Erythrocyte Sedimentation Rate as Baseline Predictor for the Development of Uveitis in Children With Juvenile Idiopathic Arthritis

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• PURPOSE: To analyze inflammatory parameters as possible predictors for the development of uveitis in juvenile idiopathic arthritis (JIA) patients. Further, to analyze the predictive value of demographic and clinical factors at the onset of arthritis.

• DESIGN: Retrospective cohort study.

• METHODS: In 358 children with oligoarthritis and rheumatoid factor–negative polyarthritis, erythrocyte sedimentation rate (ESR), C-reactive protein, leukocyte count, presence of antinuclear antibodies (ANA), presence of human leukocyte antigen (HLA-)B27, age of onset of JIA, and sex were analyzed for their predictive value for the onset of uveitis.

• RESULTS: One hundred forty-seven patients (41%) were diagnosed with chronic anterior uveitis. Young age of onset, presence of ANA, and elevated ESR appeared to be predictive factors according to univariate analyses ($P = .029$, $P = .007$, and $P = 5E^{-4}$, respectively). According to multivariate analysis, young age of onset and elevated ESR appeared to be predictive after adjusting for the other relevant factors ($P = .004$ and $P = .001$, respectively). A prediction model was developed.

• CONCLUSIONS: Elevated ESR appears to be a predictor for the occurrence of uveitis in patients with JIA. Since ESR is already routinely tested in patients with recently diagnosed arthritis, its use as a biomarker can easily be implemented in daily practice. (Am J Ophthalmol 2015;159:372–377. © 2015 by Elsevier Inc. All rights reserved.)

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JUVENILE IDIOPATHIC ARTHRITIS (JIA) IS THE MOST common rheumatic disease in childhood and is defined as arthritis without a known etiology that begins prior to the age of 16 and persists for at least 6 weeks.[1,2] Uveitis, typically chronic anterior uveitis, is the most common extra-articular manifestation in patients with JIA and JIA is the most common systemic association of uveitis in children.[3,4] The JIA subtype with the highest association with uveitis is oligoarthritis, followed by rheumatoid factor (RF)-negative polyarthritis, with an incidence of 13%–45% and 10%, respectively.[4,5]

The severity of uveitis at presentation is known to predict a severe course and worse visual outcome.[6] Since the course of chronic anterior uveitis is asymptomatic, routine ophthalmologic examination is required in patients with JIA and early treatment is critical to prevent visual loss.[6] Despite early detection, aggressive autoimmune disease can cause harmful uveitis with a worse outcome as well. Complications associated with poorly controlled or untreated uveitis include posterior synechiae, cataract, glaucoma, cystoid macular edema, and band keratopathy.[6–8]

Among patients with JIA, the oligoarticular subtype, antinuclear antibodies (ANA) positivity, young age of onset, and female sex in early-onset arthritis are predictive factors for the development of uveitis.[4,9–12] Identification of more predictors can help to improve screening protocols for routine examination in order to focus even more on those with the highest risk and to protect them from visual loss.

The aim of this study is to analyze inflammatory parameters and demographic and clinical factors at the onset of arthritis as possible predictors for the development of uveitis among patients with JIA.

PATIENTS AND METHODS

A RETROSPECTIVE COHORT STUDY OF 358 PATIENTS WITH JIA visiting the ophthalmologist or the pediatric rheumatologist at the University Medical Center of Utrecht, Leiden and Groningen in the Netherlands was performed. Only patients with the JIA subtypes oligoarthritis and RF-negative polyarthritis were included. The JIA diagnosis

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based on the criteria of the International League of Associations for Rheumatology was confirmed by a pediatric rheumatologist and all patients with JIA were screened by an ophthalmologist at least as many times as recommended by the guidelines of the American Academy of Pediatrics.[2,13,14] Patients with onset of uveitis before arthritis were excluded. Also, patients with uveitis entities other than chronic anterior uveitis were excluded. Patients were divided into 2 groups: JIA patients with (Group 1) and without (Group 2) uveitis. The patients in the second group had an ophthalmologic follow-up of at least 4 years without signs of uveitis. The collection of data from patients' medical charts for the research goals as described in this article was approved by the Institutional Review Board of the Utrecht University Medical Center and is in compliance with the Helsinki principles.

The values of the inflammatory parameters erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and leukocyte count at the time of diagnosis of JIA were collected from patients' medical charts. Only results of patients with inflammatory parameters tested 12 months or less prior to the diagnosis of JIA, 12 months or less after diagnosis of JIA, and before the start of systemic immunosuppressive therapy were included in the analyses. Information about the presence of ANA at the time of diagnosis of JIA was collected. Additional patient characteristics including date of birth, sex, date of onset of JIA, date of onset of uveitis, and presence of human leukocyte antigen (HLA-)B27 were collected from the medical charts. The age of onset of JIA was calculated from the date of birth and date of onset of JIA. The date of onset of JIA and the date of onset of uveitis were used to calculate the time interval between JIA and uveitis.

In some medical charts it was unclear whether the patient had ever been diagnosed with uveitis. Therefore, a questionnaire was sent to 42 patients with JIA, who were screened by an ophthalmologist outside the University Medical Centers. Three patients confirmed the uveitis diagnosis; these patients or their parents were asked to sign an informed consent in order to make a copy of the ophthalmologist's patient's medical chart available. This chart was additionally checked for the presence of uveitis, to be sure all patients would be placed in the correct group (uveitis vs non-uveitis). The collected additional information of all these 42 patients was obtained from the medical charts of the University Medical Centers.

Statistical analyses were performed with IBM SPSS Statistics version 20 for Windows and the R rms package. Univariate analyses were performed to find independent predictors that might enter the multivariate analysis. The Pearson χ^2 test or Fisher exact test was applied for univariate analysis of categorical variables. Since there were no normally distributed variables, confirmed by the Kolmogorov-Smirnov-test, the Mann-Whitney *U* test was used for continuous, abnormally distributed variables. Subgroup analyses were performed for patients with RF-negative polyarthritis and oligoarthritis. Statistically significant variables in univariate analysis as well as previously known predictors were selected for multivariate analysis by logistic regression. The continuous variable age of onset of JIA was dichotomized according to clinical standards based on prior literature with an age of 6 years as a cutoff point.[14] *P* values ≤.05 were regarded as statistically significant. For presentation, medians were used for the abnormally distributed variables. Based on the results of the multivariate analysis and the current screening guidelines for uveitis in patients with JIA (which includes ANA and age of onset of JIA), a prediction model was developed.[4,14] To test the ability to discriminate between patients with and without uveitis, the area under the receiver operating characteristic curve was determined. When prediction models are derived from multivariate regression analyses, overestimation of regression coefficients is a known phenomenon that results in too extreme predictions in new patients. Therefore, internal validation with bootstrapping techniques was applied, which resulted in a shrinkage factor for the regression coefficients.[15] Also, the value for the area under the receiver operating characteristic curve was corrected for optimism using the bootstrap procedure.

RESULTS

• **GENERAL CHARACTERISTICS OF STUDY POPULATION:** From a total of 358 patients with oligoarthritis and RF-negative polyarthritis entering the study, 147 (41%) were diagnosed with chronic anterior uveitis. All of these patients had at least 1+ cells in the anterior chamber at consecutive visits that needed treatment with topical steroids or immunomodulating medication.[16] The median time between JIA onset and uveitis onset was 1.0 year (range 0.0–24.3 years). Fifty percent of the patients developed uveitis within the first year after onset of JIA, 66% did so within the first 2 years, and in 85% uveitis occurred within the first 4 years. In the majority of the patients the inflammatory parameters were tested at the moment of JIA diagnosis (median time between diagnosis of JIA and laboratory records: 0 months, interquartile range: 0–0 months). The proportion of subtypes of JIA in the group of patients with uveitis could be compared to that in the group of patients without uveitis, with oligoarthritis being the most common subtype. Likewise, the female-to-male ratio was similar in both groups (Table 1).

• **AGE OF ONSET:** The median age of onset of JIA appeared to be statistically different between the 2 groups. The median age was 2.7 years in patients with uveitis and 3.1 years in patients without uveitis ($P = .029$).

TABLE 1. Demographic and Clinical Data of Patients With Juvenile Idiopathic Arthritis Grouped According to the Occurrence of Uveitis

	Uveitis	Non-Uveitis	*P* Value
Sex, no. (%)			
No. patients	147	211	.394[a]
Female	112 (76)	151 (72)	
Male	35 (24)	60 (28)	
JIA subtype, no. (%)			
No. patients	147	211	.282[b]
Oligoarthritis	108 (74)	141 (67)	
Polyarthritis	39 (26)	70 (33)	
Age (y) of onset JIA			
No. patients	148	213	
Median (range)	2.7 (0.9–9.5)	3.1 (0.7–15.0)	.029[c,d]
ANA, no. (%)			
No. patients	146	211	
Positive	113 (77)	135 (64)	.007[a,d]
Negative	33 (23)	76 (36)	
HLA-B27, no. (%)			
No. patients	54	73	
Positive	9 (17)	11 (15)	.811[a]
Negative	45 (83)	62 (85)	
ESR (mm)			
No. patients	112	197	
Median (range)	32 (2–150)	23 (2–115)	$5E^{-4}$[c,d]
CRP (mg/L)			
No. patients	105	188	
Median (range)	11.0 (0–136)	6.0 (0–303)	.053[c]
Leukocyte count $\times 10^9$/L			
No. patients	108	195	
Median (range)	9.4 (4.5–109)	9.32 (3.8–18.9)	.749[c]

ANA = antinuclear antibodies; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; HLA-B27 = human leukocyte antigen B27; JIA = juvenile idiopathic arthritis.
[a]Fisher exact test.
[b]Pearson χ^2.
[c]Mann-Whitney *U* test.
[d]Significant *P* values.

• **ANTINUCLEAR ANTIBODIES AND HUMAN LEUKOCYTE ANTIGEN B27:** Patients with uveitis were significantly more often ANA-positive compared to patients without uveitis ($P = .007$). Presence of HLA-B27 did not entail a significant difference between the 2 groups.

• **INFLAMMATORY PARAMETERS:** Statistically, ESR at the time of diagnosis of JIA was significantly more elevated in the uveitis group (median 32 mm) compared to the non-uveitis group (median 23 mm; $P = 5E^{-4}$; Table 1). Also, in the oligoarticular and polyarticular subgroups, ESR was significantly more elevated in patients with uveitis. In patients with oligoarthritis, the median value was 30 mm in patients with uveitis and 20 mm in patients without uveitis ($P = .008$). In patients with polyarthritis, the median value was 40 mm in patients with uveitis and 27 mm in patients without uveitis ($P = .010$). After analyzing ESR exclusively in patients who developed uveitis in the first year after onset of JIA, there appeared to be a strong statistical difference between the ESR in the 2 groups with 39 mm in the uveitis group and 23 mm in the non-uveitis group ($P = 1.7E^{-5}$, uveitis n = 55, non-uveitis n = 197). In the second (n = 18, ESR = 30 mm), third (n = 10, ESR = 26 mm), and fourth (n = 11, ESR = 19 mm) year after JIA diagnosis, ESR was slightly elevated in the second and third year in the uveitis group. In these 3 groups there was no statistically significant difference compared to the non-uveitis (n = 197, ESR = 23 mm) group ($P = .318$, $P = .839$, and $P = .493$, respectively). The inflammatory parameters CRP and leukocyte count at the time of diagnosis of JIA did not statistically differ between the 2 groups (Table 1).

• **MULTIVARIATE ANALYSIS AND PREDICTION MODEL:** Because of the statistically significant outcomes in univariate analysis, ANA, age of onset of JIA, and ESR were selected for multivariate analysis. Additionally, the factors sex and JIA subtype were selected. Adjusted for age of onset of JIA, ANA, sex, and JIA subtype, ESR appeared to be a statistically significant predictor for the occurrence of uveitis in patients with JIA with an odds ratio (OR) of 1.016 (95% confidence interval [CI] 1.006–1.026, $P = .001$), which means that for each elevation of 1 mm ESR, the odds for the occurrence of uveitis increase by 0.016 (Table 2). Onset of JIA before the age of 7 years was, adjusted for ANA, ESR, sex, and JIA subtype, a statistically significant predictive factor for the occurrence of uveitis in patients with JIA with an OR of 3.167 (95% CI 1.432–7.006, $P = .004$; Table 2). The predictors ANA, age of onset, and ESR were included in the prediction model (Figure 1). The area under the receiver operating characteristic curve of the model was 0.644 (95% CI: 0.582–0.706; Figure 2).

DISCUSSION

FOR THE IMPROVEMENT OF OUR KNOWLEDGE OF THE occurrence of uveitis in JIA patients the identification of predictors remains important. In this study we examined the predictive value of the inflammatory parameters ESR, CRP, and leukocyte count. We found an elevated ESR at the time of diagnosis of JIA to be predictive for the occurrence of uveitis in patients with JIA according to univariate analysis. Four previous studies examined the relationship between ESR and the occurrence of uveitis in patients with JIA.[4,10,17,18] Elevated ESR appeared to be predictive in 3 of these previous retrospective studies as well. Statistically, these studies found significantly more elevated ESR values of ≥35 mm in patients with uveitis

TABLE 2. Risk for the Occurrence of Uveitis in Children With Juvenile Idiopathic Arthritis According to Multivariate Analysis by Logistic Regression (Uveitis n = 112; Non-uveitis n = 197)

	OR[a] (95% CI[b])	*P* Value
Female sex	0.995 (0.561–1.764)	.986
Oligoarticular subtype	1.406 (0.817–2.419)	.219
Age of onset JIA ≤ 6 years	3.167 (1.432–7.006)	.004[d]
ANA positivity	1.397 (0.813–2.402)	.226
ESR	1.016[c] (1.006–1.026)	.001[d]

ANA = antinuclear antibodies; CI = confidence interval; ESR = erythrocyte sedimentation rate; JIA = juvenile idiopathic arthritis; OR = odds ratio.

[a]Odds ratios for dichotomous variables: the greater the OR, the higher the risk for the occurrence of uveitis.

[b]Confidence interval is the interval estimate of the odds ratio.

[c]Odds ratio for ESR: for every elevation of 1 ESR-point, the odds for the occurrence of uveitis increase by 0.016.

[d]Significant *P* values.

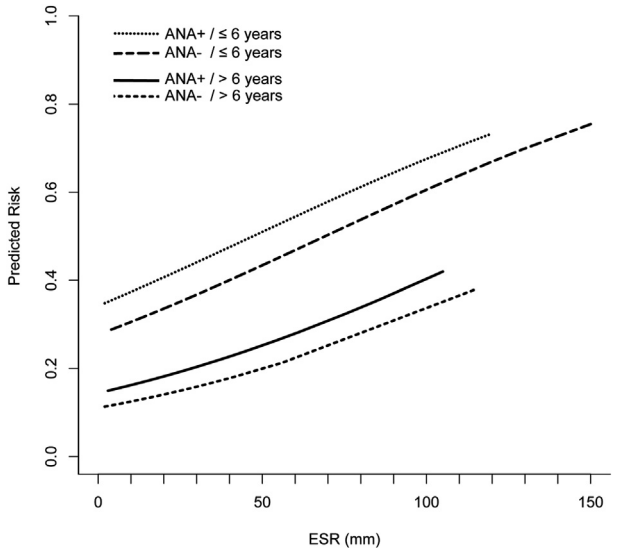

FIGURE 1. Prediction model to predict the risk for the occurrence of uveitis in patients with juvenile idiopathic arthritis. ANA = antinuclear antibodies; ESR = erythrocyte sedimentation rate; ≤6 years = age of onset of juvenile idiopathic arthritis (JIA) is 6 or below the age of 6 years; >6 years = age of onset of JIA is above 6 years. The risk for the occurrence of uveitis based on ANA, age of onset of JIA, and ESR at time of diagnosis of JIA is calculated with the formula = $e^x/(1 + e^x)$, with x = −2.171 + (0.305 × ANA) + (1.126 × age of onset) + (0.014 × ESR). The regression coefficients in this formula are derived from multivariate logistic regression with addition of the bootstrapping technique. Example of a case: A patient presents with JIA. He/she is 3 years old and has a negative ANA in the laboratory and an ESR of 50 mm. This patient has a predicted risk to develop uveitis of 0.41.

compared to ESR values of ≤35 mm in patients without uveitis. Our outcomes are perfectly in concordance with these previous studies. Additionally we found ESR to be a predictor in multivariate analysis. This is the second study demonstrating an elevated ESR to be predictive after adjusting for other predictors in a larger study population.[18] One study described ESR as not having a significant influence on the occurrence of uveitis according to multivariate analysis.[4] Patients diagnosed with uveitis prior to the onset of JIA were not excluded from this study, which might explain this contrasting outcome.

In the groups that developed uveitis 2 years and 3 years after JIA onset, ESR was more elevated in uveitis as compared to non-uveitis patients, but the difference was not statistically significant. The lack of a statistical difference can be explained by the lack of power because only 18 and 10 uveitis patients, respectively, were included in these specific groups. In the group developing uveitis 4 years after JIA onset, ESR values were comparable for both groups. ESR in the course of JIA is dependent on many factors, including autoimmune disease activity and treatment with immunomodulating medication. In some of our patients with normal ESR at JIA onset, uveitis debuted 4 years later and several months after methotrexate was stopped. So uveitis might have been suppressed by immunosuppressive therapy and in a few other cases, late uveitis onset was related to JIA flare-up.

The exact mechanism of JIA uveitis and the immunopathogenic link between JIA and uveitis is still unknown, but it is considered to be a multifactorial autoimmune disease.[19,20] In general, elevated ESR values indicate more activity of the autoimmune disease, so elevated ESR in uveitis patients might reflect a more activated state of the immune system. This might enhance influx of inflammatory cells in the eye with probably a dysbalance of T-helper cells and T-regulatory cells resulting in uveitis. However, more research is warranted to clarify the pathogenesis of uveitis in JIA and the relation with JIA activity.

According to our knowledge, the predictive value of CRP has been tested twice before. In 1 study CRP was dichotomized with a cutoff value of 5 mg/L; based on their laboratory standards, a CRP of >5 mg/L did not appear to be predictive for the occurrence of uveitis.[10] The other study did not find a difference between the mean CRPs.[18] We confirmed these outcomes and did not find CRP to be predictive in our series. However, we cannot rule out that it might prove to be significant in a larger study population.

Since uveitis is a common comorbidity in patients with JIA, many studies focusing on possible predictors for the occurrence of uveitis have been performed in the last decades.[21] The identification of some predictors led to the development of a screening protocol for ophthalmologic examination in patients with JIA in 1993, which was updated in 2006.[14,22] ANA positivity, oligoarticular JIA, and onset of

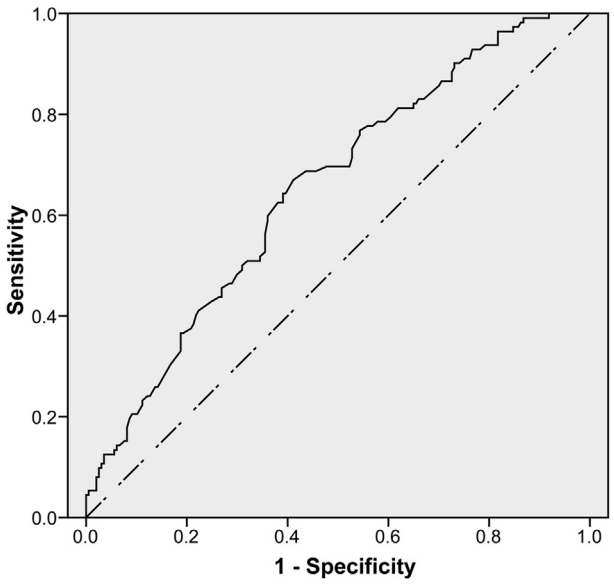

FIGURE 2. The area under the curve shows the ability of the prediction model to predict the development of uveitis in patients with juvenile idiopathic arthritis. The closer the area under the (receiver operating characteristic) curve (AUC) comes to 1, the more accurate is the prediction model. The diagonal line with interruption (AUC = 0.5) represents the situation in which the model would be useless. The continuous line represents the AUC for this prediction model (Figure 1), which is 0.644 (95% confidence interval: 0.582–0.706) after correction for optimism using the bootstrap procedure.

JIA before the age of 7 appeared to be good predictors and were included in the screening protocols.[9,12,14,23] In this study we have shown that elevated ESR seems to be a good predictor as well. Therefore we recommend that ophthalmologists and pediatric rheumatologists be aware of the increased risk of developing uveitis in children with the aforementioned risk factors and an additional elevated ESR at onset of JIA. ESR is already routinely tested in patients with JIA, so it can easily be implemented in daily practice. We developed a prediction model for development of uveitis that includes ANA, age of onset of JIA, and ESR.[4,14] We validated the model internally with bootstrapping techniques, but external validation is required before the model can really be applied. The proposition of being more aware of high-risk patients in order to protect them from severe complications and visual loss is in concordance with the ideas of Chia et al.[4,24]

In the current study we confirmed the predictive value of ANA positivity and early age of onset of JIA in univariate analyses. We could not confirm JIA subtype as a possible predictor because we only included the subtypes of JIA that are already proven to be related to the occurrence of uveitis.

In concordance with previous studies, we did not find a predictive value of HLA-B27 in our population.[12,23]

As all other retrospective studies, this study has several limitations. The study was based on a patient directory from tertiary centers. So concerning uveitis there might be a referral bias because there is a possibility that more severe cases are included in the study. This was prevented as much as possible by requesting information on uveitis status via questionnaires to patients and parents who were screened by ophthalmologists in secondary referral centers, but it might still cause some referral bias. The case-control character of this study barely makes it possible to represent the actual incidence of uveitis in patients with JIA, given that the ophthalmologic center of the University Medical Center in Utrecht is a specialized uveitis center with a high incidence of uveitis patients. We chose a minimum follow-up with ophthalmologic examinations of 4 years, but we know that in rare cases uveitis will develop even up to 20 years after JIA onset. In our study 86% of the patients with JIA developed uveitis in the first 4 years of follow-up, which means that some patients in the non-uveitis group with only 4 years of follow-up might still develop uveitis in the future.

In conclusion, elevated ESR appears to be a predictor for the occurrence of uveitis in patients with JIA. Since ESR is already routinely tested in patients with recently diagnosed arthritis, its use as a biomarker can easily be implemented in daily practice.

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Biosketch

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