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Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis

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ABSTRACT.

Purpose: **Aim of the present study was to validate a statistical model to predict a severe course of anterior uveitis (AU) in patients with juvenile idiopathic arthritis (JIA).**

Methods: **Consecutive patients with newly diagnosed uveitis have been followed for at least 1 year with a standardized protocol. For each patient, demographic, clinical and laboratory characteristics, including time interval between arthritis and uveitis onset, α_2-globulins level at arthritis onset, number of uveitis relapses/year, ocular complications and therapy and visual acuity, have reported. The validation procedure included the assessment of sensitivity, specificity and efficiency of previously published statistical model (Zulian et al.** ***J Rheumatol*** **2002;** 29: **2446–2453) in a new inception cohort of patients during a short length follow-up.**

Results: **Sixty patients with JIA, followed at 14 paediatric rheumatology–ophthalmology centres in Italy, entered the study. The mean age at arthritis onset was 4.4 years (range 1.2–15.8 years), and the mean interval time between arthritis and uveitis onset was 1.8 years (range: 0.0–14.2 years). After the first AU, patients, followed for a mean of 3.2 years, had a mean of 2.9 uveitis relapses. Twenty-two patients (36.7%) presented at least one complication. Using a probability cut-off value = 0.7, the statistical model revealed 80% sensitivity, 58% specificity and 65% efficiency.**

Conclusion: **The time interval between arthritis and uveitis onset resulted as the main predictor of severe course uveitis in JIA. The statistical model was able to predict the development of a severe course in 8 of 10 patients.**

Key words: juvenile idiopathic arthritis – outcomes – risk factors – uveitis – vision

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Introduction

Compared to the polyarticular and the systemic forms, oligoarticular juvenile idiopathic arthritis (oligo-JIA) has long been considered a benign disease (Zak & Pedersen 2000; Cassidy & Petty 2005). However, when ocular involvement is present, the outcome can be severe.

In patients with oligo-JIA, anterior uveitis (AU) has been reported with a frequency ranging between 12% and 20.1% (Grassi et al. 2007; Heiligenhaus et al. 2007). Among predictors for its development, early age at disease onset, ANA positivity, DRB1*11 HLA-aplotype and female gender have been identified (Heilligenhaus et al. 2007, Saurenmann et al. 2007; Bolt et al. 2008).

Three quarter of patients develop uveitis within 1 year and 90% by 4 years after arthritis onset (Zulian et al. 2002; Heilligenhaus et al. 2007). Around half of the patients develop complications, such as synechiae, cataract, band keratopathy (BK), cistoide macular oedema, vitreitis and glaucoma (Heilligenhaus et al. 2007).

To predict the risk of developing these complications, a statistical formula, resulted from a multivariate logistic regression analysis, and based on two parameters, time interval

between the onset of arthritis and the first AU and elevated α_2-globulins at disease onset, have been proposed (Zulian et al. 2002). We performed a multicenter prospective study to validate this model in a new large cohort of patients with JIA-related AU.

Material and Methods

To validate a previously described predictive model in a prospective cohort (Zulian et al. 2002), records from paediatric patients with newly diagnosed AU, consecutively seen between January 2001 and 2006, at 14 paediatric rheumatology and ophthalmology centres in Italy, were collected in a Microsoft Access© format. All patients were diagnosed as having AU, according to the SUN Working Group criteria (Jabs et al. 2005), and have been followed by the same ophthalmologists and paediatric rheumatologists in each centre, using a standardized protocol and treatment regimen.

All participating centres adopted the following stepladder algorithm: 1st step (new onset uveitis): topical therapy; 2nd step (recurrent/persistent AU): added systemic corticosteroids (prednisone 0.5–1 mg/kg/day orally); 3rd step (refractory or steroid-dependent AU): added methotrexate (10–15 mg/m^2/week); 4th step (MTX – refractory AU): added biological anti-TNF agents. Intervals between consecutive ophthalmologic evaluations varied between 2 weeks and 2 months, depending on the uveitis course. Data collected were gender, arthritis subtype, age at arthritis onset, age at uveitis diagnosis, α_2-globulin serum level at the JIA onset, treatment performed at baseline and during F/U, LogMAR converted best corrected visual acuity (BCVA), number of uveitis relapses per year of F/U, ocular complications present at baseline and developed during the F/U and surgical procedures.

Severe uveitis course has been defined as presence of two or more AU relapses in at least 1 year of F/U with either development of new complications, or need for immunosuppressive treatment. Conversely, mild uveitis course has been defined as single or recurrent episodes without development of new complications, or need for immunosuppressive treatment.

The collected clinical information was applied to the statistical model, proposed in 2002, and aimed to predict severe course uveitis in JIA (Zulian et al. 2002). The model allows calculating the probability of a patient to develop a severe course uveitis knowing the time interval between onset of arthritis and first uveitis and the α_2-globulin concentration at disease onset.

The statistical model formula resulted from a multivariate logistic regression analysis in which several clinical and laboratory variables had been considered (Zulian et al. 2002). The final formula was as follows: $p = [1/(1 + e^{-g})]$, where p = probability of severe course uveitis; e = natural number (2.7182); $g = -2.95 + (0.54 * \alpha_2\text{-globulin value in g/l}) - (0.17 *$ interval time in months between onset of JIA and first uveitis). According to this model, a short time interval between onset of arthritis and uveitis and a high α_2-globulin serum level represents the two crucial risk factors for the development of a severe course uveitis.

In the present study, the model has been applied to new patients with at least 1 year of follow-up since the onset of the first AU. The risk for severe uveitis, obtained by the application of the model, was compared to the real clinical course of ocular inflammation reported during the follow-up. Sensitivity, specificity and efficiency of the model have then been calculated.

Demographic, clinical and laboratory characteristics of the patients were analysed by descriptive statistics. Differences between the two groups of patients, with mild and severe course uveitis, were analysed by unpaired Student's *t*-test, Mann–Whitney *U*-test and Fisher's exact test, as appropriate. All tests of significance were two-sided, and p values < 0.05 were considered significant. All analyses have performed by using the Stats Direct statistical software (Version 2.6.5; Stats Direct Ltd, Cheshire, UK). Because all clinical information was anonymously collected from the patients' charts, Ethic Committee approval was not required.

Results

Sixty patients entered the study, 51 (85.0%) were females, with a F:M ratio of 5.7:1. According to the revised diagnostic criteria for JIA (Petty et al. 2004), 90.0% had persistent and 10.0% extended oligoarticular JIA. The mean age at arthritis onset was 4.4 ± 3.4 years (range: 1.2–15.8 years); the mean age at onset of uveitis was 6.2 ± 4.1 years (range: 2.0–20.3 years); and the mean time interval between arthritis onset and the first uveitis was 1.8 ± 3.0 years (range: 0.0–14.2 years). After the first AU, patients have been followed for 3.2 ± 1.5 years (range: 1.1–6.3 years).

In 66.7% of the patients, AU appeared after arthritis onset, in 33.3% arthritis and uveitis were diagnosed simultaneously. Uveitis was bilateral in six of ten patients, corresponding to 98 (81.7%) affected eyes.

Forty patients (66.7%) presented a mild course and 20 (33.3%) a severe course uveitis. All severe cases presented two or more AU relapses in at least 1 year of F/U and need for immunosuppressive treatment. Eleven patients also developed new complications during the F/U.

The comparison of the two groups of patients is shown in Table 1. As shown, a significant correlation between severity of uveitis course and time interval between arthritis and uveitis onset (25.8 months in mild vs. 11.8 months in severe uveitis) was present. By 24 months since the arthritis onset, 71.7% of patients developed uveitis by 24 months since the arthritis onset, and 80.0% of those with severe ocular inflammation presented the first episode of uveitis by 5 months since the arthritis onset (Fig. 1).

During the follow-up, children presented a mean of 2.9 AU relapses (range 0–6), three of four relapses were observed within the end of the third year of F/U.

Twenty-two patients (36.7%) had ocular complications: in 10, they were already present at disease onset and 12 developed them during the F/U. They include synechiae (30.0%), cataract (18.3%) and band keratopathy (BK) (13.3%). Cistoide macular oedema (CMO) was reported in 6.7% of the patients, vitreitis in 5.0% and glaucoma in 1.7%. Thirteen children (21.7%) developed more than one complication during the follow-up. Eight children (13.3%) underwent surgical treatment for cataract, variably combined with vitrectomy and glaucoma surgery in three cases.

Table 1. Demographic and clinical characteristics of patients with mild and severe course uveitis.

	Mild course uveitis (no. 40)	Severe course uveitis (no. 20)	p
Sex (F:M)	7.0 : 1	4.0 : 1	0.464
Oligoarticular JIA Subtype			
Persistent	38/40 (95.0%)	16/20 (80.0%)	0.102
Extended	2/40 (5.0%)	4/20 (20.0%)	
Age at diagnosis of arthritis (years)			
Mean ± SD	4.2 ± 3.3	4.8 ± 3.8	0.460
Age at diagnosis of uveitis (years)			
Mean ± SD	6.3 ± 4.3	5.8 ± 4.0	0.570
Time interval arthritis/uveitis (months)			
Mean ± SD	25.7 ± 36.5	12.8 ± 32.3	0.005
Alpha$_2$ globulin at onset (g/l)			
Mean ± SD	11.4 ± 3.0	10.5 ± 2.8	0.268
Immunosuppressive treatment (MTX, CyA, Anti-TNF)			
At uveitis onset (%)	20.0 (8/40)	10.0 (2/20)	0.361
At last follow-up (%)	55.0 (22/40)	45.0 (9/20)	0.648

M = male; F = female; ns = not significant; SD = standard deviation; MTX = methotrexate; CyA = cyclosporine A; Anti-TNF = Tumour necrosis factors antagonists.

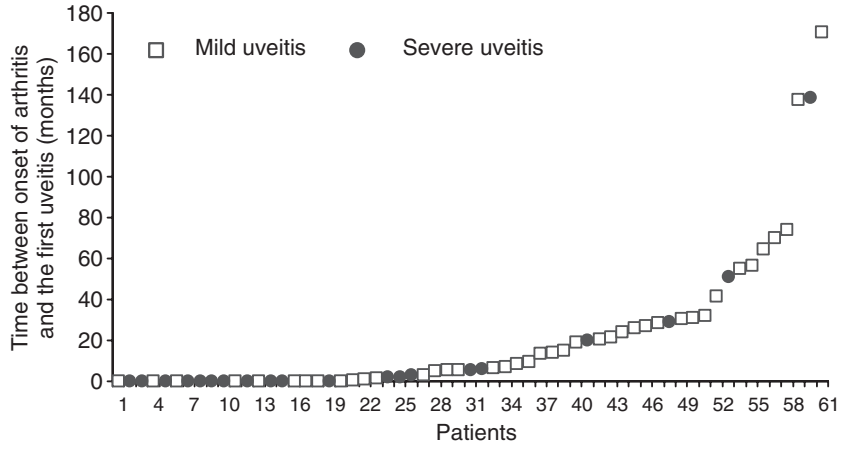

Fig. 1. Patient distribution by interval time between onset of arthritis and first uveitis.

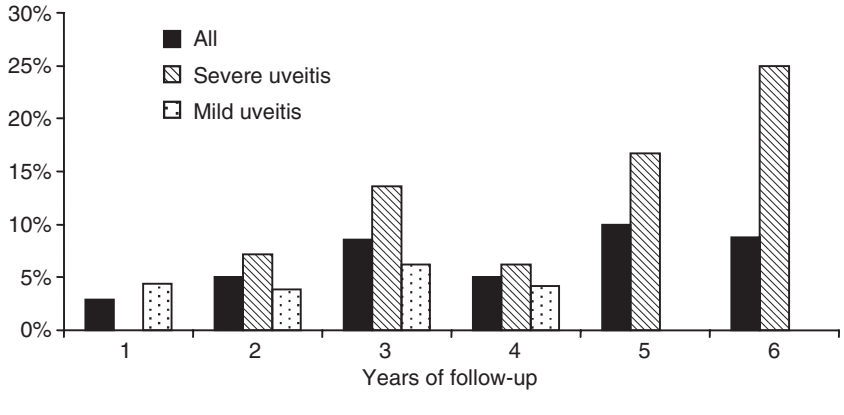

Fig. 2. Percentage of eyes with visual acuity <0.4 logMAR in severe and mild course uveitis.

The difference between initial and final BCVA has been calculated for 98 affected eyes. A BCVA loss of ≥2 lines was observed in eight eyes (8.2%) and was higher in the group with severe uveitis (15.6%) in comparison with the group with mild uveitis (4.5%). The most common complications, associated to visual loss, were cataract (83.3%), synechiae (66.7%), band keratopathy (50.0%) and CMO (50.0%). Visual acuity, at the last follow-up, showed bilateral function <0.4 logMAR in two patients (3.3%), unilateral in 7 (11.7%). The frequency of eyes with visual acuity function <0.4 logMAR was higher in patients with severe course uveitis, especially in those with the longest F/U (Fig. 2).

Table 2. Model application on observed and predicted uveitis cases.

	Observed outcome		
	Severe	Mild	
Predicted outcome			
Severe	16	17	33
Mild	4	23	27
Total	20	40	60

Cut value: 0.70.

The mean α_2-globulins level at the diagnosis of arthritis was elevated in 85% of patients (10.8 ± 2.9 g/l – range 2.6–19.8), with a similar proportion of patients with mild or severe course uveitis.

As far as treatment, 58 patients (96.7%) have been treated with topic eyedrops, 46 (76.7%) with NSAIDs, 25 (41.7%) with oral corticosteroids. Thirty-seven (61.7%) received immunosuppressive drugs for uveitis, such as methotrexate (36), cyclosporine A (10) and anti-TNFα agents (9). Ten patients (16.7%) have been treated with a combination of immunosuppressive drugs.

A table of the model application with predicted and observed severe and mild uveitis courses is presented (Table 2). Using a cut-off value of 0.70, the statistical model predicted the risk of severe course uveitis with 80.0% sensitivity, 57.5% specificity, 48.5% positive predictive value and 85.2% negative predictive value. This means that the model is reliable to predict a mild course: 85% of patients assigned to the low risk group by the test had a mild uveitis course (high negative predictive value). Conversely, <50% of patients assigned to the high-risk group by the model had severe uveitis, although 16 of 20 children with severe course uveitis were correctly assigned to the high-risk group by the model.

Discussion

Ocular involvement accounts for the most severe extra-articular manifestation

of oligoarticular JIA (Kotaniemi et al. 2003; Petty et al. 2004). It is well known that arthritis and uveitis develop with an independent course, and the articular prognosis is not influenced by the presence of uveitis and *vice versa* (Rosenberg & Oen 1986; Cimaz & Fink 1996). After the diffusion of screening recommendations (Yancey et al. 1993; Cassidy et al. 2006), visual prognosis has been improved by the earlier diagnosis of uveitis. However, it is still common experience that, in spite of the increased surveillance, some patients still have a bad outcome, require surgery for cataract or glaucoma, and have poor visual function. In fact, moderate visual impairment (BCVA ≤ 20/40) has been reported with a frequency ranging between 9.1% and 36% (Cabral et al. 1994; Saurenmann et al. 2007; Woreta et al. 2007), and some patients still have a worse outcome with blindness ranging between 5.6% and 24% (Woreta et al. 2007; Bolt et al. 2008).

In our prospective study, 8.2% of the affected eyes revealed, at the end of the F/U, a significant visual loss (≥2 lines), but a much higher proportion of complications (37.7%). The distribution of BCVA during the F/U confirmed an increased proportion of significant functional impairment (< 0.4 logMAR) in eyes of patients with severe uveitis, and its higher prevalence in those with a longer F/U.

Several studies tried to assess possible risk factors for severe course uveitis. The most frequently reported are symptomatic onset, diagnosis of uveitis before or concomitant to arthritis, chronic course, presence of complications at first visit, degree of inflammation at the initial ocular examination and a short interval time between the diagnosis of arthritis and uveitis (Wolf et al. 1987; Edelsten et al. 2002; Zulian et al. 2002; Heilligenhaus et al. 2007, Sijssens et al. 2007; Thorne et al. 2007; Woreta et al. 2007). Although recognized as possible predictor of uveitis development, presence of positive ANA does not represent a predictor of severity (Zulian et al. 2002; Heilligenhaus et al. 2007, Woreta et al. 2007).

In our study, the time interval between arthritis and uveitis onset is similar to another already reported in the literature by Saurenmann et al. (2007). Almost all patients developed their first uveitis within 7 years after JIA onset, and as many as 85% of those with severe uveitis had their onset within 2 years from JIA diagnosis. Cataract was the most common complication affecting visual outcome.

The comparison of patients with mild and severe course confirms a strong correlation between severity of uveitis and a short time interval between arthritis and uveitis onset (Table 1). It should be underlined that a significant proportion of children with severe ocular inflammation presented the first episode of uveitis by 5 months since arthritis onset. By using a α_2-globulin cut-off value of 9 g/dl, we could not discriminate patients with severe or mild course uveitis ($p = 0.37$) while interval time between arthritis and uveitis onset of 24 months significantly discriminate the two groups ($p = 0.025$).

The previously proposed statistical model (Zulian et al. 2002) confirmed a good sensitivity, being able to correctly assignee 8 of 10 severe uveitis children to the high-risk group. It is also reliable to predict a mild course uveitis (high negative predictive value). However, < 50% of patients assigned to the high-risk group by the model had severe uveitis. It may be underlined that more than half children with predicted severe course had a follow-up ≤2 years. We may speculate that, in some of these patients, a longer follow-up might reveal a severe course. Indeed, the earlier introduction of immunosuppressive drugs or biological treatments (Jabs et al. 2000) during the last few years may have influenced the outcome and lowered the specificity of the model. In fact, 13 children with a false prediction of severe course uveitis have been treated with various immunosuppressive treatments for uveitis relapses by 12 months since the uveitis onset. The more aggressive therapy, received during the early phase of the ocular inflammation, could have prevented a severe uveitis course.

Although the model seems to overestimate the risk of a severe uveitis course in a short period, it allows the clinician to carefully check and earlier treat those patients potentially at risk of developing ocular complications, improving the long-term outcome.

In conclusion, the present study evidences that, in the short period, the statistical model is reliable to predict a mild course but is less accurate to predict a severe course of ocular inflammation. The time interval between arthritis and uveitis onset has been confirmed as the only crucial factor for the development of severe course uveitis in JIA. This parameter should be considered, in future clinical trials, to select the group of patients to treat early more aggressively, to prevent irreversible complications.

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