Chronic Uveitis in Children with and without Juvenile Idiopathic Arthritis: Differences in Patient Characteristics and Clinical Course

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ABSTRACT. ***Objective.*** Anterior uveitis (AU) in childhood may be the first manifestation of juvenile idiopathic arthritis (JIA). We identified factors that may help to differentiate JIA-associated AU from the more common idiopathic AU (IAU) before the onset of arthritis.

Methods. Children with IAU and with JIA-associated AU were analyzed for their demographics, age at onset of uveitis, uveitis course and complications, ocular surgery, antiinflammatory medication, and best corrected visual acuity (BCVA).

Results. AU was associated with JIA in 88 cases, and was idiopathic in another 49. In the JIA group, 60% of patients were female compared to 47% in the IAU group ($p = 0.154$). Antinuclear antibody (ANA) was significantly more frequent in the JIA group (88% vs 33%; $p < 0.001$, OR 14.4, 95% CI 5.8–35.6). Insidious uveitis onset occurred more often in JIA than in IAU patients (67% vs 31%; $p < 0.001$, OR 4.6, 95% CI 2.2–9.8). Persistent uveitis was found in 82% of JIA patients, and in 57% of IAU patients ($p = 0.003$, OR 3.4, 95% CI 1.5–7.4). Median age of AU onset was 5 years in JIA and 9 years in IAU ($p < 0.001$). Uveitis complications at first presentation at our institutions were more frequent in JIA than in IAU patients (79% vs 61%; $p = 0.027$, OR 2.5, 95% CI 1.1–5.3). During followup, 69 surgical procedures (51% of patients, 1.31 per patient) were performed in the JIA group, and 18 in IAU patients (0.57 per patient) ($p = 0.008$). BCVA was better in the IAU patients at first presentation ($p = 0.001$).

Conclusion. The IAU and JIA-associated AU in childhood differ in their clinical course. ANA positivity, presence of uveitis complications at first manifestation, insidious onset, duration over 3 months, BCVA of 20/50 or less, and an age of 3 years or younger might help to detect AU associated with JIA. JIA uveitis manifests earlier, has more complications, and more often requires systemic immunosuppression and surgical intervention. (First Release May 15 2008; J Rheumatol 2008;35:1403–7)

Key Indexing Terms:
UVEITIS ARTHRITIS JUVENILE RHEUMATOID

Previous studies have shown that only about 5% (range 2.3%–9.8%) of uveitis patients are younger than 16 years[1-3]. In about 30% of these children systemic disease can be observed[4]. About half the patients with anterior uveitis (AU) have juvenile idiopathic arthritis (JIA)[4,5]. Idiopathic anterior uveitis (IAU) mostly accounts for the remaining patients[4,5].

AU often occurs with or after onset of arthritis. However, in about 10% of the children, uveitis may be the first manifestation of rheumatic disease. As repeatedly described, the clinical course of AU in JIA is intriguing by its insidious onset, chronic course, and poor visual prognosis versus other uveitic entities[6-10]. We sought to differentiate the typical clinical patterns of patients with IAU versus those with JIA-associated AU.

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Accepted for publication Feburary 29, 2008.

MATERIALS AND METHODS

The medical records of all patients with anterior noninfectious uveitis who were 16 years of age or younger at the time of first manifestation of uveitis were retrospectively reviewed at 2 tertiary referral uveitis centers. Patients were seen either shortly after uveitis diagnosis, or later for advanced care. Therefore, data on clinical course, type of onset, and time of onset were partly provided by the referring ophthalmologist. Patients were seen from 1995 to 2005. Only patients with uveitis diagnosis at least 1 year before were included. The study design complied with ethical standards according to the Declaration of Helsinki. Our institutions do not require approval from the local ethics committees for chart review studies. Classification of arthritis was based on the ILAR classification system[11]. AU was classified according to recommendations of the International Uveitis Study Group and confirmed with recent modifications[12,13]. Briefly, the primary site of inflammatory cells was the anterior chamber and included iritis, iridocyclitis, and anterior cyclitis.

In addition to documentation of a detailed medical history and consultation with a pediatric rheumatologist, all patients underwent a panel of diagnostic tests, including syphilis, rheumatoid factor, HLA-B27, complete blood cell count, urinalysis, angiotensin-converting enzyme, and radiographic examination of the chest and sacroiliac joints. Patients with ocular findings suggestive of other well-known infectious or endogenous enti-

ties of anterior uveitis, e.g., tuberculosis, herpetic trabeculitis, iritis, Fuchs heterochromic cyclitis, TINU syndrome (tubulointerstitial nephritis and uveitis), or sarcoidosis, were excluded from the study. Patients with only AU at first diagnosis and who later developed arthritis as a sign of JIA were reclassified into the JIA group. Uveitis in the absence of associated infection or systemic disease was classified as "idiopathic" (IAU), which also included ANA- or HLA-B27-positive patients[13].

Patient demographics (age, gender, age at onset of uveitis and arthritis) were recorded. Patients also underwent clinical ophthalmologic examinations including best-corrected visual acuity (BCVA), slit-lamp evaluation, Goldmann applanation tonometry, and indirect ophthalmoscopy (with the use of 20 or 90 dpt lenses). The presence of typical uveitis-related complications was documented, e.g., band-keratopathy, cataract-formation, secondary glaucoma [optic neuropathy or persistent intraocular pressure (IOP) ≥ 26 mm Hg], posterior synechiae, vitreous opacities, macular edema, ocular hypotony (IOP ≤ 6 mm Hg), phthisis, or retinal detachment. Followup visits were scheduled every 3 to 6 months.

Further, the course of inflammation was classified as acute, with sudden onset and limited duration, or chronic, with insidious onset and nearly asymptomatic course of uveitis in a white globe and duration > 3 months. Any topical and systemic antiinflammatory medication and the type and number of any eye operations until the final visit were documented.

Statistical analysis was performed using SPSS software (version 11.0.0). Chi-squared test was used for categorical values of complications, and Student t test for linear values. Odds ratio (OR) was used to estimate the relative risks for the association of AU with JIA. Logistic regression analysis was applied to identify predictors of JIA-associated uveitis. Results were expressed as OR and confidence intervals (CI). A significance level of 5% was used for all studies.

RESULTS

A total of 137 patients with uveitis were included, aged 16 years or younger at uveitis diagnosis. Of the 88 patients with JIA, 75 had oligoarthritis (58 persistent, 17 extended), 12 had polyarthritis, and one had undifferentiated arthritis. AU was diagnosed before the onset of arthritis in only 7 of these patients. Another 49 children had IAU without underlying associated disease.

Girls in the JIA group only slightly outnumbered those in the IAU group (p = 0.154). Of the JIA patients, 61 (69%) had bilateral disease compared to 29 (59%) in the IAU group (p = 0.263; Table 1). Antinuclear antibody (ANA) was significantly more frequent in the JIA group (72 patients, 88%) versus the IAU group (15 patients, 33%; p < 0.001, OR 14.4, 95% CI 5.8–35.6). The distribution of the HLA-B27 seropositivity did not differ significantly (Table 1).

In the JIA group, uveitis occurred earlier (median 5 yrs) compared to the IAU group (median 9 yrs; p < 0.001). The 75th percentile was 7.75 years in the JIA and 12.5 years in the IAU group. The 95th percentile was 13 years in JIA patients, as compared to 15 years in the IAU group. An age of 3 years and under at first manifestation of AU had significantly higher probability of JIA (OR 6.8, 95% CI 1.9–23.7, p ≤ 0.001), while cases occurring at an age of 10 years and older were significantly more likely to be related to IAU (OR 5.2, 95% CI 2.2–11.8, p ≤ 0.001).

Additionally, the course of uveitis differed markedly between patients with IAU and JIA-associated AU. Insidious uveitis onset occurred significantly more often in patients with JIA [JIA 59 (67%) patients vs IAU 15 (31%) patients; p < 0.001, OR 4.6, 95% CI 2.2–9.8], and similarly, persistent duration of symptoms over 3 months [JIA 72 (82%) patients vs IAU 28 (57%) patients; p = 0.003, OR 3.4, 95% CI 1.5–7.4]. In 25 of 29 patients of the JIA group who had a sudden onset of uveitis, HLA-B27 marker was examined, and 10 (40%) tested positive. In contrast, only 4 (18%)

Table 1. Demographics for all patients, and those with followup > 1 year at our institutions.

Characteristics	All Patients JIA, n = 88	IAU, n = 49	p
Male/female (%)	35 (40)/53 (60)	26 (53)/23 (47)	0.154
Age at diagnosis of arthritis, yrs	4.7 ± 1.8	NA	
HLA-B27-positive, n = 88 patients, (%)	15 (23)	5 (16)	0.59
ANA-positive, n = 119 patients, (%)	72 (88)	15 (33)	< 0.001
Mean time since diagnosis, yrs, (range)	6.6 (1–24.2)	3.7 (1–19.3)	0.004
BCVA first visit, logMAR	0.36 ± 0.37 (146 eyes)	0.19 ± 0.27 (74 eyes)	0.001
	Patients with Followup > 1 year JIA, n = 55	IAU, n = 19	0.012
Male/female (%)	20 (36)/35 (64)	10 (53)/9 (47)	0.28
Age at diagnosis of arthritis, yrs	4.5 ± 1.5	NA	
HLA-B27-positive, n = 57 patients (%)	8 (18)	1 (8)	0.69
ANA-positive, n = 71 patients (%)	50 (94)	9 (50)	< 0.001
Mean time since diagnosis, yrs, (range)	7.3 (1–24.2)	6.1 (1–19.3)	0.32
Mean followup period, yrs, (range)	3.8 (1.0–14.4)	3.5 (1.05–12.0)	0.68
BCVA last visit, logMAR	0.35 ± 0.37 (92 eyes)	0.23 ± 0.32 (27 eyes)	0.13
Difference in BCVA, final vs first visit, logMAR	–0.05 ± 0.27	0.04 ± 0.33	0.35

JIA: anterior uveitis associated with juvenile idiopathic arthritis; IAU: idiopathic anterior uveitis; NA: not applicable. BCVA: best corrected visual activity; logMAR: logarithm of minimum angle of resolution.

patients with sudden uveitis onset (n = 22) in the IAU group were HLA-B27-positive (p = 0.123, only for sudden onset in uveitis patients; Table 1).

Visual acuity at first presentation at our institutions was significantly lower in the JIA versus the IAU group (Table 1). At first presentation, 70 (79%) JIA patients had any complication compared to 30 patients (61%; p = 0.027, OR 2.5, 95% CI 1.1–5.3) in the IAU group. Patients with JIA had an average number of 2.1 (range 0–6) complications at first presentation from uveitis, whereas the mean number of complications in the IAU group was 1.2 (range 0–5) per patient (p = 0.003). Band keratopathy and cataract formation, 2 complications typical for chronic course of uveitis, were significantly more common in JIA than in IAU patients (Table 2).

Seven patients (5 girls) needed to be reclassified, as they developed arthritis after uveitis (time from uveitis to arthritis 7.2 ± 3.3 mo). The average age at uveitis manifestation was 4.6 ± 1.2 years. No significant differences regarding ANA (6 patients), HLA-B27 positivity (2 patients), ocular complications (4 patients, mean number 2 complications) at first presentation, and immunosuppressive therapy were found between JIA patients with initial presentation of either arthritis or uveitis.

Eighteen patients (20.5%) in the JIA group and 15 IAU group patients (30.6%) presented only once at our institutions. For assessment of subsequent clinical course, especially with respect to visual acuity and development of uveitis complications, only patients with a followup period longer than 1 year at our institutions [JIA 55 (62.5%), IAU 19 (38.8%); p = 0.012] were included in further analysis. The groups seem representative for the entire patient series, as sex distribution, frequencies of ANA or HLA-B27 markers (Table 1), and age at onset of uveitis did not differ significantly. Visual acuity did not change significantly in the groups during the followup period, and no significant difference was noted between the 2 groups (Table 1). There was a slight increase in the mean number of complications in the IAU group from 1.3 to 1.7 and in the JIA group from 2.1 to 2.4, but the differences did not reach significance.

Table 2. Number of complications at first presentation for patients with JIA associated anterior uveitis or with idiopathic anterior uveitis (IAU).

Complication	JIA (%)	IAU (%)	p
Any complications	7 (80)	30 (61)	0.27
Mean no. of complications per patient	2.1, n = 88	1.3, n = 49	0.003
Band keratopathy	39 (44)	13 (26)*	0.045
Posterior synechiae	45 (51)	18 (37)	0.112
Glaucoma	11 (12)	2 (4)	0.135
Cataract	30 (34)	8 (16)*	0.03
Vitreous opacities	15 (17)	10 (20)	0.65
Hypotony	9 (10)	2 (4)	0.33
Cystoid macular edema	10 (11)	4 (8)	0.77
Phthisis	2 (4)	0 (0)	0.54

*p < 0.05.

The higher number of complications in the JIA group is in accord with the higher number of surgical procedures performed in this group. Overall, 69 surgical procedures were performed in JIA patients (mean 1.3 per patient) compared to 18 procedures (mean 0.57 per patient) in the IAU group (p = 0.008). Cataract extraction was the most frequent surgery, performed in nearly 46% of the JIA patients (p = 0.046), followed by glaucoma surgery, which was necessary significantly more often in the JIA (16 patients) versus the IAU group (1 patient; p = 0.021; Table 3).

Patients with JIA-associated AU more often required systemic antiinflammatory medication versus patients with IAU. All patients were receiving topical corticosteroids for an extended period of time. Systemic corticosteroids were administered at least temporarily in 63% of the JIA cases and in only 30% of patients from the IAU group (p < 0.001). At this point, we are unable to differentiate whether the systemic corticosteroids were given for arthritis or uveitis. Also, immunosuppressive drugs, e.g., methotrexate (preferably parenteral), were used more frequently in the JIA group (69%) than in IAU patients (25%) (p < 0.001). Cyclosporin A and azathioprine were given less frequently than methotrexate and corticosteroids (Table 4).

Analysis of ANA-positive and -negative IAU patients compared to JIA with a followup longer than 1 year is shown in Table 5. Results in the ANA-positive IAU group and the JIA group were more alike than in the ANA-negative group and the JIA group.

DISCUSSION

Anterior uveitis is the predominant form of uveitis in childhood[4,5]. Currently, the majority of noninfectious AU seen in tertiary centers is related to JIA. At our institutions, about

Table 3. Number of surgical procedures for patients with JIA associated anterior uveitis or with idiopathic anterior uveitis (IAU).

Surgical Procedures	JIA (%)	IAU (%)	p
Cataract	38 (46)	10 (26)	0.046
Pars plana vitrectomy	6 (7)	4 (8)	0.745
Retinal surgery	5 (6)	2 (5)	1
EDTA chelation	4 (5)	1 (3)	1
Glaucoma	16 (20)	1 (6)	0.021

p < 0.05 for cataract and glaucoma surgery.

Table 4. Systemic immunosuppressive medications for patients with JIA associated anterior uveitis or with idiopathic anterior uveitis (IAU).

Drugs	JIA (%)	IAU (%)	p
Corticosteroids	55 (63)	14 (30)	< 0.001
Methotrexate	59 (69)	12 (25)	< 0.001
Azathioprine	11 (14)	3 (8)	0.544
Cyclosporin A	17 (20)	3 (6)	0.044

p < 0.05 for systemic steroids, methotrexate, and cyclosporin A.

Table 5. Severity of eye disease in patients with JIA-associated anterior uveitis versus patients with idiopathic anterior uveitis according to their ANA status. Period of followup > 1 year.

	JIA	IAU		
		ANA+	ANA–	p
No. of patients	55	9	10	
Average no. of complications	2.4	2.1	1.4	0.288
Average no. of surgical procedures	1.3	0.66	0.9	0.84
Immunosuppressed patients, no. (%)	42 (76.4)	8 (88.9)	6 (60)	0.332
Difference in BCVA, final vs first visit, logMAR	–0.05 ± 0.27	0 ± 0.41	0.08 ± 0.24	0.648

BCVA: best corrected visual acuity; logMAR: logarithm of minimum angle of resolution.

64% belong to the JIA group and another 36% are idiopathic AU. Rosenberg and coworkers found 75% of patients with AU associated with JIA and 22% with IAU in a group of 45 children[14]. De Boer, *et al* found 40% with AU associated with JIA and 40% with unknown disease out of a group of 44[4]. We sought to identify factors that might enable clinicians to differentiate between cases of AU associated with JIA and cases that are unrelated.

While the association with JIA can often be easily identified by observing the medical history, AU may be the first sign of JIA in a significant proportion of AU patients. We sought to define the most appropriate factors predicting associated JIA before arthritis onset, as the number of JIA children who had uveitis before arthritis is about 10% (in our series 7 patients)[15]. As patient characteristics did not differ between JIA patients presenting with arthritis or uveitis, the whole group of JIA children, including those who needed to be reclassified, was used for further analysis to deduce predictive factors for JIA uveitis. Due to difficulty recruiting a sufficient number of JIA children who developed iritis before arthritis, the power of our statistical calculations is reduced.

Also in this retrospective case series, a bias caused by the referral pattern at the tertiary care center to more severe cases cannot be excluded. In addition, using 1 year as minimal time since first diagnosis also might have disturbed data collection. Also, as the patients who needed to be reclassified did not differ in any aspect from the other JIA patients, it is unlikely that the IAU group (mean time since first diagnosis 3.7 yrs, 15% percentile of followup 1.96 yrs, 50% 2.7 yrs) falsely includes significant numbers of JIA patients. However, JIA may appear even after many years[15], or arthritis may not be apparent as ILAR criteria do not define subclinical arthritic manifestations[11].

The significant difference ($p = 0.012$) in JIA children followed up for longer than 1 year suggests that the clinical course of uveitis in JIA is more severe in many cases. The data reported above show that JIA-associated uveitis is more frequent in females and is more often bilateral. The higher probability to develop JIA (OR 6.8, 95% CI 1.9–23.7, $p \leq 0.001$) might also be influenced by longer followup and easier detection of arthritic manifestations.

In both groups of patients, a chronic clinical course, as defined by duration ≥ 3 months, was noted more often in the JIA group. Further, insidious course was more frequent in patients with JIA. This important observation is in agreement with previous observations that JIA uveitis typically occurs in a white globe[1,15,16]. A chronic course (OR 4.6, 95% CI 2.3–9.8) and insidious onset of uveitis (OR 3.4, 95% CI 1.5–7.4) are predictors for an association with JIA. In our study ANA positivity was associated with development of JIA (OR 14.4, 95% CI 5.8–35.6). The absolute figure of 88% ANA positivity in the JIA group is in the same range reported in other studies, varying from 66% to 90%[16,17].

The frequency of complications differed between the 2 groups, as no complications were detected at the first visit in only 18 (20%) JIA and 19 (39%) IAU patients. Also, the average number of initial complications per patient was higher in the JIA group. Although this trend has been described, the number of complications per JIA patient (average 2.1 per patient) is higher than observed by Kotaniemi and coworkers, who reported a frequency of 24%, only 12% of which had 2 to 4 complications[16]. This apparent difference most probably results from a different referral pattern, as the patients seen at our institutions are mostly JIA patients who do not respond to topical steroids, and who are referred to us by ophthalmologists and pediatric clinics.

After a followup of 1 year or longer at our institutions, the number of complications in each patient increased slightly in both the JIA and IAU groups. In this respect no obvious difference was noted between the groups in our case series. This suggests that more severe cases were followed up at our institution (Table 4). Therefore, the presence of complications at first diagnosis of AU indicates higher probability of association with JIA (OR 2.5, 95% CI 1.1–5.3). Others have shown that this may also be related to poor visual prognosis, and that presence of complications may indicate the need for more aggressive treatment[18]. The main complication noted in our patients was cataract formation, in agreement with previous publications[10,16]. Also, band-keratopathy, a complication that typically appears after chronic course of uveitis, was detected more often in patients with JIA. The glaucoma incidence in our series was also within the same range as in previous articles, which showed an incidence of 17%–30%[8,10,19]. The pattern of complications

did not differ, as both groups compared in our series consisted of the anatomic type of anterior uveitis. But importantly, complications were more common in patients with JIA. The incidence of glaucoma in a group of idiopathic uveitis of different anatomic localization was 2% in a previous publication[10], which correlates well with the incidence of 4% at first presentation in the IAU group. Severe complications, such as phthisis bulbi and ocular hypotony, were slightly more frequent in our JIA group, which is also in accord with previous publications[4,10].

Due to the more severe course of disease, immunosuppressive medications were administered more often in JIA-associated uveitis than in patients with IAU. We could not distinguish whether arthritis or uveitis was the main reason for immunosuppression in many of the children with JIA. Accordingly, only a small number of IAU patients required immunosuppression.

The number of surgical procedures can be interpreted as being a consequence of the complications, and the JIA group of patients required markedly more procedures than the patients with IAU. Cataract surgery, the most important procedure, was performed in 46% of patients in the JIA group. These figures are comparable with another study[10]. Also, the number undergoing EDTA chelation and glaucoma surgery was larger than in the JIA group. Our number of cataract extractions was 26% in our IAU group versus 14% in the study of Tugal-Tutkun, *et al*[10]; the differences might be related to the different referral pattern. Our observations on glaucoma surgery are in accord with the heterogeneous group of patients with idiopathic uveitis from Tugal-Tutkun, *et al*[10]. The number of filtering surgeries in the IAU patients was only 2% (1 patient), compared to 14% in the JIA group[10].

As the mean BCVA was worse and the number of patients with visual acuity of 20/50 or less at first presentation (OR 2.9, 95% CI 1.5–5.6, p = 0.001) was higher in JIA patients, poor initial vision may help distinguish JIA uveitis from IAU. At the last visit with an approximate followup of 1 year, there was only a minimal change in the visual acuity under treatment as compared to the first visit. At final visit, the difference in BCVA between the 2 groups was reduced, probably because only more severe cases were selectively monitored at our institution.

We found no differences between JIA patients manifesting arthritis or uveitis regarding serological markers, clinical course, or need for therapy.

Subgroup analysis of ANA-negative and positive children with IAU and JIA revealed no statistical similarity between ANA-positive and JIA groups according to characteristics of severity of uveitis. ANA-positive IAU patients might develop JIA later on; if examined thoroughly, subclinical arthritis might be detected[20]. ANA positivity did not predict complications in JIA in a recently published report[15].

Awareness of the possible differences between AU and JIA is important. The observations noted above show that ANA positivity, presence of uveitis complications, insidious onset of uveitis, duration longer than 3 months, visual acuity of 20/50 or less, and age 6 years or younger at diagnosis of uveitis might help to identify JIA-related AU. This may also apply for patients in whom uveitis onset is manifested prior to arthritis. However, the issue of defining factors to predict JIA in patients with AU requires further investigation.

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