Early Predictors of Severe Course of Uveitis in Oligoarticular Juvenile Idiopathic Arthritis

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ABSTRACT. ***Objective.*** To determine whether demographic, clinical, and laboratory variables at onset of arthritis can predict the development and the severity of anterior uveitis (AU) in oligoarticular juvenile idiopathic arthritis (JIA).

Methods. In a retrospective study, a cohort of 366 patients with oligoarticular onset JIA from 3 pediatric rheumatology centers were evaluated. Patients were classified in 3 groups: severe uveitis (SU) with a mean ≥ 2 uveitis relapses/year with complications or need for immunosuppressive therapy; mild uveitis (MU) with a mean ≤ 1 uveitis relapse/year with no complications; and no uveitis. Variables that were significant with univariate tests or were clinically relevant for each outcome underwent multivariate logistic regression analysis.

Results. There were 316 patients available for analyses: 66 in the SU group, 64 in the MU group, and 186 in the no uveitis group. Multivariate analysis showed the following factors to be significant as predictors of AU onset: low age at onset (OR 0.96), α_2-globulin plasma concentration (OR 1.34), and HLA-A19 (OR 2.87), B22 (OR 4.51) and DR9 (OR 2.33), while HLA-DR1 conferred protection (OR 0.13). This model was not good in predicting which patient would develop uveitis (sensitivity 55%, specificity 26%). Time interval between onset of arthritis and the first AU and elevated α_2-globulin level in the serum were the best predictors of AU severity (OR 1.62 and 0.85, respectively). When applied prospectively, the model revealed good sensitivity (89.2%), specificity (76.1%), and efficiency (86.3%).

Conclusion. Clinical and laboratory variables measurable at onset of arthritis can be used to predict severity of the course of AU in oligoarticular JIA, but not its onset. More accurate prediction can shorten or lengthen the intervals between ophthalmologic evaluations and can change the therapeutic approach undertaken on the basis of expected disease severity. (J Rheumatol 2002;29:2446–53)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS UVEITIS PREDICTION OUTCOME

Oligoarticular onset juvenile idiopathic arthritis (JIA) is the most frequent chronic inflammatory rheumatic condition in childhood[1]. Compared to polyarticular and systemic JIA, oligoarticular JIA has long been considered a benign disease[2-4]. However, recent studies have shown a high rate of polyarticular progression, erosions, and ocular complications represented by chronic anterior uveitis (AU) in these patients[5,6]. Chronic AU, indeed, may occur in 13–34% of patients with JIA and is most often observed in young girls with oligoarticular onset JIA[7-10]. Uveitis is usually asymptomatic and early detection requires routine slit lamp examination. Reports suggest that up to 38% of patients with JIA associated uveitis develop severe visual impairment[11] and up to 16–22% develop blindness[7,12].

Untreated or poorly controlled uveitis appears to be associated with ocular complications such as synechiae, band keratopathy, cataract, and glaucoma. At present it is not possible to predict which children will develop uveitis and to what extent.

In a large cohort of patients with oligoarticular JIA we investigated whether any demographic, clinical, and laboratory variables at arthritis onset could predict the development of uveitis and/or its course.

MATERIALS AND METHODS

Study design and patient selection. We reviewed the databases of 3 pediatric rheumatology centers in Italy including the Children's Hospitals of Padua and Florence and the "G. Pini" Hospital in Milan. The charts of 366 patients (298 female, 68 male) who met criteria for the diagnosis of oligoarticular type JIA[13] were studied retrospectively. Data obtained from each clinic were collected anonymously. Children with acute uveitis or family history of psoriasis or previous eye disease unrelated to JIA were excluded. Patients with oligoarticular onset but subsequent polyarticular course (extended pauci) were included in the study.

Among the eligible patients, 50 children were excluded: 21 for lack of

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precise data, 16 with followup < 2 years, and 13 with onset of uveitis before that of arthritis. The age at disease onset, the sex, and the uveitis ratio of excluded patients were not significantly different from those of the study group. Thus 316 patients with a minimal followup of 2 years entered the study: 130 (41%) with chronic uveitis and 186 (59%) without. The diagnostic criteria for uveitis were those defined by the International Uveitis Study Group[15]: presence of cells and/or proteins in the anterior ocular chamber or keratitic precipitates on the corneal endothelium or lens. These patients were then divided into 3 subtypes based on uveitis severity: (1) Severe uveitis (SU): patients with a mean ≥ 2 uveitis relapses/year lasting more than one month despite topical treatment and with complications such as band keratopathy, cataract, synechiae, or glaucoma or need for immunosuppressive therapy. (2) Mild uveitis (MU): patients with a mean ≤ 1 uveitis relapses/year lasting less than one month with topical treatment and with no ocular complications. (3) No uveitis (NoU): patients with no episode of uveitis during the observation period.

Slit lamp examination had been performed at least every 3 months or more frequently if uveitis was detected, according to the recommendations of the American Academy of Pediatrics[13]. During the time of the study, all patients were evaluated by the same team of ophthalmologists and pediatric rheumatologists in each center.

Assessment of predictive variables. Table 1 presents the list of independent (predictor) variables that we attempted to record for each patient. After informed consent was obtained, the patients' charts were reviewed to obtain information about predictive variables recorded at onset of arthritis or during the first 3 months of their illness. In the event that the patient had returned for numerous visits during the first 3 months, the value that represented the worst score for the particular variable was recorded — i.e., highest erythrocyte sedimentation rate (ESR), lowest hemoglobin, etc.

Laboratory investigations at the time of diagnosis of arthritis included ESR, C-reactive protein (CRP), white blood cell count, hemoglobin, platelets, α_2-globulin concentration, antinuclear antibodies (ANA), and serologic tests for HLA haplotypes A, B, C, DR and DQ. ESR and CRP were considered abnormal if > 35 mm and > 0.5 mg/dl, respectively, according to our laboratory standards; white blood cell count and hemoglobin were considered abnormal if greater or less than 2 SD values for age. Platelet count was considered abnormal if > 400×10^3/mm^3 and α_2-globulin concentration if > 8 g/l[16]. ANA titer, tested on HEp2 cell line, was considered positive if > 1:80. Serologic HLA typing Class I and Class II antigens were tested using standard typing sera and microcytotoxicity assays (Table 1).

Statistical analysis. *Univariate analysis*. During the initial phase we were interested in screening independent (predictor) variables that might enter the multivariate analyses. We considered $p < 0.05$ statistically significant and qualified the variable to enter the multivariate phase of the analyses. Because multiple logistic analysis requires many more patients when variables are polychotomized rather than dichotomized[17], we focused on binary conversion. We chose cutoff points that have either appeared in the literature or are clinically relevant. Many of the predictor variables are binary (e.g., HLA-DR5 positive or negative). We tested for an association between the binary prediction and the binary outcome (e.g., JIA with uveitis or JIA without uveitis vs HLA-DR5 positive or negative) by a simple 2 × 2 chi-squared analysis. Some independent predictor variables were measured on continuous level scales but have both normal and abnormal ranges (e.g., ESR). In these situations, we converted the predictor into a binary outcome (e.g., ESR elevated > 35 mm or normal) and then followed the same procedure (above) for predictors that were binary by nature. Age at onset and time interval between onset of the arthritis and first uveitis are continuous variables with no abnormal range. In these cases we used the Student t test to compare the uveitis and non-uveitis groups and the MU and SU groups.

First we evaluated the distribution of clinical and laboratory variables in the 2 groups of patients (with or without uveitis) to identify those that could predict the onset of uveitis. Afterwards the predictors of outcome, severe or mild uveitis, were analyzed in the same way. Finally, the uveitis-free intervals between 2 of the groups, SU and MU, were analyzed by using actuarial estimates and compared by the Kaplan-Meier test.

Multivariate analysis. Because predictor variables were of several data levels, multiple logistic regression (stepwise, unconditional, model computed) was used in this phase of the analysis. On the basis of the preliminary analysis, selected variables were utilized as predictive variables in 2 different logistic analyses. The first step considered only the clinical variables at onset of arthritis. The significant variables obtained in this model were added to the laboratory variables in the second set of analyses. The variables so selected were added to the HLA haplotype for the final set of analyses. We developed the prediction model utilizing data from patients from Milan and Padua (the study group). Subsequently, we tested the validity of this model on patients from Florence (the validation group).

We obtained 2 final models: the first predicts the onset of uveitis and the second its outcome (severe or mild). We compared the prognosis assessed by the 2 models for each patient with the real outcome, and then calculated the efficiency, sensitivity, and specificity of the method. The reliability and strength of the model were validated utilizing the Florence group data (validation group) with the purpose of selecting, among these new patients, those who will develop uveitis and those who will have the severe forms.

All statistical analyses were carried out using the statistical package SAS version 6.11 for Windows[18].

Table 1. Independent variables and their respective normal values assessed within the first 3 months of illness.

Predictor Variables
Sex (female, male)
Age at onset of arthritis
Seasonality
Interval time between arthritis onset and first uveitis
Antinuclear antibodies (< 1:80)
ESR (≤ 35 mm)
CRP (≤ 0.5 mg/dl)
White blood cell count (between 2 SD of normal for age)
Hemoglobin (between 2 SD of normal for age)
Platelets (150,000–400,000/mm^3)
α_2-globulin (≤ 8 g/l)
HLA haplotypes (see text)

RESULTS

Three hundred sixteen patients, all Caucasian, seen over the period January 1996 to December 1999, fulfilled the inclusion criteria (oligoarticular onset JIA with at least 2 years followup) to enter the study.

Table 1 summarizes the clinical characteristics of the patients; 130 (41%) had at least one episode of uveitis, 186 (59%) never had uveitis (NoU). Among those with uveitis, 64 had mild uveitis (MU) and 66 had severe uveitis (SU).

The mean age at onset of arthritis was not significantly different among the 3 groups: 37 ± 21 months for the NoU group, 29 ± 18 months for MU, and 38 ± 21 months for SU. As well, the length of followup was comparable among the 3 groups — 95 ± 63, 110 ± 66, and 89 ± 57 months, respectively. Two hundred fifty-six patients (81%) were female, with a F/M ratio of 4.2 to 1. The F/M ratio was comparable (3.6 to 1 and 2.9 to 1) in the NoU and SU groups, with a greater female predominance in the MU group, 8.1 to 1. As shown in Table 2, no significant difference for age at onset,

followup, or sex was found between the study group (Padua and Milan) and the validation group (Florence).

Two hundred seventy-six patients (87%) had onset by the age of 5 years, and 10 (3%) were more than 8 years old. The patients of the MU group had earlier onset, but the difference compared to the other 2 groups was not significant (Figure 1).

Among the patients with ocular involvement, the mean duration of the interval between onset of articular disease and the diagnosis of eye involvement was 1.8 years (median 11 mo, SD 29.5 mo, range 1–144 mo). The patients with SU presented with their first uveitis earlier (median 4 mo, range 0–24) than those with MU (median 24 mo, range 0–144). The uveitis-free survival curve reveals significant differences between the 2 groups, SU and MU (Figure 2). The Kaplan-Meier test confirms this significance ($p < 0.001$). The overall impression is that the earlier the onset of ocular involvement, the worse is its course. Fifty percent of patients with SU had ocular involvement less than 6 months after the onset of arthritis, 90% by one year, 100% by 2 years. By contrast, only 15% of patients with MU presented the first uveitis during the first year of the disease, 45% by 2 years.

Identification of independent predictor variables — univariate analysis. Predictor variables that yielded significant results for any outcome are shown in Tables 3 and 4. For each category of predictor (e.g., ANA positive or negative), the significance and the OR value are shown. At onset

Table 2. Clinical characteristics of the patients with oligoarticular JIA (n = 316).

	Study Group (Padua + Milan)	Validation Group (Florence)	Total	F:M
No uveitis				
No. patients	136	50	186	3.6:1
Age at onset, mo, mean ± SD	39 ± 22	30 ± 15	37 ± 21	
Follow up, mo, mean ± SD	98 ± 64	89 ± 61	95 ± 63	
Mild uveitis				
No. patients	56	8	64	8.1:1
Age at onset, mo, mean ± SD	30 ± 19	28 ± 12	29 ± 18	
Follow up, mo, mean ± SD	114 ± 69	89 ± 35	110 ± 66	
Severe uveitis				
No. patients	47	19	66	2.9 : 1
Age at onset, mo, mean ± SD	35 ± 18	43 ± 22	38 ± 21	
Follow up, mo, mean ± SD	87 ± 55	96 ± 62	89 ± 57	
Total				
No. patients	239	77	316	4.2:1

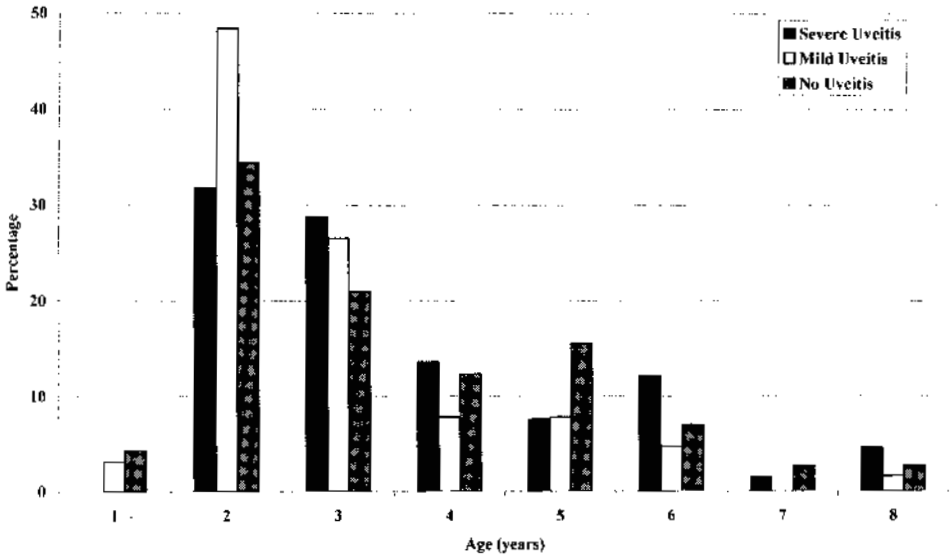

Figure 1. Age at onset of arthritis according to the presence and severity of eye involvement in the 3 groups of patients.

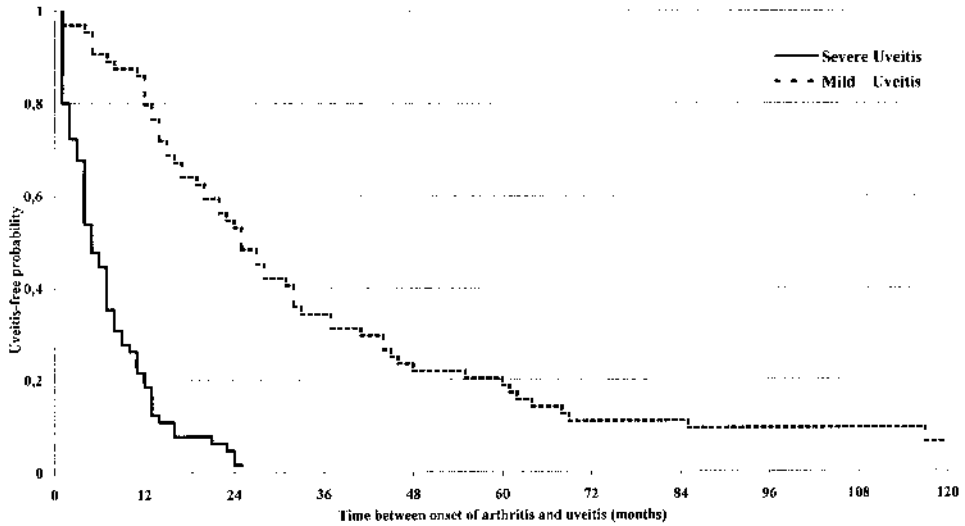

Figure 2. Kaplan-Meier survival curve showing the uveitis-free probability in the groups with severe (SU) and moderate uveitis (MU) according to the time between onset of arthritis and the first uveitis.

Table 3. Statistical significance of the predictor variables for uveitis onset by univariate analysis.

Predictor Variables at Baseline Evaluation	Uveitis vs Non-Uveitis	
	Significance	OR*
Sex	NS	1.10
Season		
Autumn	NS	0.85
Summer	NS	1.00
Winter	NS	1.39
Spring	NS	0.96
Age at onset	NS	0.87
Antinuclear antibodies (≥ 1:80)	$p < 0.05$	2.07
ESR (> 35 mm)	$p < 0.05$	1.71
CRP (> 0.5 mg/dl)	NS	1.52
WBC (> 2 SD of normal for age)	NS	1.27
Hemoglobin (< 2 SD of normal for age)	$p < 0.001$	0.37
Platelets (> 400,000/mm^3)	NS	1.54
α_2-globulin (> 8 g/l)	NS	1.48
HLA–A (1,2...), B (1,2...), C (1,2...), DR (1,2...), DQ(1, 2...)	NS	
HLA-B22	$p < 0.05$	3.15
HLA-DR1	$p < 0.0005$	0.27
HLA-DR2	$p < 0.01$	2.29

*Odds ratio based on the 2×2 table of the dichotomous predictor as explained in the text. The greater the OR, the greater the risk of less favorable outcome if the predictor is present. A value of 1 indicates no effect on risk. A value close to 0 indicates protection from the less favorable outcome if the predictor is present.

Table 4. Statistical significance of the predictor variables for severe course uveitis by univariate analysis.

Predictor Variables at Baseline Evaluation	Mild vs Severe Course Uveitis	
	Significance	OR*
Sex	$p < 0.05$	0.35
Season		
Autumn	$p < 0.05$	2.48
Summer	NS	0.51
Winter	NS	0.96
Spring	NS	0.66
Age at onset	NS	0.58
Time between the onset of arthritis and 1st uveitis	$p < 0.001$	0.22
Antinuclear antibodies (≥ 1:80)	NS	0.51
ESR (> 35 mm)	NS	0.96
CRP (> 0.5 mg/dl)	NS	1.44
WBC (> 2 SD of normal for age)	NS	1.33
Hemoglobin (< 2 SD of normal for age)	NS	1.32
Platelets (> 400,000/mm^3)	NS	1.15
α_2-globulin (> 8 g/l)	$p < 0.001$	3.40
HLA-A (1,2...), B (1, 2...), C (1, 2...), DR (1, 2...), DQ(1,2...)	NS	

* Odds ratio based on the 2×2 table of the dichotomous predictor as explained in the text. The greater the OR, the greater the risk of less favorable outcome if the predictor is present. A value of 1 indicates no effect on risk. A value close to 0 indicates protection from the less favorable outcome if the predictor is present.

no clinical variable can differentiate patients that will develop uveitis from those without this complication. Among the laboratory variables, the presence of ANA and high ESR are risk factors (OR 2.07 and 1.71, respectively), while low hemoglobin is protective (OR 0.37) (Table 3). Among the various HLA haplotypes, HLA-B22 and HLA-DR2 are risk factors for uveitis onset (OR 3.15 and 2.29, respectively), while HLA-DR1 is protective (Table 3). As for the uveitis course, male sex, the onset of JIA in autumn, and a short interval between the onset of arthritis and first uveitis are the significant risk factors for a severe course of uveitis (Table 4). Among the laboratory variables, only an

increased α_2-globulin serum concentration represents a risk factor for severe course (OR 3.4). No HLA haplotype is significantly associated with a severe course of uveitis (Table 4).

Multivariate analyses. Table 5 provides a summary of results from multiple logistic regression procedures regarding uveitis onset. The best-fitting model for prediction of onset of uveitis included the age at onset (OR 0.96), α_2-globulin level (OR 1.34), and HLA-A19 (OR 2.87), B22 (OR 4.51), DR9 (OR 2.33) and HLA-DR1 (OR 0.13). Older age and the presence of HLA-DR1 seem to be protective. Increased α_2-globulins and the presence of HLA-A19, B22, and DR9 are risk factors for development of uveitis. Although this model is robust (p = 0.001, concordant nodes 75.2%), it cannot clearly predict the development of uveitis in an early stage of JIA (sensitivity 78%, specificity 61%, efficiency 65%). The validation test, applied to the Florence group, confirmed this result (specificity 25.6%, efficiency 36.2%). This means that the model has a quite good positive predictive value but a weak negative predictive value.

The model for severity of uveitis yielded 2 risk factors with significant OR: time interval between arthritis onset and appearance of the first AU (OR 0.85) and α_2-globulin level (OR 1.62) were the best predictors of AU severity (Table 6). This model is significant (p < 0.0001, concordant nodes 89%). The validation test revealed good performance (sensitivity 89.2%, specificity 76.1%, efficiency 86.3%). It is therefore possible to correctly predict the evolution

TAble 5. Best predictor model for uveitis onset by multiple logistic regression.

Outcome Variable	Predictor Variables in "Best Fit" Model	OR (95% CI)
Uveitis onset, no. of patients in analysis 316	Age at onset	0.96 (0.94–0.99)
	α_2-globulin	1.34 (1.15–1.57)
	HLA-A19	2.87 (1.35–6.87)
	HLA–B22	4.51 (1.36–22.07)
	HLA-DR1	0.13 (0.04–0.27)
	HLA-DR9	2.33 (1.07–8.92)
	Significance	Validation
	Significance p < 0.001	
	Sensitivity 78%	Sensitivity 54.7%
	Specificity 61%	Specificity 25.6%
	Efficiency 65%	Efficiency 36.2%
	Concordant nodes * 75.2%	Cutoff 0.40

*Concordant nodes indicate the quality of the model. Good models have concordant nodes > 70%.

Table 6. Best predictor model for severe course uveitis by multiple logistic regression.

Outcome Variable	Predictor Variables in "Best Fit" Model	OR (95% CI)
Uveitis Severity, no. of patients in analysis 103	α_2-globulin	1.62 (1.15–2.23)
	Time between the onset of arthritis and 1st uveitis	0.85 (0.72–0.91)
	Significance	Validation
	Significance p < 0.0001	
	Sensitivity 83.4%	Sensitivity 89.2%
	Specificity 80.1%	Specificity 76.1%
	Efficiency 82.8%	Efficiency 86. 3%
	Concordant nodes * 89%	Cutoff 0.50

*Concordant nodes indicate the quality of the model. Good models have concordant nodes > 70%.

To calculate the probability to develop a severe uveitis in a patient at first episode of uveitis, knowing the α_2-globulin value at onset and the interval (months) between the onset of JIA and the first AU, the formula is: $p = [1/(1+e^{-g})] \times 100$ where $g = -2.95 + 0.54$ (α_2-globulin value in g/l) – 0.17 (no. months between onset of JIA and 1st uveitis), e = natural number (2.7182). Example: Patient with α_2-globulin at onset 12.8 g/l, first AU 3 months after the onset of JIA: $g = (-2.95) + (0.54 \times 12.8) - (0.17 \times 3) = 3.4$; $p = [1/1+e^{-3.4})] \times 100 = (1/1 + 0.032) \times 100 = 97$. The patient has 97% probability of developing a severe uveitis.

toward severe ocular involvement in 9 out of 10 patients and toward a mild uveitis course in 3 out of 4 patients.

DISCUSSION

It is well known that ocular involvement is one of the most serious sequelae in patients with oligoarticular JIA[7,10,11]. It is also well known that arthritis and uveitis, in this group of patients, have different courses[7,10,19] and that the articular prognosis is not influenced by the presence of uveitis or vice versa[20,21]. The prevalence of ocular involvement in oligoarticular JIA varies from 13% to 45%[7,8,10,19-26]. In our study the prevalence of uveitis (41%) was higher than that reported in other studies[3,19], but comparable with that observed in a recent study from Europe[5]. This high prevalence is in part related to the referral bias due to the selection of the most difficult to treat patients by our tertiary ophthalmologic centers, in part due to the close collaboration between pediatric rheumatologists and ophthalmologists in the 3 participating centers, which has reduced the dispersion and increased the accuracy of all the clinical information.

In the early 1990s, several studies pointed out the need for early and accurate detection of ocular disease in oligoarticular JIA. These studies led to development of official guidelines for ophthalmologic examination in children with juvenile rheumatoid arthritis (JRA) by the American Academy of Pediatrics (AAP) published in 1993[13]. According to this document, patients with oligoarticular JIA with onset at the age of 7 years or less and positive for ANA are at high risk for developing uveitis and need ophthalmologic examinations every 3–4 months. Patients older than 7 years and ANA negative have a lower risk and need an ophthalmologic evaluation every 6 months.

Recently, the visual prognosis has been improved by early detection of iridocyclitis[8,25,28]. However, it is a common experience that, in spite of increased surveillance, 25% of patients with uveitis have very poor prognosis: they require surgery for cataract or glaucoma and are at high risk for vision loss[9,12,26]. Functional blindness has been reported in 15–40% of affected eyes[5,11,19,26,28]. However, following the AAP recommendations, some patients with oligoarticular JIA, who will never present uveitis, undergo many unnecessary eye examinations for many years, while for other patients with high risk of severe eye disease the recommended 3 month interval evaluation may not be appropriate. Indeed, in our experience some patients have developed ocular complications during the 3 month interval between 2 eye examinations. Such patients with high risk may need more frequent eye evaluations.

Some authors in the early 1970s empirically observed that the time between onset of arthritis and first uveitis correlated negatively with the severity of the eye disease — the earlier the eye involvement, the worse its course[7,28]. Later studies confirmed this observation, but no specific measures capable of predicting the course of uveitis were recognized[5,12,23,25,26].

We started from this practical issue to determine if, at the onset of arthritis, any clinical or laboratory feature will predict the development and severity of uveitis.

Studies have pointed out the role of ANA positivity in increasing the risk of uveitis, while ANA negativity has been found to be associated with increased severity of ocular involvement[25,28,30]. As in other reports[9,12], we found that the presence of ANA correlates with the development of uveitis in oligoarticular JIA by univariate analysis (Table 3). But in contrast, we were unable to confirm that ANA absence represents a risk factor for severe course of AU. Indeed, the univariate analysis showed that elevated ESR at onset of arthritis is a risk factor for the development of uveitis, while low hemoglobin seems to confer protection for this ocular complication.

In the hope of predicting which individuals are at increased risk for chronic uveitis, much effort has gone into investigating a correlation with particular HLA genes. HLA-DR5, particularly DRB1-1104, and DR8 have been linked to the occurrence of uveitis in oligoarticular JIA[26,29-35], while HLA-DR1 seems to confer some protection[27,30-35]. While our study confirms that HLA-DR1 is in some way protective for the development of AU, we were unable to show an increased association between HLA-DR5 and DR8 and uveitis onset.

As for the severity course, univariate analysis showed that males were more susceptible to severe ocular involvement than females (Table 4). Indeed, 71% of male patients with AU had a severe course versus only 46% of females with AU. A short interval between arthritis onset and the first episode of uveitis was the other significant clinical feature that differentiated MU from SU patient groups. This finding is well illustrated by the uveitis-free survival curve (Figure 2). It is evident that the earlier the onset of ocular involvement, the worse its course. We do not have a clear explanation for this phenomenon. It could be the expression of a more aggressive eye disease in a subgroup of patients with oligoarticular JIA or it could be the consequence of a misdiagnosed or undertreated ocular inflammatory process. The only way to verify these hypotheses is to more frequently check the patients during the first months after the onset of arthritis and to more aggressively treat those with early onset uveitis.

Among the laboratory variables, elevation of α_2-globulins at onset of arthritis seems to be associated with a severe uveitis course (OR 3.4) (Table 4). No HLA allele was significantly associated with varying severity levels of AU.

As known, univariate analysis considers each variable by itself and not its potentiating interactions with others. For this reason we performed a multivariate analysis that mimics the mental process of the clinician approaching a new patient with oligoarticular JIA and/or ocular involve-

ment. Our 2 models that predict the risk of developing ocular involvement and detect the group of patients with more severe ocular disease have been created following the logical process of the clinical setting. The group of patients utilized for validation (the Florence group) had not been entered in the multivariate analysis and, for this reason, did not influence the prediction model itself.

Very few baseline variables yielded significant results to predict the development of AU. Those shown in Table 5 entered the model; these were age at onset, α_2-globulin level, HLA-A19, B22, DR9 and HLA-DR1. Some of the variables, such as HLA-B22 and HLA-DR1, were already significant by univariate analysis; others entered the model and became significant because of their interactions with other variables. However, when this model was applied prospectively to the Florence group of patients, sensitivity and specificity were lost.

By contrast, the best-fitting model for the prediction of severity of AU included only 2 variables: α_2-globulin concentration at disease onset and time interval between onset of arthritis and first uveitis (Table 6). These 2 predictors (variables), already significant by univariate analysis, can predict the severity of the eye involvement course as soon as the patient presents the first episode of AU. While early onset uveitis can easily be considered the expression of a more severe disease, we cannot fully explain why high α_2-globulin level represents a predictor of both onset and severity of uveitis in these patients.

Determination of α_2 electrophoretic fraction of the protein profile includes some of the most important acute phase proteins, such as ceruloplasmin, haptoglobulin, and α_2-macroglobulin (α_2-m). The latter represents the most important member of this family. α_2-m acts as a proteinase scavenger in plasma and in inflammatory fluid[36,37]. It is a serum–pan protease inhibitor that, among other activities, binds some cytokines and growth factors such as tumor necrosis factor-α, interleukin 1ß (IL-1ß), IL-2, IL-6, platelet derived growth factor, and transforming growth factor-ß[38-41]. Binding of α_2-m to these molecules results in neutralization of some of them, while enhancing the ability of others to regulate cell functions. In synovial fluid α_2-m binds elastase, and this complex can degrade cartilage matrix in RA[42]. Indeed, α_2-m gene polymorphism has recently been found to be associated with severity of RA[43]. We did not evaluate α_2-m plasma level in our patients, but it could represent a possible early marker of eye involvement in oligoarticular JIA.

The prospective validation of the model confirmed its good efficiency (86%), sensitivity (89%), and specificity (76%). This means that 9 out of 10 patients with severe course and 3 out of 4 patients with mild course would have been correctly identified by this model at the onset of the initial episode of uveitis.

Another characteristic of this model is its easy application by a simple calculation, as shown in Table 6. Indeed, the probability of development of severe uveitis in a patient at his first episode can be calculated by adding the α_2-globulin value at onset and the interval (months) between the onset of JIA and the first appearance of AU to the formula.

Accurate prediction of the severity of eye involvement presents 2 major advantages: (1) it can shorten or lengthen the intervals between ophthalmologic evaluations, and (2) it can indicate early and more aggressive treatment for those patients with risk factors for severe disease course. Using this statistical model, the actual guidelines for the ophthalmologic approach in children with oligoarticular JIA could be adjusted to individual patients.

We found that a short interval of time between arthritis onset and the first appearance of anterior uveitis and an early elevation of α_2-globulin serum concentration represent risk factors for the development of severe course uveitis in oligoarticular JIA. Further prospective controlled studies are needed to verify this hypothesis. Validation of this model in a prospective clinical trial and in different patient populations will allow its widespread application in clinical practice.

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