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Occurrence and Risk Factors of Uveitis in Juvenile Psoriatic Arthritis: Data From a Population-based Nationwide Study in Germany

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ABSTRACT. ***Objective.*** Data on uveitis in juvenile psoriatic arthritis (JPsA), a category of juvenile idiopathic arthritis (JIA), are scarce. We describe prevalence and risk factors for JPsA-associated uveitis (JPsA-U).

Methods. Cross-sectional data from the German National Pediatric Rheumatological Database (2002–2014) were used to characterize JPsA-U and assess risk factors for the development of uveitis.

Results. Uveitis developed in 6.6% of 1862 patients with JPsA. Patients with JPsA-U were more frequently female (73.0 vs 62.9%, $P = 0.03$), antinuclear antibody (ANA) positive (60.3 vs 37.0%, $P < 0.001$), younger at JPsA onset (5.3 ± 4.1 vs 9.3 ± 4.4 yrs, $P < 0.001$), and treated with disease-modifying antirheumatic drugs (DMARDs) significantly more frequently compared with JPsA patients without uveitis. On a multivariable analysis of a subgroup of 655 patients enrolled in the study ≤ 1 year after arthritis onset, mean clinical Juvenile Arthritis Disease Activity Score for 10 joints during study documentation was significantly associated with uveitis development. Children with early onset of JPsA (aged < 5 yrs vs ≥ 5 yrs) were significantly more frequently ANA positive (48.4% vs 35.7%, $P < 0.001$), affected by uveitis (17.3% vs 3.8%, $P < 0.001$), and treated with DMARDs (52.9% vs 43.8%, $P < 0.001$), but less often affected by skin disease (55.3% vs 61.0%, $P = 0.03$).

Conclusion. The characteristics of patients with JPsA developing uveitis are similar to those of patients with uveitis in other JIA categories, such as oligoarticular JIA. Children with early-onset JPsA are at a higher risk for ocular involvement. Our data support the notion of a major clinical difference between those patients with early vs late onset of JPsA.

Key Indexing Terms: epidemiology, juvenile idiopathic arthritis, juvenile psoriatic arthritis, psoriasis, uveitis

Juvenile idiopathic arthritis (JIA) comprises 7 distinct categories, which are characterized by specific clinical and laboratory features.[1] Children affected by JIA have a varying risk for development of extraarticular manifestations of disease, depending on the subgroup they are diagnosed with. One major concern in patients with JIA is ocular involvement manifesting as uveitis.[1,2] According to epidemiological data from various countries, the risk for development of uveitis seems to be highest in children with the oligoarticular subtype of JIA (oligoJIA), and lowest in systemic JIA with nearly zero risk.[1,3] As a consequence, most data retrieved from registries report mainly on uveitis patients with oligoarticular or rheumatoid factor–negative polyarticular JIA, whereas conclusive data on uveitis in other JIA subgroups are lacking. We therefore analyzed a large cohort of patients with JIA, documented in the German National Pediatric Rheumatological Database (NPRD), a nationwide registry, and focused on the subgroup of children with juvenile psoriatic arthritis (JPsA). Data from the NPRD have been used previously for identifying risk factors for the development of uveitis in JIA and establishing nationwide guidelines for uveitis screening,[4] as well as for analyzing uveitis in certain JIA categories.[5]

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METHODS

Patient data. For this analysis, all patients with JPsA recorded in the NPRD between 2002 and 2014 were considered. The registry documents physician- and patient-reported data once a year (for more details regarding the NPRD, see previously published data[4,5]). Briefly, pediatric rheumatologists reported patient age, sex, diagnosis (in accordance with International League of Associations for Rheumatology criteria[6]), age at disease onset, number of swollen or tender joints and/or joints with limited range of motion, presence of uveitis, current treatment, global assessment of disease activity (on a 21-point numerical rating scale [NRS]), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), and HLA-B27 status. Patients (or their parents) assessed their overall well-being on an NRS (0–10) and their functional capacity using the Childhood Health Assessment Questionnaire (CHAQ).[7] The clinical Juvenile Arthritis Disease Activity Score for 10 joints (cJADAS10) was calculated by the documenting physician.[8,9]

In some of the patients with uveitis, data from the ophthalmological documentation (so-called uveitis add-on module [UM]) were available for analysis, documenting anatomical types of uveitis, laterality, best-corrected visual acuity (BCVA), uveitis complications, and characteristics of flare (sudden or insidious onset), according to the Standardization in Uveitis Nomenclature guidelines.[10]

The NPRD was approved by the Ethics Committee at the Charité – Universitaetsmedizin Berlin (approval number EA1/044/07). Patient and/or parent informed consent to participate in the study was obtained according to the Declaration of Helsinki, and the design of the work conforms with the standards currently applied in Germany.

Statistical analysis and definitions. Data were analyzed by using the statistics program R (version 4.0.2; R Foundation for Statistical Computing). Data were tested for normal distribution by Shapiro-Wilk test. For further analysis, *t* test, Mann-Whitney *U* test, chi-square test, Wald test, ANOVA, or Kruskal-Wallis test were applied as appropriate. Logistic regression analyses were applied to identify correlates of uveitis occurrence. Results were expressed as mean and SD, hazard ratio (HR), and 95% CI. A significance level of 5% was used for all analyses. Kaplan-Meier analysis was applied to analyze the onset of uveitis as a function of JPsA disease duration.

Baseline is defined as the first NPRD documentation, either by rheumatological or ophthalmological assessment. Due to the registry's structure, initial documentation did not necessarily take place at the initial manifestation of disease, but patients might have been included in the NPRD with some delay after disease onset. Therefore, different patient groups were used for statistical analysis of different questions, as described below. All patients with JPsA with at least 1 rheumatological documentation were referred to as the JPsA group. Most patients with JPsA were not included in the study immediately after disease onset and therefore, data on early course of disease were not available. We therefore analyzed prognostic factors for uveitis development in a subgroup of patients with JPsA who were enrolled in the study ≤ 1 year after arthritis onset (JPsA_1 group). As several studies on JPsA in children could identify major clinical differences between patients being younger at arthritis onset vs those who were older,[11,12] we additionally stratified patients from the JPsA cohort according to disease onset: those with arthritis onset aged < 5 years (JPsA<5 group) vs those aged ≥ 5 years (JPsA≥5 group).

RESULTS

Patient characteristics. Data from 24,841 patients with JIA enrolled in the NPRD from 2002 to 2014 were available for analysis (see description of several JIA categories with more frequent ocular involvement in Supplementary Table 1, available with the online version of this article). Of those, 1862 were diagnosed with PsA (JPsA group). Development of uveitis was documented in 10.8% (n = 2693) of all NPRD JIA cases; among all JPsA patients (JPsA-U group), 6.6% (n = 122) developed uveitis, whereas no information on uveitis occurrence was available in 6.0%. (n = 111). In 22 (18.0%) of patients with JPsA-U, detailed information on uveitis characteristics at first and current visit to the attending ophthalmologist was additionally available through the UM.

Characteristics of patients with uveitis. Clinical characteristics of all groups are shown in Table 1. Compared with patients without uveitis, patients with JPsA-U were significantly more frequently female (73.0 vs 62.9%, $P = 0.03$), ANA positive (60.3 vs 37.0%, $P < 0.001$), and younger at JPsA onset (5.3 ± 4.1 vs 9.3 ± 4.4 yrs, $P < 0.001$).

Physician global assessment of disease activity (PGA) and subjective assessment by patients/parents did not differ significantly between the latest study documentation prior to uveitis onset and first documentation after uveitis onset. During the course of disease, patients with JPsA-U received disease-modifying antirheumatic drug (DMARD) treatment significantly more frequently than patients with JPsA (DMARDs in 77.0% vs 44.3%; conventional synthetic DMARDs [csDMARDs] in 73.0% vs 42.5%; biologic DMARDs in 27.9% vs 13.3%, all $P < 0.001$).

JPsA patient groups with JIA onset at age < or ≥ 5 years. Children from the JPsA<5 group less often had skin involvement diagnosed as psoriasis (PsO), were ANA positive more frequently, and had lower mean cJADAS10 scores during NPRD documentation (Table 1). Children aged < 5 years at JPsA onset received DMARD treatment more frequently (all DMARDs: 52.9% vs 43.8%, $P < 0.001$; csDMARDs 50.0% vs 42.1%, $P = 0.004$) than those who were older at JIA onset. Uveitis developed more frequently in those aged < 5 years at JPsA onset (17.3% [73/423] vs 3.8% [49/1306], $P < 0.001$).

Age distribution and uveitis development. As it is known that young age at JIA onset constitutes a risk factor for development of uveitis in oligoJIA, we analyzed age distribution in the JPsA_1 group (Figure 1A). Indeed, approximately 45% of those patients diagnosed with uveitis in the course of disease developed arthritis prior to their 4th birthday, whereas this was the case in < 15% of patients with JPsA_1 without ocular involvement.

However, longer duration of arthritis disease did not lead to a lower likelihood for development of uveitis. The probability of first uveitis documentation dropped only slightly between the first and fifth year of JPsA disease duration (Figure 1B).

Risk factors for development of uveitis. In order to identify correlates for the development of uveitis in the JPsA_1 group, we conducted a univariable Cox regression analysis encompassing the variables shown in Supplementary Table 2 (available with the online version of this article). Among the patient characteristics, we found young age at JPsA onset (HR 0.88, 95% CI 0.81–0.95, $P = 0.002$) and higher disease activity at baseline documentation (PGA: HR 1.24, 95% CI 1.05–1.46, $P = 0.01$, and ESR: HR 1.04, 95% CI 1.01–1.06, $P = 0.002$) to be associated with uveitis development.

We then conducted a multivariable Cox regression analysis in the JPsA_1 group, including the following variables: ANA positivity, age at arthritis manifestation, and mean cJADAS10

Table 1. Characteristics of patients with JPsA documented through the German National Pediatric Rheumatological Database.

	JPsA	JPsA_1[a]	JPsA w/o Uveitis	JPsA-U	*P*	JPsA_1[a] w/o Uveitis	JPsA_1-U	*P*	JPsA < 5[b]	JPsA ≥ 5[b]	*P*
General characteristics											
n	1862	655	1629	122	–	626	29	–	444	1395	–
Sex, F / M, %	63.5 / 36.5	63.4 / 36.6	62.9 / 37.1	73.0 / 27.0	0.03	63.3 / 36.7	65.5 / 34.5	> 0.99	66.7 / 33.3	62.6 / 37.4	0.13
Age at PsA onset, yrs	9.0 ± 4.5	10.2 ± 4.6	9.3 ± 4.4	5.3 ± 4.1	< 0.001	10.4 ± 4.5	6.7 ± 4.8	< 0.001	2.8 ± 1.2	11.0 ± 3.2	< 0.001
Age at 1st uveitis documentation, yrs	8.3 ± 4.8	9.1 ± 5.3	NA	8.3 ± 4.8	NA	NA	9.1 ± 5.3	NA	6.8 ± 4.9	10.0 ± 4.3	0.15
Baseline characteristics											
Age, yrs	12.1 ± 4.5	10.7 ± 4.6	12.1 ± 4.3	11.7 ± 5.9	0.50	10.9 ± 4.5	7.1 ± 4.9	< 0.001	8.1 ± 5.1	13.3 ± 3.4	< 0.001
JPsA disease duration, yrs	3.1 ± 3.6	0.5 ± 0.3	2.8 ± 3.2	6.4 ± 6.2	< 0.001	0.5 ± 0.3	0.4 ± 0.3	0.12	5.3 ± 5.1	2.3 ± 2.6	< 0.001
Uveitis disease duration, yrs	3.3 ± 4.7	–0.7 ± 1.8	NA	3.3 ± 4.7	NA	NA	–0.7 ± 1.8	NA	4.6 ± 5.3	1.8 ± 3.5	0.18
ANA positive, % (n[c])	38.3 (1296)	39.0 (500)	37.0 (1150)	60.3 (73)	< 0.001	37.9 (478)	63.6 (22)	0.02	48.4 (287)	35.7 (994)	< 0.001
HLA-B27 positive, % (n[c])	16.2 (1539)	16.3 (522)	16.2 (1356)	20.2 (109)	0.28	15.8 (495)	25.9 (27)	0.18	16.1 (366)	16.2 (1159)	> 0.99
Characteristics throughout study documentation											
Psoriasis, ever, % (n[c])	59.5 (980)	59.0 (388)	59.3 (923)	57.1 (42)	0.15	59.5 (375)	46.2 (13)	0.37	55.3 (215)	61.0 (749)	0.03
Mean cJADAS10 (n[c])	5.5 ± 5.4 (779)	6.0 ± 5.7 (298)	5.5 ± 5.5 (711)	5.7 ± 5.1 (46)	0.89	5.9 ± 5.7 (285)	6.7 ± 6.1 (13)	0.81	4.7 ± 5.2 (167)	5.8 ± 5.5 (607)	0.002
DMARD therapy, % (n[c])											
Any	45.8 (1862)	39.7 (655)	44.3 (1629)	77.0 (122)	< 0.001	37.7 (626)	82.8 (29)	< 0.001	52.9 (444)	43.8 (1395)	< 0.001
csDMARD	43.8 (1862)	39.5 (655)	42.5 (1629)	73.0 (122)	< 0.001	37.5 (626)	82.8 (29)	< 0.001	50.0 (444)	42.1 (1395)	0.004
bDMARD	14.1 (1862)	9.9 (655)	13.3 (1629)	27.9 (122)	< 0.001	9.1 (626)	27.6 (29)	0.006	16.0 (444)	13.7 (1395)	0.26

All values are given as mean ± SD unless otherwise stated. For definition of groups described here, see Methods. [a] JPsA_1: subgroup of JPsA patients with disease onset < 1 year prior to study inclusion. [b] Subgroup of JPsA patients with disease onset prior to or after 5th birthday. [c] No. of patients who had this item documented. ANA: antinuclear antibody; bDMARD: biologic DMARD; cJADAS10: clinical Juvenile Arthritis Disease Activity Score for 10 joints; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drugs; JPsA: juvenile psoriatic arthritis; JPsA-U: JPsA-associated uveitis; NA: not applicable; PsA: psoriatic arthritis.

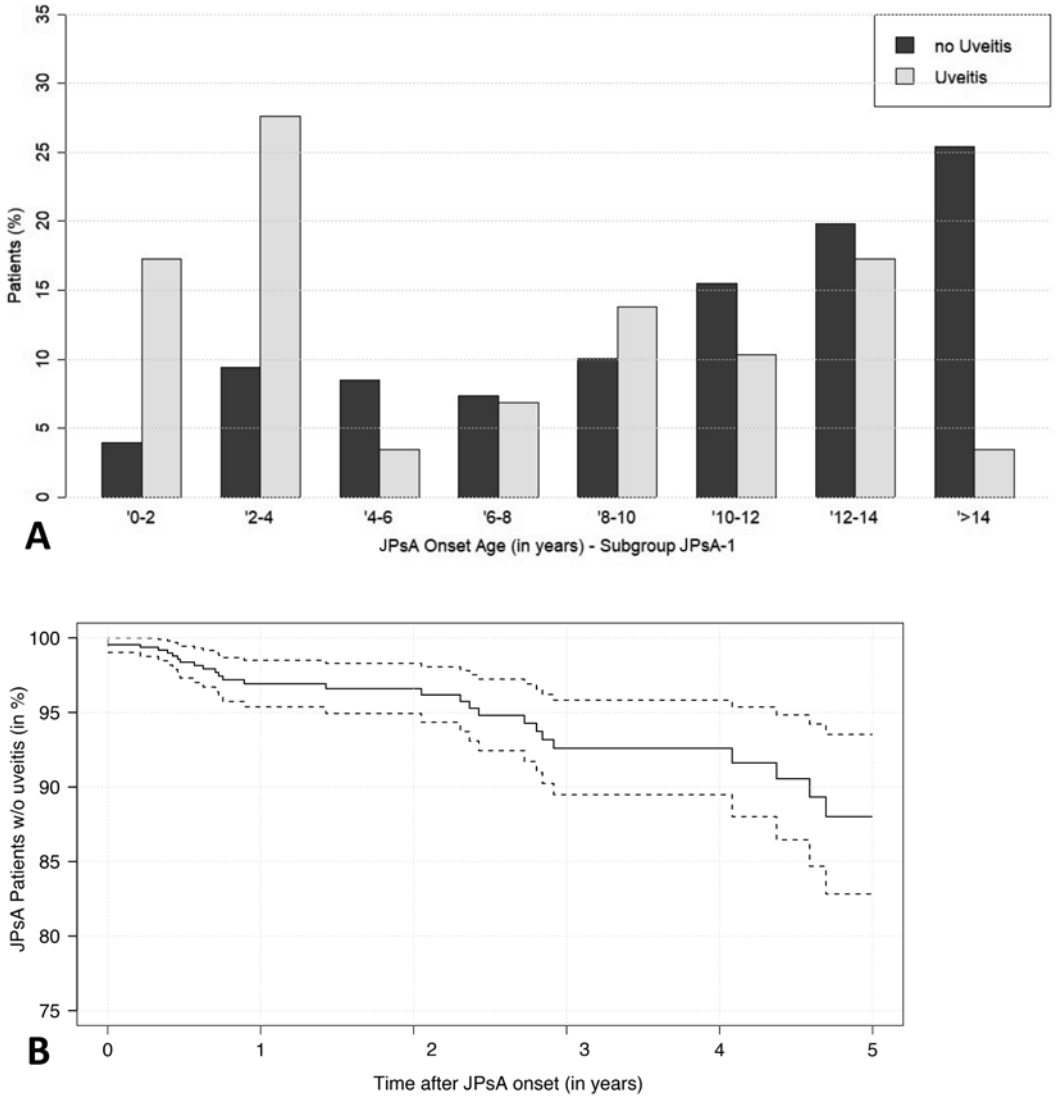

Figure 1. Development of uveitis in relation to JPsA onset. All data refer to the group of patients with JPsA included in the study < 1 year after JPsA onset (JPsA_1 group, see Methods). (A) Age at JPsA onset in patients with and without uveitis. (B) Kaplan-Meier analysis (right-censored model) of developing uveitis during the course of JPsA. Solid line: JPsA_1 group; dotted lines: 95% CI. JPsA: juvenile psoriatic arthritis.

(until first uveitis documentation). Here, we found only mean cJADAS10 to be significantly associated with development of uveitis (HR 1.16, 95% CI 1.02–1.31, $P = 0.03$; other variables not shown).

Subgroup of patients with UM. Unfortunately, only very few patients with JPsA-U were documented through the UM. Seventeen patients had 1 UM documentation, 3 patients had 2 documentations, and 2 patients were documented 4 times. All these patients had anterior uveitis. Except for 1 patient with band-shaped keratopathy of the central cornea, none of the patients had uveitis complications at initial documentation. As could therefore be expected, baseline BCVA of the study eye (the eye with worse BCVA at study inclusion) was 0.0 logMAR in 15/17 of the eyes documented, and 0.2 and 0.7 in the 2 remaining cases. At baseline, uveitis was unilateral in 7 patients, and bilateral in 8 patients. Uveitis flares were clinically symptomatic (acute onset) in 4 patients, and asymptomatic (insidious onset) in another 10 patients. Only 3 of those 14 patients were HLA-B27 positive (2 had symptomatic onset). Therefore, no analysis of a possible link between genetic background and clinical presentation was possible.

DISCUSSION

Data on uveitis in JPsA are rare, and risk factors for the development of uveitis have not been analyzed as yet. Various large studies identified risk factors for the development of uveitis in JIA per se, such as oligoarticular disease, young age at JIA onset, and ANA positivity.[3,13] However, it is yet unknown whether the latter (or different clinical characteristics) are applicable in all JIA categories other than oligo- and polyarthritis. Indeed, data

on enthesitis-related arthritis (ERA) show that risk factors for uveitis development in this JIA category might differ from those in other JIA categories.[5] In the cohort analyzed in our present study, patients with uveitis were more frequently female and ANA positive than those without ocular involvement; however, the only item significantly associated with presence of uveitis on multivariable analysis was mean cJADAS10 score until uveitis onset.

Previous studies on JPsA identified clinical differences between children with early and late onset of arthritis.[11,12] Data from the Childhood Arthritis and Rheumatology Research Alliance registry documenting 361 children with JPsA demonstrate the presence of uveitis in 11.2% of cases,[12] which is more frequent than observed here. The authors found their cohort to comprise 2 clinically distinct populations, distinguishable by age at JPsA onset (age ≤ 4 or > 4 yrs).[12] Uveitis was markedly more frequent in children younger at JIA onset (18.8 vs 8.8%), and those were significantly more often ANA positive, but less frequently diagnosed with PsO,[12] which was true for our JPsA<5 group as well. In addition, a case series found early onset of arthritis (before 6th birthday) in 5 out of 6 children with JPsA-U.[14] Our data confirm these previous observations, showing a significantly increased proportion of patients with uveitis in those children with JIA onset aged < 5 years compared to those aged ≥ 5 years. In contrast, a study on 139 children diagnosed with JPsA did not find differences in uveitis frequency between those with JIA onset < 5 vs ≥ 5 years[11]; however, ophthalmological data were available for only 50% of patients. Although uveitis was more frequent in younger patients in our cohort, the data demonstrate that older children are nevertheless at risk of developing asymptomatic uveitis, underscoring the necessity for prolonged ophthalmological screening.

These findings are similar to what is known from other cohort studies on JIA, in which the majority of children diagnosed with uveitis belong to the oligoJIA category.[2,3,13] Indeed, Butbul and colleagues[15] found rather similar clinical characteristics in children with JPsA compared to oligoJIA regarding not only ANA positivity, development of extended oligoarthritis, and disease activity, but also development of uveitis. They suggested that, due to these similarities, it might be unfounded to define those JIA subgroups according to presence of PsO.[15]

Unfortunately, we were only able to characterize ocular disease in more detail in a small subgroup of patients, due to methodological reasons. However, we found that uveitis onset was asymptomatic in the majority of patients for whom this information was available. Indeed, none of the 6 children from the largest published case series on JPsA-U[14] had acute, symptomatic onset of uveitis, whereas this is frequently observed in adults with JPsA.[16] It has been speculated that clinical presentation of uveitis is linked to HLA-B27 status (ie, symptomatic flares in HLA-B27–positive individuals). However, data from an ERA cohort demonstrate that this might not necessarily be true, as HLA-B27–positive children might have asymptomatic flares as well.[5]

Limitations of our data result from the structure of the NPRD registry. The majority of patients were included in the study after > 1 year of JIA disease duration, among them patients with uveitis; these were not available for uni- and multivariable analysis, limiting the informative value. In addition, we were not able to analyze the effect of treatment on uveitis occurrence, as the NPRD does not document indications for treatment. Medication is documented only once a year, which is why we are not able to identify whether a certain drug was given prior to onset of uveitis, or due to onset of uveitis. As medication is known to have an effect on uveitis occurrence,[13] this is a relevant limitation.

Our data descriptively demonstrate similarities regarding clinical characteristics of patients with uveitis between the most frequently assessed JIA subgroup of children with oligoarthritis and those with JPsA. These data strengthen the hypothesis that patients with early onset of JIA are at a particularly high risk for ocular involvement in general, regardless of JIA subgroup. However, due to the characteristics of the NPRD registry, other factors that have been found to significantly affect the occurrence and course of uveitis (such as systemic treatment[2,13]) could not be assessed in a more comprehensive way. Regarding both our data as well as published data on this topic, there certainly is a need for additional investigation on the issue of JPsA-U.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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