Risk Factors and Longterm Outcome of Juvenile Idiopathic Arthritis-Associated Uveitis in Switzerland

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ABSTRACT. ***Objective.*** To determine rate, risk factors, and longterm outcome of uveitis in children with juvenile idiopathic arthritis (JIA) in Switzerland and compare the results with a study of a different center in Switzerland from 1992.

Methods. Retrospective analysis of the charts and ophthalmologists' reports of all patients with JIA in a tertiary care outpatient clinic between January 1, 1997, and December 31, 2005, for diagnosis, course, and outcome of uveitis.

Results. Uveitis occurred in 35/265 patients (13.2%) of our JIA cohort, which is similar to the 16% reported in the 1992 cohort. A positive test for antinuclear antibodies was the strongest risk factor. The JIA subgroup with the highest rate of uveitis was "other arthritis," followed by oligoarticular JIA. Extended and persistent course of oligoarticular JIA had a similar uveitis incidence, but all patients with extended-course disease developed uveitis before more than 4 joints were affected. After a mean followup of 5.62 years (range 0.5–15.17), 12/35 (34%) patients with uveitis had developed uveitis complications. Best corrected visual acuity was normal in 91% of patients. Only 5.6% of the affected eyes were legally blind as compared to 17.6% in the 1992 cohort.

Conclusion. The rate of uveitis was 13.2% in our cohort of Swiss children and has not changed since 1992. Despite the high rate of uveitis complications, the longterm visual outcome was excellent. (First Release Feb 15 2008; J Rheumatol 2008;35:703–6)

Key Indexing Terms:
UVEITIS JUVENILE IDIOPATHIC ARTHRITIS
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Uveitis is the most common extraarticular manifestation of juvenile idiopathic arthritis (JIA). The incidence, course, and outcome of this important complication of JIA vary widely between centers and countries[1,2]. Some authors have found a decreasing rate of uveitis in children with JIA[3]. An earlier Swiss study published in 1993 showed a uveitis rate of 16%, and 17.6% of affected eyes developed visual loss[4]. The purpose of our study was to determine the rate of uveitis, the risk factors, and the longterm visual outcome in a single-center cohort of patients with JIA in Switzerland, and to compare the results with the earlier study.

MATERIALS AND METHODS

The charts of all 265 patients with a diagnosis of JIA seen between January 1, 1997, and December 31, 2005, at the University Children's Hospital in Zürich, Switzerland, were reviewed for rheumatologic, ophthalmologic, and medication details of the disease course. We used the International League of Associations for Rheumatology 1997 criteria for the definition of JIA[5] and the International Uveitis Study Group Recommendations[6] for the definition of uveitis. The charts of patients with oligoarticular JIA were reviewed for the cumulative involvement of more than 4 joints. The date when involvement of 5 or more joints was first recorded was noted as the date of diagnosis of extended oligoarticular course. The final ocular outcome was best corrected visual acuity (VA) as measured by an ophthalmologist at the last ophthalmologic followup visit. The legal limits for obtaining a driving license and legal blindness in Switzerland were used as cutoff for the 3 categories of visual acuity, "good" = 0.6 or better, "impaired" = 0.6–0.1, and "legal blindness" = 0.1 or worse.

Statistical analyses were performed using the JMP IN 5.1 program (SAS Institute Inc., Cary, NC, USA). Chi-square, one-way analysis of variance (ANOVA), Kaplan-Meier survival analysis, and Cox proportional hazards regression analyses were used to assess for differences between groups.

RESULTS

Risk of uveitis. After a mean followup time of 4.82 years (range 0.08–16.58 yrs) 35 of the 265 patients (13.2%) had developed uveitis. For the patients' characteristics see Table 1. In 9 patients (25%) uveitis was diagnosed prior to or at the time of diagnosis of JIA, and 90% of patients developed uveitis within 2.65 years from the diagnosis of JIA. For the distribution of JIA subgroups in patients with and without uveitis see Table 2. Uveitis was most common in the subgroup "other arthritis" (3/12 patients, 25%), followed by extended oligoarticular JIA (5/29 patients, 17.2%) and persistent oligoarticular JIA (17/101 patients, 16.8%). Eight of the 12 patients including the 3 patients with uveitis were assigned to the subgroup "other arthritis" because of a his-

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Table 1. Patients' characteristics.

Characteristic	Total, n = 265	Patients with Uveitis, n = 35	Patients without Uveitis, n = 230	p, Difference Between Groups
All patients (%)	265 (100)	35 (13.2)	230 (86.8)	
Female (%)	174 (66)	25 (14.5)	149 (85.5)	
Mean age at diagnosis of JIA, yrs (range)	6.49 (0.67–15.67)	4.61 (1.0–14.25)	6.77 (0.67–15.67)	0.003
ANA positive (%)	133 (50.1)	33 (25)	100 (75)	< 0.0001
ANA negative (%)	132 (49.9)	2 (1.5)	130 (98.5)	
Mean followup time of JIA, yrs (range)	4.82 (0.08–16.58)	6.43 (1.25–15.58)	4.57 (0.08–16.58)	0.004
Mean age at diagnosis of uveitis, yrs (range)	5.46 (1.17–12.75)	5.46 (1.17–12.75)	NA	

JIA: juvenile idiopathic arthritis; ANA: antinuclear antibodies; NA: not applicable.

Table 2. Patients with uveitis by different JIA subgroups.

JIA Subgroup	All Patients, n = 265		Uveitis, n = 35	
	Total (%)	% Female	Total (%)	% Female
All subgroups	265	66	35 (100)	71
Oligoarticular persistent	100 (38)	67	17 (48.6)	82
Oligoarticular extended	29 (11)	79	5 (14.3)	60
Polyarticular RF-negative	57 (21.5)	75	7 (20)	57
Polyarticular RF-positive	4 (1.5)	100	0 (0)	0
Systemic	20 (7.5)	55	0 (0)	0
Enthesitis-related	28 (10.5)	32	2 (5.7)	50
Psoriatic	6 (2)	50	0 (0)	0
Other arthritis	21 (8)	67	4 (11.4)	75

RF: rheumatoid factor; JIA: juvenile idiopathic arthritis.

tory of psoriasis in 1 parent. Of note, in all 5 patients with extended oligoarticular JIA the diagnosis of uveitis was made prior to the diagnosis of extended oligoarticular disease course. The difference in the risk for developing uveitis between the JIA subgroups was not statistically significant (Kaplan-Meier p = 0.07).

A positive antinuclear antibody (ANA) test was the strongest risk factor for development of uveitis (Kaplan-Meier p < 0.0001), followed by the age at diagnosis of JIA (1-way ANOVA p = 0.003) and the followup time (1-way ANOVA p = 0.004). HLA-B27 testing was available in 119/265 patients (44.9%) of the total cohort and in 19/35 patients with uveitis (54.3%) but was not a risk factor for uveitis (Kaplan-Meier p = 0.94). The risk factors for development of uveitis found in the univariate analysis (positive ANA, age at diagnosis of JIA, followup time) were then tested in a Cox regression proportional hazard analysis for interdependence. Only positive ANA remained as a strong risk factor for development of uveitis in this model (p < 0.00001, risk ratio 16.7 for positive ANA). The age at diagnosis of JIA was the second most important factor but did not reach statistical significance (p = 0.056, risk ratio 0.9).

Treatment of JIA consisted of nonsteroidal antiinflammatory drugs in 259/265 (97.7%) patients and intraarticular steroid injections were performed in 145/265 (54.7%). Immunosuppressive drugs used were methotrexate (MTX) in 122/265 (46%), leflunomide in 10/265 (3.8%), and tumor necrosis factor-α (TNF-α) blockers in 24/265 (9.1%) patients. Three patients developed uveitis at 1.5 months, 4 months, and 6 months after the start of MTX treatment, respectively. New-onset uveitis did not occur during the treatment with TNF-α blockers or leflunomide. We did not find a difference in the rate of new-onset uveitis between patients treated with and those treated without immunosuppressive agents.

Treatment and course of uveitis. Chronic anterior uveitis was found in 32/35 patients with uveitis (91%): 2/35 (6%) had acute anterior uveitis and 1/35 (3%) had panuveitis. Uveitis was bilateral in 23/35 patients (66%). In 10/12 patients (83%) with unilateral involvement, the uveitis affected the right eye. For details of patients with uveitis see Table 3. Uveitis was treated with corticosteroid eye drops in 33/35 patients (94%). Systemic immunosuppressive agents were used in 21/35 (60%) patients with uveitis. Refractory

Table 3. Characteristics of patients with uveitis.

Characteristic	Total, n = 35	With Uveitis Complications, n = 12	Without Uveitis Complications, n = 23
Female (%)	25	9	16
Number of affected eyes	58	17	41
Mean age at diagnosis of uveitis, yrs (range)	5.46 (1.17–12.75)	4.79 (2.33–11.92)	5.81 (1.17–12.75)
Mean interval from diagnosis of JIA to diagnosis of uveitis, yrs (range)	0.84 (–2.5–4.0)	0.93 (–0.5–4.0)	0.79 (–2.5–3.42)
Mean followup time for uveitis, yrs (range)	5.62 (0.5–15.17)	6.68 (1.17–15.17)	5.06 (0.5–12.5)

uveitis was the indication to start immunosuppression in 11/35 (31%) patients, and in 8 patients a combination therapy of 2 immunosuppressive drugs was used. The median time to initiation of MTX treatment in patients with uveitis was 1.3 years (range 0 to 14.5 yrs) after the diagnosis of JIA and 0.16 years (range –2.1 to 12.5 yrs) after the diagnosis of uveitis. TNF-α blocker treatment was started after a median interval of 3.1 years (range 0.9 to 7.4 yrs) after the diagnosis of uveitis. All 4 patients treated with infliximab had important improvement of their uveitis after initiation of this treatment. One patient treated with etanercept for her joint disease experienced a flare of her previously silent uveitis.

Uveitis complications developed in 12/35 patients (34%) with uveitis (17/58 affected eyes, 29%) after a mean interval of 2.71 years (range 0–11) from diagnosis of uveitis. The most common complications were synechiae in 10 patients/35 eyes (28%/25%), cataracts in 9 patients/13 eyes (26%/22%), band keratopathy in 5 patients/7 eyes (14%/12%), glaucoma in 3 patients/4 eyes (8.5%/7%), and macular edema in 2 patients/2 eyes (5.7%/3.5%). Seven patients underwent a total of 21 surgeries for uveitis complications (1 surgery can include more than 1 intervention). The interventions performed were: 6 cataract extractions, 5 synechiolyses, 5 EDTA abrasions, 5 glaucoma surgeries, 3 partial vitrectomies. The interval from onset of uveitis to the diagnosis of uveitis complications was similar for patients treated with and without systemic immunosuppressive drugs.

Visual acuity data were available for 32/35 (91%) patients (53/58 eyes, 91.4%) with uveitis after a mean ophthalmologic followup time of 5.62 years (range 0.5–15.17). Twenty-nine of 32 patients (90.6%) had normal visual acuity, 1 patient (3.1%) had impaired visual acuity in 1 eye, and 2 patients (6.25%) had legal blindness in 1 eye each at last ophthalmologic followup. None of our patients had a bilateral reduced visual acuity at last followup.

Comparison with the 1992 cohort. There was no statistically significant difference in the rate of uveitis between the study of Korner-Stiefbold, *et al* from 1993[4] (10/64 patients, 16%) and the present study (35/265 patients, 13.2%), chi-square p = 0.76. Three of 17 eyes (17.6%) from the 1992 cohort and 3/53 eyes (5.6%) from our present cohort had decreased visual acuity at last followup (Fisher's exact test p = 0.15).

DISCUSSION

We evaluated the rate and longterm outcome of uveitis in children with JIA in Switzerland. The prevalence of uveitis of 13.2% in our cohort is within the range reported from neighboring European countries[4,7,8] and no difference in the rate of uveitis among children with JIA between the 1992 cohort and our cohort was found.

The only independent risk factor for the development of JIA-related uveitis in our study was a positive ANA test, a well known strong risk factor for the development of JIA-related uveitis[9,10]. Patients with uveitis were significantly younger at the diagnosis of arthritis; however, in the multivariate analysis age at onset of arthritis did not reach statistical significance, most probably due to the small number of patients in our cohort. Similar to results other authors have shown we found important differences in the rate of uveitis for the different subtypes of JIA[7]. The uveitis rate was highest (25%) in the subgroup "other arthritis." All 3 patients with uveitis in this subgroup had oligoarticular joint involvement with onset at preschool age and tested ANA-positive, all of which are factors associated with a high risk for developing uveitis. These patients were assigned to the subgroup "other arthritis" because of a history of psoriasis in 1 parent. This raises the question whether a family history of psoriasis might actually represent a disease biology with an additional risk for the development of uveitis.

Some authors found a higher risk for uveitis in patients with the extended oligoarticular disease course and recommended a more intense uveitis screening for these patients[11]. We therefore looked specifically at the evolution of eye and joint involvement in patients with oligoarticular disease onset. However, in our cohort all patients developed uveitis before the diagnosis of extended oligoarticular disease course, i.e., when they were still thought to have persistent oligoarthritis. This is in keeping with the findings in a large Canadian cohort of patients with JIA, where the majority of patients developed uveitis before 5 or more

joints were affected by the arthritis[12]. This supports the conclusion that the distinction between persistent and extended oligoarticular course of JIA is not helpful for determining the risk of a patient with oligoarticular onset JIA to develop new-onset uveitis and should not influence uveitis screening guidelines.

Despite a relatively high complication rate (34% of the patients with uveitis), the longterm visual outcome in our cohort was excellent, as only 3/53 eyes (5.6%) had reduced visual acuity at last ophthalmologic followup. This rate is much lower than in the majority of other studies[9,13]. Compared to the study of Korner-Stiefbold, *et al*[4] the complication rate was equal in our cohort. The visual outcome in our patients seems to be much better, with a decreased visual acuity in 5.6% versus 17.6% of affected eyes, but this difference was not statistically significant.

Our study is limited by the small number of patients with uveitis, which does not allow for more detailed analysis of our findings. Nevertheless, we are able to confirm an unchanged risk for the development of uveitis in children with JIA in Switzerland.

We were able to show that the rate of JIA-related uveitis in Switzerland is comparable to the rate found in other European countries and has not changed over time. Uveitis remains an important and sight-threatening complication of JIA and further efforts to improve treatment of JIA-related uveitis must go on.

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