7% each). The prevalence of HLA-B27 positivity was 45% amongst JSpA-U (N=22), with fewer than half of patients with ERA-U HLA-B27 positive (44%). The overall prevalence of symptomatic uveitis was 79%. Neither the likelihood of uveitis, nor of symptomatic uveitis, varied by HLA-B27 status either in the entire cohort nor in those with ERA.

Conclusions About one-tenth of patients developed uveitis, the majority of which was symptomatic. Fewer than half of the patients with uveitis were HLA-B27 positive. HLA-B27 status was not statistically associated with either the development of uveitis or symptomaticity of uveitis.

Introduction

Spondyloarthritis (SpA) represents a group of inflammatory arthritides affecting both adults and children with several distinctive features such as the presence of enthesitis, the potential involvement of spine and sacroiliac joint, a strong association with HLA-B27 and development of uveitis that is more often acute onset and/or symptomatic [1].

International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA) [2] does not recognize a specific category for Juvenile SpA (JSpA) patients. Yet, spondyloarthritis includes enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (PsA), undifferentiated arthritis (UA), reactive arthritis (ReA), and the arthropathies associated with inflammatory bowel disease (IBD-A)[1]. Adult SpA has been extensively studied and similar manifestations are assumed to be true for JSpA, although they have not been verified in children.

More than one-third of adult SpA patients develop ocular inflammation that usually is characterized by acute episodes of uveitis [3, 4]. While children with JSpA are de facto expected to follow similar courses as adults, there are limited data on JSpA associated uveitis in children. In children with JSpA, uveitis is thought to be symptomatic acute anterior uveitis [5].

This study aimed to estimate the prevalence of uveitis and to look at the presence of HLA-B27 in relation to uveitis occurrence and ocular symptoms in a cohort of JSpA patients.

Methods

This is a cross sectional/retrospective study involving patients with JSpA followed in a tertiary referral hospital. All patients evaluated by a pediatric rheumatologist at the Children's Hospital of Philadelphia (CHOP) from February 2016 to August 2019 and diagnosed with ERA, PsA, UA or IBD-A were approached to participate in the JSpA Registry, with a 91% recruitment rate. A RedCAP registry included responses from electronic questionnaires completed by the consenting patients and clinical data collected retrospectively from the electronic and paper medical records.

History of uveitis was established using either chart review of ophthalmology records or patient/caregiver reports; both were recorded when available. In the registry, patients were asked about ocular symptoms that occurred since the last visit. Ocular symptoms were defined as the presence of pain, redness, or photosensitivity.

Data were analyzed using Stata 15.1. Differences in categorical demographic and clinical characteristics between subcohorts were assessed using the chi-squared test. Nominal statistical significance was defined as a 2-tailed p value of ≤ 0.05. The study was reviewed and approved by the institutional review board of CHOP.

Results

Two hundred twenty-three patients were enrolled in the study (Table 1). The prevalent diagnosis was ERA (62%) followed by PsA, UA and IBD-A (18%, 13%, 12%, respectively). 13 patients with IBD-A meet also criteria for either ERA (12 patients) or UA (1 patient). Amongst the entire JSpA cohort, as well as in the patients with undifferentiated JIA, sex was equally distributed (50% male). The ERA and IBD-A cohorts had higher male prevalences (both 59%), whereas the PsA subset showed a female preponderance (20% male) (distribution of sex by group, $p < 0.05$). The rate of HLA-B27 positivity of the whole cohort was 38%; those with ERA had the highest rate of HLA-B27 positivity (46%). HLA-B27 data was missing from 23 JSpA patients (11%): 6 ERA (4%); 7 PsA (17%); 4 UA (13%) and 27 IBD (50%).

Table 1. General cohort characteristics.

	All JSpA (N=223)	ERA (N=138)	PsA (N=41)	UA (N=30)	p-value*	IBD-A† (N=27)
Males (N, %)	111 (50%)	81 (59%)	8 (20%)	16 (53%)	0.000	16 (59%)
HLA-B27+ (N, %)^	75 (38%)	61 (46%)	4 (12%)	9 (35%)	0.001	7 (39%)
Uveitis	24 (11%)	18 (13%)	3 (7%)	2 (7%)	0.538	3 (11%)**
HLA-B27+ U (N, %)††	10 (45%)	8 (44%)	0 (0%)	1 (100%)	0.320	1 (50%)
Symptomatic-U (N, %)	19 (79%)	15 (83%)	2 (67%)	1 (50%)	0.291	3 (100%)

Enthesitis-related arthritis (ERA), psoriatic juvenile idiopathic arthritis (PsA), undifferentiated juvenile idiopathic arthritis (UA), arthropathies associated with inflammatory bowel disease (IBD-A), juvenile spondyloarthritis (JSpA), number of patients (N). HLA-B27+-Uveitis (HLA-B27+-U). Symptomatic-Uveitis (Symptomatic-U. * p value for chi2 test comparing distribution between JSpA subcohorts (ERA, PsA, UA). †12 patients meet criteria for ERA and one patient meets criteria for UA. **One patient meets criteria for ERA and one patient meets criteria for UA. ^HLA-B27 status not available for 23 subjects – 6 ERA, 7 PsA, 4 UA, and 14 IBD-A (6 of which did not meet criteria for ERA, PsA, or UA). ††HLA-B27 status not available for two uveitis subjects -1 PsA and 1 UA (also IBD-A).

Uveitis occurred in twenty-four patients (11%) of the JSpA cohort (JSpA-U) (Table 1). Although ERA patients had the highest uveitis prevalence (ERA-U) (13%), there was no statistically significant difference between the JSpA subcohorts (distribution of uveitis by group, $p < 0.538$). 11% ($n = 3$) of those with IBD-A had uveitis, one of whom had ERA and another UA. Half of those with uveitis were male, both in the entire JSpA cohort and the ERA subcohort (46% and 50%, respectively), whereas PsA patients with uveitis were mostly female (67%). The rate of HLA-B27 positivity was 45% amongst JSpA-U. This ranged from 0% in PsA to 100% in UA, but the difference between subcohorts was not statistically significant. The overall prevalence of symptomatic uveitis was 79%; of the JSpA subcohorts, ERA patients showed the highest prevalence of symptomatic uveitis (83%) (distribution of symptomaticity by group, $p = 0.291$). All IBD-A-associated-uveitis was both HLA-B27 positive and symptomatic.

In analysis restricted to HLA-B27 positive patients, the overall uveitis prevalence was 11% (reaching 13% for ERA subset) (Table 2). The majority of the uveitis in these ERA patients was symptomatic (88%). Uveitis was symptomatic in the one IBD-A patient with HLAB-27 positive uveitis.

Table 2. Patients with HLA-B27 sorted by the presence of uveitis

	All JSpA (n=75)	ERA (n=61)	PsA (n=4)	UA (n=9)	p*	IBD-A (n=7**)
Uveitis	10 (13%)	8 (13%)	0	1 (11.11%)	1.000	1 (14%)
Symptomatic Uveitis	8 (80%)	7 (88%)	0	0	0.222	1 (100%)

Enthesitis-related arthritis (ERA), psoriatic juvenile idiopathic arthritis (PsA), undifferentiated juvenile idiopathic arthritis (UA), arthropathies associated with inflammatory bowel disease (IBD-A), juvenile spondyloarthritis (JSpA). All HLA-B27 positive patients (All HLA-B27+). HLA-B27+ patients with uveitis (HLA-B27+ U), HLA-B27+ patients with symptomatic uveitis (HLA-B27+ symptomatic U).* p value for the chi2 test comparing subcohorts (ERA, PsA, UA). **Six of these patients meet criteria for ERA.

We further investigated the type of "ever" ocular symptoms reported by patients (Table 3). The majority of patients reported both eye pain and light sensitivity, although more patients described a history of red eyes than of eye pain or light sensitivity. Ocular symptoms were reported also by patients without verified uveitis, especially in the ERA subset (data not shown).

Table 3. Ocular symptoms among patients with uveitis

	All JSpA	ERA	PsA	UA	IBD-A
Red eyes	19 (79%)	14 (78%)	3 (100%)	2 (100%)	1 (33%)
Eye pain or light sensitivity	17 (71%)	13 (72%)	2 (67%)	1 (50%)	2 (67%)

Enthesitis-related arthritis (ERA), psoriatic juvenile idiopathic arthritis (PsA), undifferentiated juvenile idiopathic arthritis (UA), arthropathies associated with inflammatory bowel disease (IBD-A), juvenile spondyloarthritis (JSpA).

The presence of HLA-B27 was not statistically associated with uveitis occurrence or with the presence of ocular symptoms (chi2 test or logistic regression) either in the JSpA-U cohort as a whole or in ERA-U subset (data not shown).

Discussion

To date, few data have been published on uveitis prevalence among children and adolescents with spondyloarthritis. Herein we report ocular manifestations in a large cohort of JSpA patients. The prevalence of uveitis was 11%, the rate of HLA-B27 positivity of 38%, and the majority of patients had symptomatic uveitis (79%). Those patients with HLA-B27 positivity were neither more likely to have uveitis, nor symptomatic uveitis, than were other patients.

Current knowledge on uveitis in JSpA patients has been abstracted from adults with SpA and JIA associated uveitis. Indeed, the previous reported JSpA cohorts are small and analysis does not focus on

ocular inflammation. Two recently published JSpA cohorts, one from France (114 patients) and one from Germany (118 patients) shared similar features: ERA patients as the prevalent subset (69% and 52%), male predominance (63% and 73%) and a rate of HLA-B27 positivity ranging from 43% and 66% [6, 7]. Data on uveitis were provided just in the German cohort: the uveitis rate was 7%, without further description of associated characteristics [6].

Similarly to these cohorts, the ERA subset was the most represented in our cohort (60%).

The high rate of PsA patients in our cohort (18%) may explain the absence of male prevalence and the lower rate of HLA-B27 positivity compared to the other cohorts [6, 7]. This may also contribute to the higher rate of uveitis in our cohort compared to the German JSpA cohort (11% vs 7%).

Focusing on ocular manifestations, studies in the German and Canadian registries examined the prevalence and presentation of uveitis in different JIA subtypes [8, 9]. The uveitis prevalence in the PsA subset in our study was comparable to those in the two registries (7% in our study and 10% in both German and Canadian registries). Whereas in our study, the ERA subcohort had a higher percentage of uveitis than in the Canadian and German registries (13% vs 8% and 7%, respectively), and the UA subcohort had a higher percentage than the Canadian but not German registries (7% vs 1% and 7%, respectively) [8, 9]. Amongst ERA patients, the rate of symptomatic uveitis in our cohort was higher than in the German registry (83% vs 67%), but the rate of HLA-B27 positivity among ERA patients with uveitis was lower than in the German cohort (44% vs. 75%) [9]. No information regarding symptoms related to uveitis and HLA-B27 prevalence were available in the Canadian registry [8].

Comparing our results to what is described in adult SpA, we identified a lower prevalence of uveitis. About one-third of SpA patients develop uveitis [3, 4], whereas in our cohort, the uveitis prevalence was 11%. Similarly to SpA, JSpA patients were more likely to develop symptomatic rather than asymptomatic uveitis. While the prevalence of uveitis is significantly higher in HLA-B27 positive, than in HLA-B27 negative, adults [4], that was not the case in our cohort.

This observational study has some limitations. As patients must consent to inclusion, this study only approximates the prevalence of uveitis in JSpA patients. There may have been selection bias due to differential consent amongst patients with different underlying diagnoses. Another limitation is the dependence on patient recall of symptomaticity of uveitis rather than determination from chart review of individual ophthalmologic visits. This could result in either under or over-reporting of symptoms, but there is little reason to suspect that this would vary amongst patients of different underlying diagnoses. Missingness of data on HLA-B27 status was another limitation. While it was relatively high in the IBD population and might impact determination of the association of HLA-B27 with uveitis and symptomaticity in these patients, it was quite low in the ERA subcohort.

In conclusion, we have described characteristics of uveitis in a large cohort of JSpA patients. The prevalence of uveitis was lower than hypothesized and than has been reported in adult SpA patients. About one tenth of patients developed uveitis. Fewer than half of the patients with uveitis were HLA-B27

positive. As expected, the majority reported ocular symptoms along with uveitis. Finally, in this cohort, HLA-B27 status was not associated with either the development, or with symptomaticity, of uveitis.

Abbreviations

SpA	Spondyloarthritis
JSpA	Juvenile spondiloarthritis
ILAR	International League of Associations for Rheumatology
JIA	Juvenile idiopathic arthritis
HLA-B27	Human leukocyte antigen B27
ERA	enthesitis-related arthritis
PsA	juvenile psoriatic arthritis
UA	undifferentiated arthritis
ReA	reactive arthritis
IBD-A	the arthropathies associated with inflammatory bowel disease
AAU	acute anterior uveitis
CHOP	Children's Hospital of Philadelphia
JSpA-U	JSpA patients with uveitis
ERA-U	ERA patients with uveitis

Declarations

Ethics approval and consent to participate: The study was reviewed and approved by the institutional review board of the Children's Hospital of Philadelphia.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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