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Risk Factors and Biomarkers for the Occurrence of Uveitis in Juvenile Idiopathic Arthritis

Data From the Inception Cohort of Newly Diagnosed Patients With Juvenile Idiopathic Arthritis Study

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Objective. **To analyze the prognostic value of demographic, clinical, and therapeutic factors and laboratory biomarkers and to assess their role in predicting uveitis occurrence in patients with juvenile idiopathic arthritis (JIA).**

Methods. **Patients with JIA were enrolled within the first year after JIA diagnosis. Demographic and clinical parameters were documented. Serum samples were collected at study enrollment, at 3-month follow-up visits within the first year, and then every 6 months. A multivariable Cox regression analysis was performed to evaluate the impact of demographic, clinical, laboratory, and therapeutic parameters on uveitis onset.**

Results. **We included 954 JIA patients (67.2% female, 54.2% antinuclear antibody [ANA] positive, mean ± SD age at onset 7.1 ± 4.6 years). Uveitis occurred in 133 patients (observation period 44.5 months). Young age at JIA onset and ANA positivity were significantly associated with the onset of uveitis (both $P < 0.001$). Treatment of arthritis with methotrexate alone (hazard ratio [HR] 0.18 [95% confidence interval (95% CI) 0.12–0.29], $P < 0.001$) or combined with etanercept (HR 0.10 [95% CI 0.04–0.23], $P < 0.001$) or adalimumab (HR 0.09 [95% CI 0.01–0.61], $P = 0.014$) reduced the risk of uveitis onset and the occurrence of uveitis-related complications. Predictors of uveitis onset included elevated erythrocyte sedimentation rate at baseline (HR 2.36 [95% CI 1.38–4.02], $P = 0.002$) and continuing moderate or high disease activity during follow-up as measured by the 10-joint clinical Juvenile Arthritis Disease Activity Score (HR 4.30 [95% CI 2.51–7.37], $P < 0.001$). Additionally, S100A12 levels ≥250 ng/ml at baseline were significantly associated with the risk of uveitis (HR 2.10 [95% CI 1.15–3.85], $P = 0.016$).**

Conclusion. **Apart from demographic risk factors and treatment modalities, JIA disease activity scores and laboratory biomarkers could be used to better define the group of JIA patients at high risk of uveitis onset.**

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of diseases with arthritis onset before age 16 years. In ~9–13% of patients with JIA, uveitis becomes manifest (1,2) and may lead to vision-threatening complications (3–5). Previous studies have identified different risk factors for uveitis onset in JIA, namely, oligoarthritis subtype, young age at arthritis onset, short duration of JIA disease, and antinuclear antibody (ANA) positivity (6–8). Uveitis occurrence is subject to geographic variations, with

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a higher rate in northern countries (e.g., Scandinavian countries and Germany) and a lower frequency in eastern and southern Asia (1,2,7). Furthermore, disease-modifying antirheumatic drug (DMARD) treatment in JIA patients may reduce the risk of uveitis onset, especially if instituted early in the course of disease (9).

Different molecular biomarkers have recently been investigated in arthritis patients in order to detect residual inflammation and the risk of arthritis flares after remission or after discontinuing treatment. A laboratory biomarker that offers the potential of a reliable outcome measure would be desirable for clinicians. An elevated erythrocyte sedimentation rate (ESR) may indicate activity of an autoimmune disease. Indeed, previous studies indicated an elevated risk of uveitis in JIA patients with an elevated ESR (10–13), while no such correlation was found in others (2,14). For other factors (e.g., C-reactive protein [CRP]), no correlation with uveitis risk in JIA has been found previously (10,12,13).

A new and promising approach is the determination of serum levels of S100 proteins, a group of damage-associated molecular pattern molecules expressed in cells of myeloid origin. S100 molecules mediate inflammatory responses of the innate immune system and recruit inflammatory cells to the site of tissue damage (15). S100A8/A9 complexes (myeloid-related protein 8 [MRP-8]/MRP-14; calprotectin) and S100A12 are calcium-binding proteins that mediate inflammatory responses through the receptor for advanced glycation end products and Toll-like receptors, after release from activated or necrotic cells (16). It has been shown that the MRPs S100A8 and S100A9 play a distinct role in neutrophil and monocyte activation (17). Analysis of these factors represents a promising tool for monitoring inflammation in JIA patients and in other (auto)inflammatory or autoimmune diseases (15,17–20). Indeed, serum levels of S100A8 and S100A9 have been shown to be useful for assessing the risk of further arthritis flares after methotrexate (MTX) withdrawal in JIA (21). Increased levels of S100A12 reflect neutrophil activation (15,20) and—similar to S100A8/A9—are useful for detecting low-level inflammation and predicting risk of relapses in JIA (19,22). Although it has been shown that elevated S100 serum levels reflect intraocular inflammation in JIA (23), no data are available about the impact of S100 serum protein levels on uveitis occurrence, outcome, and response to treatment. This would be a desirable monitoring instrument and prospective marker for assessing JIA patients at risk of uveitis manifestations or of a severe course of this ocular disease.

The aim of this study was to analyze the role of demographic factors, DMARD treatment, and laboratory biomarkers—particularly S100A12—to predict occurrence of uveitis in the prospective, controlled Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis (ICON-JIA).

PATIENTS AND METHODS

Patients and controls. The ICON-JIA study is a prospective, controlled, observational, multicenter study. We included patients with JIA defined according to the International League of Associations for Rheumatology classification (24) and with recent disease onset (diagnosis <12 months before enrollment). Eleven pediatric rheumatology centers in Germany are participating in this study (during the recruitment period, the units reached >33% of patients with incident JIA expected in the population in Germany). For more details on the ICON-JIA cohort study, see Sengler et al (25). For this analysis, the observation period ended at the last follow-up visit in patients without uveitis and on the date of occurrence of uveitis in patients who developed uveitis during the follow-up period. The loss to follow-up was low, with an annual dropout rate of 3.4% over the study period.

Data and blood sample collection. Patients were examined by a pediatric rheumatologist and an ophthalmologist quarterly during the first year and every 6 months thereafter. Various demographic and clinical data (e.g., count of joints with active disease [range 0–70] and global assessment of disease activity on a Numerical Rating Scale [21-point; 0–10]) and medical and family history were collected with standardized case report forms and questionnaires. JIA disease activity was evaluated using the 10-joint clinical Juvenile Arthritis Disease Activity Score (cJADAS-10). The cJADAS-10 (range 0–30) includes the physician's global assessment of disease activity, the parents' global assessment of overall well-being, and the number of joints with active disease (maximum of 10). The cJADAS-10 thresholds proposed by Consolaro and Ravelli (26) were applied to define disease activity states for oligoarticular and polyarticular JIA (≤1 = inactive; >1–≤1.5 and >1–≤2.5 = minimal; >1.5–≤4 and >2.5–≤8.5 = moderate; >4 and >8.5 = high, respectively).

At enrollment and at the follow-up visits every 3 months within the first year and every 6 months thereafter, standard inflammation markers (e.g., ESR, CRP level, and platelet count) and S100 proteins, cytokines, and chemokines were measured from serum samples. A double-sandwich enzyme-linked immunosorbent assay system was used to determine S100A12 levels. The ESR cutoff of ≥20 mm/hour was applied to define elevated ESR levels in accordance with the definition of the JADAS-10 (27). The readers of the laboratory assays were blinded with regard to the diagnosis. Additionally, immunoglobulins, autoantibodies (rheumatoid factor [RF] and ANAs), and HLA–B27 status were determined at inclusion. Ophthalmologic screening was performed according to current screening recommendations (2); findings were directly recorded with standardized questionnaires by the ophthalmologist who cared for the patient, and uveitis was classified according to the Standardization of Uveitis Nomenclature Working Group criteria (28).

Statistical analysis. Descriptive data were reported as the mean ± SD or the median and interquartile range for continuously distributed variables, as appropriate. Distributions of categorical variables were described by absolute and relative frequencies. A multivariable Cox regression analysis was performed to evaluate the associations of demographic, clinical (JADAS-10 score, etc.), laboratory (S100A12 and ESR), and

therapeutic parameters with uveitis onset. These analyses also included time-dependent covariates (change in disease severity across time and change in therapy) to model the change in the underlying risk of incidence of uveitis. A clinically meaningful threshold of 250 ng/ml for S100A12 levels was determined at the maximum of the Youden index based on receiver operating characteristic curve analysis (29). Missing values in categorical predictor variables were modeled by an additional category. Hazard ratios (HRs) are reported with 95% confidence intervals (95% CIs). *P* values less than 0.05 were considered significant. All statistical analyses were conducted using SAS software, version 9.3 (SAS Institute).

Ethics committee approval. The study was approved by the ethics committee of the Charité Universitätsmedizin Berlin. Subjects' consent was obtained according to the Declaration of Helsinki, and the design of the work conforms to the standards currently applied in Germany.

RESULTS

Demographic data. A total of 954 JIA patients were included in the study (67.2% female, 54.2% ANA positive, mean ± SD age at onset 7.1 ± 4.6 years) (Table 1). The mean ± SD follow-up time was 44.5 ± 22.8 months. Uveitis occurred in 133 patients (13.9%) during the observation period. Uveitis developed in 4 of these patients (0.4% of all JIA patients; 3.0% of all with uveitis) before the first JIA symptoms became manifest, with a mean ± SD duration of 11.0 ± 5.6 months between uveitis onset and first JIA symptoms. New uveitis onset was recorded for 65 (6.8% of all JIA patients; 48.9% of all with uveitis), 24 (2.5% of all JIA patients; 18.0% of all with uveitis), and 19 (2.0% of all JIA patients; 14.3% of all with uveitis) patients in the first, second, and third year, respectively, after first JIA symptoms. In 52 patients (5.5% of all JIA patients; 39.1% of all with uveitis), uveitis occurred after first JIA symptoms became manifest and before ICON-JIA study enrollment. A total of 21 patients (2.2% of all JIA patients; 15.8% of all with uveitis) developed uveitis after 3 years or later after JIA onset (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40544/abstract).

Established risk factors for uveitis. The established risk factors for uveitis onset were analyzed in the total sample of 954 patients. Female sex, young age at JIA onset, the JIA category of oligoarthritis, and ANA positivity were significantly associated with the onset of uveitis in univariate analyses (Table 2). Moreover, ANA positivity (HR 2.79 [95% CI 1.66–4.69], $P < 0.001$) and age <3 years at JIA onset (HR 2.8 [95% CI 1.9–4.0], $P < 0.001$) were also significantly associated with risk of uveitis in multivariable analysis. The multivariable model had good power to predict the risk of uveitis (Harrel's C = 0.77).

Table 1. Demographic and clinical data on the JIA patients at enrollment in the ICON-JIA study*

	Total sample (n = 954)†	Sample excluding patients with uveitis before enrollment in the ICON-JIA study (n = 898)‡
Female	641 (67.2)	601 (66.9)
Age at symptom onset, mean ± SD years	7.1 ± 4.6	7.3 ± 4.7
Time from symptom onset to diagnosis, median (IQR) months	3.0 (1.0–7.0)	3.0 (1.0–7.0)
Time from diagnosis to enrollment, median (IQR) months	1.6 (0.4–4.4)	1.5 (0.4–4.2)
JIA category		
Systemic arthritis	35 (3.7)	35 (3.9)
Oligoarthritis	445 (46.7)	410 (45.7)
Psoriatic arthritis	39 (4.1)	38 (4.2)
Enthesitis-related arthritis	100 (10.5)	94 (10.5)
RF-positive polyarthritis	15 (1.6)	15 (1.7)
RF-negative polyarthritis	252 (26.4)	242 (26.9)
Undifferentiated arthritis	68 (7.1)	64 (7.1)
cJADAS-10, mean ± SD	9.8 ± 6.2	9.9 ± 6.3
Inactive disease	56 (6.1)	51 (5.9)
Minimal disease activity	24 (2.6)	22 (2.6)
Moderate disease activity	173 (18.9)	164 (19.0)
High disease activity	664 (72.4)	626 (72.5)
ANA positive§	517 (54.2)	469 (52.2)
RF positive§	31 (3.3)	31 (3.5)
HLA–B27 positive§	146 (15.3)	139 (15.5)
ESR, mean ± SD mm/hour¶	22.8 ± 21.7	22.7 ± 21.9
S100A12, mean ± SD ng/ml#	337.5 ± 806.8	347.8 ± 833.0
Uveitis	133 (13.9)	77 (8.6)

* Except where indicated otherwise, values are the number (%). JIA = juvenile idiopathic arthritis; ICON-JIA = Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis; IQR = interquartile range; cJADAS-10 = 10-joint clinical Juvenile Arthritis Disease Activity Score.

† Sample for the analysis of "classic" risk factors.

‡ Sample for the analysis of clinical parameters and biomarkers for the risk of uveitis during follow-up.

§ Percentages refer to the total numbers of 954 and 898 patients in the total sample and the sample excluding patients with uveitis before enrollment, respectively. Test results were missing for antinuclear antibody (ANA) positivity (44 patients [4.6% of all patients]), rheumatoid factor (RF) positivity (177 patients [18.6% of all patients]), and HLA–B27 positivity (234 patients [24.5% of all patients]).

¶ Erythrocyte sedimentation rate (ESR) was reported in 794 and 744 patients, respectively.

Measured in 529 and 494 patients in the total sample and the sample excluding patients with uveitis before enrollment, respectively.

Impact of treatment on uveitis onset. The influence of treatment on the risk of uveitis was analyzed in 898 patients (the sample excluded patients with uveitis onset before enrollment in the ICON-JIA study [see Table 1]). Treatment of arthritis with MTX significantly reduced the risk of subsequent uveitis onset (HR 0.16 [95% CI 0.11–0.24], $P < 0.001$). This effect was also statistically significant after adjustment for established uveitis risk factors (HR 0.14 [95% CI 0.09–0.21], $P < 0.001$).

Table 2. Risk of incident uveitis from onset of first JIA symptoms in the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis study (n = 954)*

	Patients without uveitis at follow-up (n = 821)	Patients with uveitis at follow-up (n = 133)	Incidence of uveitis at follow-up (n = 133)†	Univariate analysis			Multivariable analysis§	
				HR (95% CI)	*P*	C‡	HR (95% CI)	*P*
Female	542 (66.0)	99 (74.4)	99 (15.4)	1.50 (1.01–2.23)	0.048	0.55	0.97 (0.64–1.45)	0.865
Age at JIA symptom onset, mean ± SD years	7.7 ± 4.6	3.8 ± 3.0	–	0.79 (0.74–0.84)	<0.001	0.75	0.82 (0.78–0.88)	<0.001
JIA category								
Oligoarthritis	360 (43.9)	85 (63.9)	85 (19.1)	2.16 (1.51–3.10)¶	<0.001	0.59	1.36 (0.94–1.96)¶	0.104
RF-negative polyarthritis	219 (26.7)	33 (24.8)	33 (13.1)					
RF-positive polyarthritis	15 (1.8)	0 (0.0)	0 (0.0)					
Psoriatic arthritis	37 (4.5)	2 (1.5)	2 (5.1)					
Enthesitis-related arthritis	92 (11.2)	8 (6.0)	8 (8.0)					
Systemic arthritis	35 (4.3)	0 (0.0)	0 (0.0)					
Undifferentiated arthritis	63 (7.7)	5 (3.8)	5 (7.4)					
ANA positive, no. (% tested)	404 (49.2)	113 (85.0)	113 (21.9)	5.00 (3.03–8.23)	<0.001	0.66	2.79 (1.66–4.69)	<0.001
RF positive, no. (% tested)	31 (3.8)	0 (0.0)	0 (0.0)	–	–	–	–	–
HLA–B27 positive, no. (% tested)	135 (16.4)	11 (8.3)	11 (7.5)	0.52 (0.28–0.97)	0.040	0.54	0.80 (0.42–1.50)	0.481

* Except where indicated otherwise, values are the number (%). HR = hazard ratio; 95% CI = 95% confidence interval; RF = rheumatoid factor.
† Incidence of uveitis within a group (row percentage).
‡ Harrel's C, a measure to evaluate the predictive power of parameters to predict the risk of uveitis ranging between 0.5 and 1 (0.5 = prediction by chance, 1 = perfect prediction). The multivariable model had good power to predict the risk of uveitis (Harrel's C = 0.77).
§ Predictors in the multivariable model were female sex, age at first symptoms of juvenile idiopathic arthritis (JIA), oligoarthritis (versus all other JIA categories), antinuclear antibody (ANA) positivity, and HLA–B27 positivity.
¶ The reference is all other categories of JIA.

Patients receiving MTX monotherapy (HR 0.18 [95% CI 0.12–0.29], $P < 0.001$; n = 414) or MTX combined with etanercept (HR 0.10 [95% CI 0.04–0.23], $P < 0.001$; n = 170) showed a reduced risk of uveitis onset. This effect might rely mostly on the effect from MTX, as the uveitis risk was not altered with etanercept monotherapy (HR 0.76 [95% CI 0.28–2.07], $P = 0.589$; n = 16). However, the study might have been underpowered for the analysis of

Table 3. Univariate and multivariable analysis of the impact of cJADAS-10, ESR, and S100A12 levels on the incidence of uveitis in the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis study, at enrollment and during follow-up*

	Univariate analysis		Multivariable analysis†	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Parameters at enrollment (visits with available measurements)				
cJADAS-10 (882)‡	1.00 (0.96–1.04)	0.867	1.02 (0.98–1.07)	0.308
Moderate or high disease activity	1.56 (0.57–4.28)	0.390	1.72 (0.62–4.78)	0.301
ESR (770)‡	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
ESR ≥20 mm/hour	2.98 (1.78–5.00)	<0.001	2.36 (1.38–4.02)	0.002
S100A12 (517)‡	1.40 (1.14–1.72)	0.001	1.50 (1.15–1.96)	0.003
S100A12 ≥250 ng/ml	2.66 (1.47–4.82)	0.001	2.10 (1.15–3.85)	0.016
Time-varying parameters at follow-up (visits with available measurements)				
cJADAS-10 (6,104)‡	1.10 (1.05–1.15)	<0.001	1.17 (1.11–1.23)	<0.001
Moderate or high disease activity	3.41 (2.01–5.77)	<0.001	4.30 (2.51–7.37)	<0.001
ESR (4,329)‡	1.03 (1.01–1.04)	<0.001	1.03 (1.01–1.05)	0.001
ESR ≥20 mm/hour	2.57 (1.48–4.46)	0.001	2.44 (1.37–4.36)	0.003
S100A12 (1,901)‡	1.18 (0.81–1.72)	0.379	1.21 (0.81–1.82)	0.351
S100A12 ≥250 ng/ml	1.45 (0.57–3.70)	0.438	1.54 (0.60–3.99)	0.372

* 95% CI = 95% confidence interval.
† Adjusted for age at disease onset, oligoarthritis, antinuclear antibody positivity, and treatment with methotrexate and biologic disease-modifying antirheumatic drugs.
‡ Hazard ratio (HR) for the increase by 1 unit in the 10-joint clinical Juvenile Arthritis Disease Activity Score (cJADAS-10) and the erythrocyte sedimentation rate (ESR), and for the increase by 50 units in the S100A12 level.

etanercept monotherapy. Treatment with adalimumab as monotherapy (n = 17) or in combination with MTX (n = 55) was also associated with a lower risk of uveitis onset (HR 0.09 [95% CI 0.01–0.61], $P = 0.014$; n = 72).

Laboratory and clinical biomarkers as risk factors for uveitis onset. ESRs (in mm/hour) and S100A12 levels (in ng/ml) were available at enrollment for 770 and 517 patients, respectively. A total of 216 patients (42%) with S100A12 measurement at baseline started DMARD treatment prior to the first S100A12 measurement (median duration of 1.5 months between start of DMARD treatment and S100A12 measurement at baseline). During the follow-up period, ESRs and S100A12 levels could be analyzed for 4,329 and 1,901 visits, respectively. Patients without uveitis during the observation period had a mean ± SD ESR of 21.8 ± 21.3 mm/hour at enrollment compared to 32.5 ± 26.4 mm/hour in patients with uveitis manifestations (see Supplementary Figure 2A, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40544/abstract). Similarly, mean ± SD S100A12 levels were 338 ± 849 ng/ml in patients without uveitis at enrollment and 434 ± 681 ng/ml in patients with uveitis at follow-up (see Supplementary Figure 2B). Both ESR and S100A12 were significantly associated with risk of uveitis onset in univariate and multivariable analyses (Table 3). Elevated S100A12 levels (≥250 ng/ml) during the JIA disease course did not show a significant association with the risk of uveitis at follow-up (HR 1.45 [95% CI 0.57–3.70], $P = 0.438$) (Table 3).

Importantly, clinically active arthritis—in fact, moderate or high active disease state as measured by the cJADAS-10—during the follow-up period significantly predicted subsequent uveitis onset (HR 3.41 [95% CI 2.01–5.77], $P < 0.001$). Patients with an elevated ESR (≥20 mm/hour) at the visit before uveitis onset were at higher risk of developing uveitis (HR 2.44 [95% CI 1.37–4.36], $P = 0.003$) (Table 3 and Figure 1), after adjustment for the established risk factors and arthritis treatment. In a multivariable analysis, moderate or high active disease state as measured by the cJADAS-10 and elevated ESRs was also significantly associated with uveitis onset (Table 3).

Identifying children at risk of uveitis onset is especially important for JIA subgroups in which (silent) chronic anterior uveitis may occur, as uveitis may go unnoticed for a longer time period in these children compared to children in other JIA subgroups (e.g., enthesitis-related arthritis [ERA], with acute anterior uveitis). Therefore, we

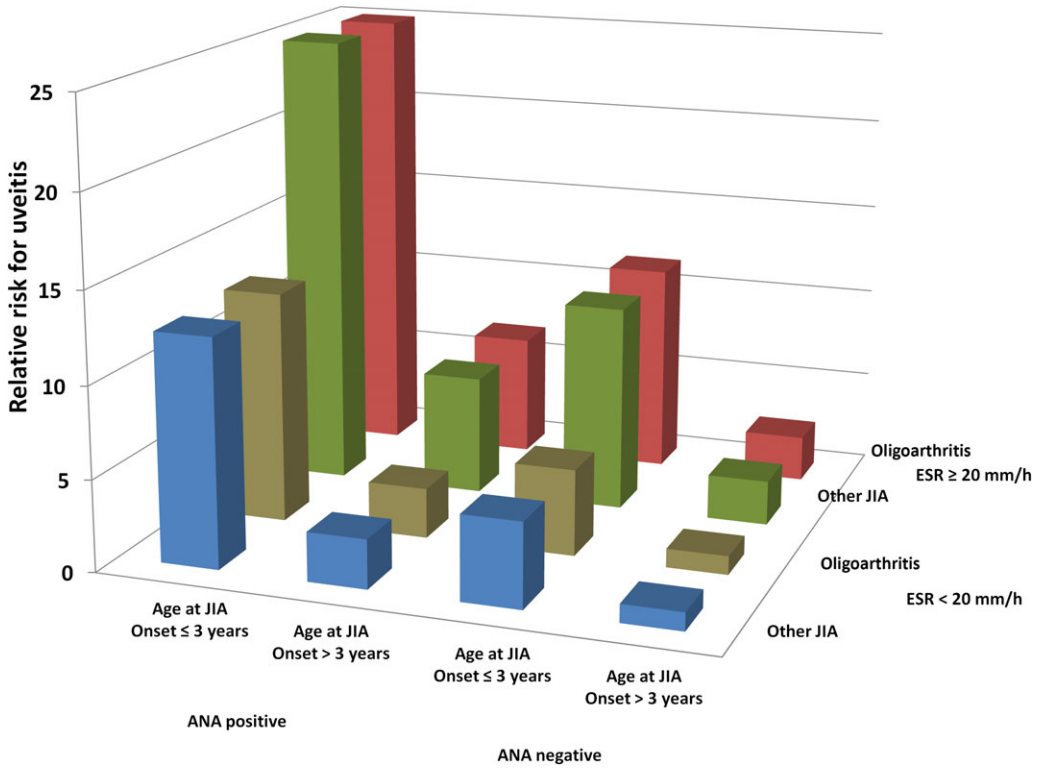

Figure 1. Relative risk of uveitis onset based on age at onset of juvenile idiopathic arthritis (JIA), antinuclear antibody (ANA) positivity, and erythrocyte sedimentation rate (ESR) at follow-up, adjusted for the 10-joint clinical Juvenile Arthritis Disease Activity Score and treatment with methotrexate (MTX) and MTX/biologic disease-modifying antirheumatic drugs.

performed a subgroup analysis for those children who typically may develop chronic anterior uveitis (i.e., oligoarthritis, RF-negative polyarthritis, psoriatic arthritis, and undifferentiated arthritis) (see Supplementary Tables 1 and 2, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40544/abstract). The risk factors for uveitis manifestations (Supplementary Table 1) and the predictive value of ESR and S100A12 (Supplementary Table 2) in this subgroup were similar to those in the whole JIA cohort in the ICON-JIA study, without any remarkable differences (Tables 2 and 3, respectively). The subgroup analysis for children with ERA, who may typically develop acute anterior uveitis instead of chronic anterior uveitis, was underpowered (n = 8 patients with uveitis) due to a low number of uveitis events or even none in the individual categories of the risk factors.

Clinical characteristics at first uveitis documentation. A detailed characterization of uveitis at initial documentation was available for 116 patients (87%), providing information on 162 affected eyes. At first uveitis documentation, bilateral uveitis was seen in 47 patients (40.5%), and an anterior chamber cell grade ≤2+ was found in 92% of patients (0.5+ in 20.7%, 1+ in 27.6%, and 2+ in 28.7% of patients). Uveitis-related complications were present in 28.7% of patients at first uveitis documentation (mainly posterior synechiae in 20.9% of patients and cataracts in 7.8%).

Patients with and those without uveitis-related complications at first uveitis documentation did not differ remarkably with regard to sex, JIA category, ANA positivity, and age at disease onset (Table 4). JIA patients being treated with DMARDs, specifically MTX or biologic DMARDs before uveitis onset, had slightly fewer uveitis-related complications at first uveitis documentation (Table 4). In the exploratory analysis of patients with uveitis onset after ICON-JIA study enrollment, parameters such as the cJADAS-10, ESR, and S100A12 level were analyzed with regard to the presence of secondary complications of uveitis at first documentation of disease (Table 5).

Table 4. Presence of uveitis-related ocular complications at initial uveitis documentation (univariate analyses)*

	No uveitis-related complications (n = 82)	Any uveitis-related complications (n = 33)
Female sex	64 (78.1)	24 (72.7)
Oligoarticular JIA	54 (65.9)	21 (63.6)
ANA positivity	69 (84.2)	30 (90.9)
HLA–B27 positivity	5 (6.1)	3 (9.1)
Age at JIA onset, mean ± SD years	3.4 ± 2.7	4.6 ± 3.3
Age at JIA onset ≤3 years	50 (61.0)	14 (42.4)
JIA disease duration, mean ± SD months	17.4 ± 16.9	6.0 ± 23.1
Uveitis onset after JIA onset	1 (1.2)	3 (9.1)
Previous therapy		
No DMARDs	56 (68.3)	30 (90.9)
Methotrexate	23 (28.1)	3 (9.1)
Etanercept	6 (7.3)	2 (6.1)
Adalimumab	1 (1.2)	0 (0.0)

* Except where indicated otherwise, values are the number (%). JIA = juvenile idiopathic arthritis; ANA = antinuclear antibody; DMARDs = disease-modifying antirheumatic drugs.

Table 5. Presence of uveitis-related ocular complications at initial uveitis documentation for patients with uveitis onset after enrollment in the Inception Cohort of Newly diagnosed patients with Juvenile Idiopathic Arthritis study*

	No uveitis-related complications (n = 54)	Any uveitis-related complications (n = 8)
Parameters at enrollment		
cJADAS-10, mean ± SD	9.57 ± 5.05	9.88 ± 8.00
Moderate or high disease activity	51 (94.4)	7 (87.5)
ESR, mean ± SD mm/hour	32.27 ± 22.72	37.03 ± 27.61
ESR ≥20 mm/hour	37 (68.5)	6 (75.0)
S100A12, mean ± SD ng/ml	497.53 ± 777.64	412.80 ± 131.26
S100A12 ≥250 ng/ml	19 (51.4)	4 (80.0)
Parameters at follow-up		
cJADAS-10, mean ± SD	4.95 ± 4.27	3.00 ± 2.98
Moderate or high disease activity	32 (65.3)	3 (60.0)
ESR, mean ± SD mm/hour	20.57 ± 15.37	13.60 ± 7.79
ESR ≥20 mm/hour	19 (38.0)	1 (20.0)
S100A12, mean ± SD ng/ml	204.15 ± 147.50	81.00 (–)
S100A12 ≥250 ng/ml	6 (31.6)	0 (0.0)

* Except where indicated otherwise, values are the number (%). cJADAS-10 = 10-joint clinical Juvenile Arthritis Disease Activity Score; ESR = erythrocyte sedimentation rate.

DISCUSSION

As uveitis manifestations in patients with JIA are often initially asymptomatic and may lead to irreversible vision impairment, identifying children at risk of uveitis is crucial. Current screening guidelines, based on JIA category, ANA positivity/negativity, age at JIA onset, and JIA disease duration, recommend screening intervals between 3 and 12 months (2,30). Using additional demographic, clinical, and laboratory biomarkers to even better define patients at risk of uveitis onset would be highly desirable. Furthermore, early DMARD treatment might be considered for the high-risk group with high rates of uveitis onset and ocular complications if the number needed to treat as well as a better outcome for such an approach could be justified by confirmed evidence.

In this study cohort, uveitis occurred in 13.9% of children with JIA, which is consistent with previous

publications reporting an overall prevalence of uveitis in JIA of ~9–13% (1,7,31,32); however, higher rates from Nordic countries of up to 20.5% have also been reported (14). In this large, prospective, multicenter study, demographic risk factors, namely, young age at JIA onset, JIA category, and ANA positivity, were significantly associated with the risk of uveitis onset. These findings corroborate the results of previous studies (2,9,14,33). In our study, female sex was found to be a significant risk factor for uveitis in the univariate analysis but not in the multivariable analysis. This corresponds to the results from other cohorts, in which sex was not found to be an independent risk factor (1,2,14,34,35). This may be explained by the predominance of females among those with onset of oligoarticular JIA at young age and by the higher percentage of ANA-positive females (35). A lower risk of uveitis onset within this group of JIA patients with intermediate follow-up duration was found for HLA–B27–positive children; however, this was significant only in the univariate analysis. HLA–B27 positivity in uveitis cases has been described previously, particularly in the ERA subgroup, and uveitis occurrence might increase with longer follow-up duration (2,36).

Children receiving conventional synthetic or biologic DMARDs had a significantly lower risk of uveitis onset in the current study, especially when receiving MTX and/or adalimumab. Preliminary evidence for a protective effect of MTX in JIA was found in a retrospective study by Papadopoulou et al, with uveitis developing in 10.5% of patients receiving MTX compared to 20.2% in those not receiving MTX (odds ratio 0.46, $P = 0.049$) (37), while such a role of immunosuppressive drugs was not clearly confirmed in other studies (14,38). Ravelli et al (39) recently reported an open-label trial comparing intraarticular corticosteroids alone to intraarticular corticosteroids plus MTX in JIA and found no significant difference in new-onset uveitis between patients who received MTX and those who did not ($P = 0.4957$). A protective effect of DMARD treatment has also been suggested in one of our previous studies, in which the uveitis prevalence decreased significantly between 2002 and 2013 from 13% to 11.6% in a national pediatric database, corresponding to an increasing rate of both synthetic (mostly MTX) and biologic DMARD use in the same time period (31). Finally, in another prospective study by our group based on a national database of 3,512 children with JIA in Germany, we found that DMARD treatment significantly reduced the risk of uveitis (for MTX alone, HR 0.63, $P = 0.022$; for tumor necrosis factor inhibitors, HR 0.56, $P < 0.001$; for a combination of the 2 medications, HR 0.10, $P < 0.001$) (9). A maximum of 300 ICON-JIA study patients may also have been included in our previous study, which would represent 8.5% of the patient group examined. The different results for the potential protective effect of MTX on uveitis manifestations might be explained by differences in study populations, study designs (particularly differences in ophthalmologic screening and documentation, for example, frequent prospective uveitis documentation only in the ICON-JIA study specifically focusing on uveitis occurrence and course), follow-up periods, analysis power, and adjustment for other risk factors.

Furthermore, our study gave new insight into the role of clinical activity scores and biomarkers (e.g., ESR and S100A12) as prognostic markers for uveitis in JIA. In 4 previous studies, elevated ESR predicted uveitis manifestations (10–13), while this was only true for the ERA subgroup of JIA in another study from a German cohort (2). It may be speculated that a high ESR correlates with the activity of autoimmune processes in JIA, potentially under the influence of Treg cells (13). Furthermore, the fact that high cJADAS scores indicate a higher risk of uveitis onset supports this theory and also supports previous notions (9). In our study, an ESR ≥20 mm/hour at enrollment indicated a significant risk of uveitis onset (HR 2.36, $P = 0.002$). As ESR is tested routinely in children with JIA, its use as a biomarker could easily be implemented more systematically in clinical practice and also in screening guidelines, as also suggested by Haasnoot et al (13). When analyzing the absolute ESR (instead of a cutoff of ≥20 mm/hour), only a modest HR of 1.02 ($P < 0.001$) was found, which means that for each 1-mm elevation of ESR, the odds for the occurrence of uveitis increase by 2%. Haasnoot et al (13) also found an almost identical ratio (HR 1.016, $P = 0.001$).

Interestingly, S100A12 levels at enrollment predicted uveitis onset. In a pilot study, elevated S100A12 levels were found in the serum and aqueous humor of patients with autoimmune uveitis (23), indicating a promising potential for this biomarker. Previous data support the use of S100A12 and S100A8/9 levels as a disease activity marker for predicting disease relapse and to help make therapeutic decisions in JIA (21,40,41). However, in our study S100A12 levels during the course of JIA disease did not show a significant relationship with the occurrence of uveitis, which might be explained by the influence of antiinflammatory treatment (23) (e.g., DMARDs), the limited number of samples available for S100A12 analysis, and high variations in levels. It must be considered that the HR indicated a positive association of uveitis risk with S100A12 levels during the course of disease, although without statistical significance. This might have been caused by low statistical power due to missing S100A12 measurements (compared to the numbers of available ESR measurements).

The ocular characteristics of eyes with uveitis at study inclusion (n = 116 patients with complete ophthalmological documentation) were similar to those previously reported (2,31,34). Occurrence of ocular complications during the course of JIA-associated uveitis was described in up to 90% of patients (32,42–47). At study inclusion, uveitis-related complications were already found in 28.7% of our patients, compared to 20–64% in previous reports (2,34,48). Such differences may be explained by the introduction of screening programs, the adoption of new JIA treatment regimens in the past few decades, and early and more aggressive treatment, particularly with biologic DMARDs (31). In this regard, the inclusion of patients within 1 year after JIA diagnosis (and not directly after JIA or uveitis onset) has to be considered for our study. Similarly, posterior synechiae and cataracts were the most common ocular complications at first presentation in previous observations (2,34,48). In our study, risk factors for the presence of early ocular uveitis-related complications were young age at disease onset and absence of any DMARD treatment. Interestingly, children treated with MTX, especially, demonstrated a significantly lower occurrence of uveitis-related complications at study inclusion. Such a relationship has also been found in previous studies (31).

The strengths of this study are its prospective multicenter design with a clearly defined inception cohort (inclusion of JIA patients within the first year of JIA diagnosis only) that included a remarkably large number of patients with documented ophthalmologic and pediatric rheumatic conditions based on clearly defined outcome criteria. Allowing the inclusion of children within 1 year and not directly at JIA onset might represent a certain limitation of this study; however, this made it possible to include this large cohort of children. Although the majority of the patients likely developed uveitis during the observation period, the possibility cannot be excluded that more children could develop uveitis after the mean follow-up period of 44.5 months. It must be mentioned that the ICON-JIA study did not explicitly distinguish between insidious (chronic) and acute-onset anterior uveitis. Due to this lack of differentiation in the data collection, we performed a subgroup analysis excluding all patients at risk of acute anterior uveitis (i.e., ERA, systemic arthritis, and RF-positive polyarthritis), and we found no relevant differences compared to the analysis of the whole JIA cohort (see Results).

It would be interesting to know the ANA titer and its influence on uveitis risk. However, the ICON-JIA study is an observational study that does not include the determination of ANAs in a central laboratory. The results of the ANA determinations were only reported by the pediatric rheumatologists, and these were carried out as part of the diagnostic procedure at the routinely assigned local laboratory. The cutoff for a positive titer of ANA may vary among the ICON-JIA study center laboratories. Therefore, only the ANA status (positive, negative, not determined) was recorded and not the ANA titer itself. The cutoff of 250 ng/ml that we used to define elevated S100A12 levels was estimated in our sample. This cutoff has to be confirmed in other cohorts before it may be applicable in general. Missing values in categorical predictor variables were modeled by an additional category. A complete case sensitivity analysis showed that the results from the regression analyses were comparable to the results reported herein. Because of this, the risk of biased estimates may be limited (49). The analysis of uveitis-related complications at first uveitis documentation had an exploratory character because the study was not powered for this analysis.

In conclusion, this prospective study has confirmed demographic risk factors for uveitis in a large, prospective, multicenter setting. Furthermore, it adds knowledge about the predictive value of JIA disease activity scores and laboratory biomarkers (e.g., ESRs and S100A12 levels) for the risk of uveitis manifestations in JIA. Indeed, these parameters are promising tools to better define the group of JIA patients at high risk of uveitis onset. High S100A12 levels and ESRs at JIA onset and high ESRs and high cJADAS-10 scores during follow-up have been found to be significant risk factors for uveitis manifestations.

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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. Tappeiner 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.

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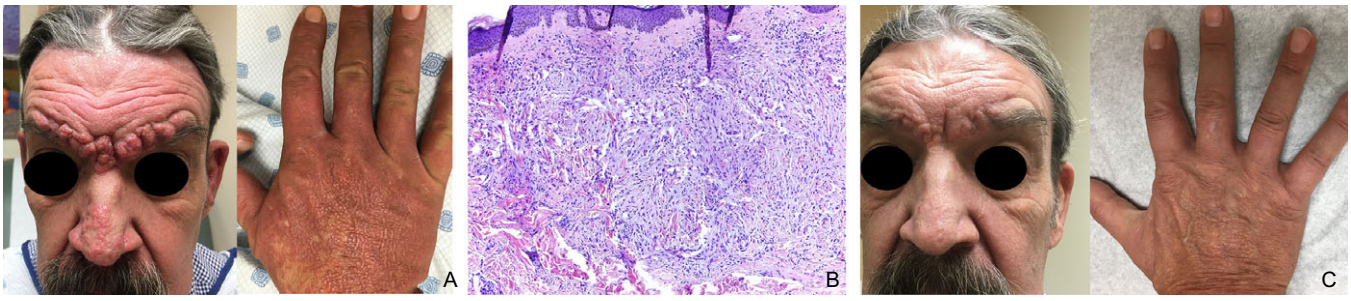
Clinical Images: Monoclonal gammopathy–associated scleromyxedema presenting as leonine facies



The patient, a 61-year-old man previously in good health, was referred to the scleroderma clinic for a 2-year history of slowly progressive cutaneous eruption involving the dorsal hands, extremities, and central area of the face. Physical examination revealed nodular, erythematous, indurated lesions on the forehead and erythematous papular lesions on the nose with coalescence of firm erythematous papulonodules, resulting in a leonine facies. On the dorsal hands, arms, and legs were numerous, shiny, firm, closely set, slightly translucent papules measuring 1–2 mm with background erythema (**A**). Skin biopsy demonstrated a spindled fibroblastic proliferation in the dermis with increased mucin and variable fibrosis (**B**). The clinical and histologic findings were diagnostic of scleromyxedema. Scleromyxedema is a rare disorder of unknown pathogenesis characterized by a generalized lichenoid papular cutaneous eruption and resulting in diffuse skin induration that may simulate scleroderma. Rarely, larger exophytic nodules, as seen in this patient, may be present. The majority of scleromyxedema cases occur in association with a monoclonal gammopathy. The patient was found to have an IgGλ M protein spike. This patient did not exhibit any CRAB features (hypercalcemia, renal insufficiency, anemia, and bone lesions), and evaluation including hematologic studies culminated in a diagnosis of IgGλ monogammopathy of unclear significance, with plans for ongoing observation. For his scleromyxedema, the patient received intravenous immunoglobulin (IVIG) at doses of up to 2 gm/kg/month (1), with significant improvement in the appearance of lesions after 16 months (**C**). He continues to receive a maintenance dose of 1 gm/kg IVIG every 4 weeks.

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