• Clinical Research •

Ocular involvement and visual prognosis in juvenile idiopathic arthritis associated uveitis

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Received: 2024-01-17 Accepted: 2025-03-26

Abstract

● **AIM:** To characterize a Portuguese population of patients with juvenile idiopathic arthritis (JIA) and to evaluate possible associations between clinical factors and ocular involvement.

● **METHODS:** Patients diagnosed with JIA in the previous 20y in Hospital Garcia de Orta were included. Data were assessed from Reuma.pt database. Associations between demographic (age and sex), clinical (articular involvement, extra-articular manifestations, biological therapy), laboratory data [anti-nuclear antibodies, anti-cyclic citrullinated peptide (CCP) antibodies, rheumatoid factor, human leukocyte antigen B27 (HLA-B27), C-reactive protein, erythrocyte sedimentation rate] and ocular involvement were assessed. Statistical analysis was performed using Chi-square for categorical variables and Mann-Whitney test for continuous variables.

● **RESULTS:** Totally 91 patients were included, 11 (12%) with previous episodes of uveitis. There was a statistically significant preponderance of early age at JIA diagnosis (mean 4.73 *vs* 9.58y, *P*=0.008), antinuclear antibodies positivity (*P*=0.01), and oligoarticular subtype (*P*=0.04) in the Juvenile idiopathic arthritis-associated uveitis (JIA-U) group. Ocular complications occurred in 36.4% of patients (*n*=4): cataracts (*n*=2), band keratopathy (*n*=1) and posterior synechiae (*n*=1). The occurrence of complications was corelated with a shorter period between JIA diagnosis and the first JIA-U episode (mean 0.67 *vs* 4.88y, *P*=0.012) but not with age at JIA diagnosis or articular involvement. There was erythrocyte sedimentation rate elevation in the 12mo preceding uveitis (mean 40.5 mm/h, range 13-83).

● **CONCLUSION:** The occurrence of JIA-U shortly after JIA diagnosis is shown to be a potential risk factor for ocular complications.

● **KEYWORDS:** juvenile idiopathic arthritis; uveitis; erythrocyte sedimentation rate

DOI:10.18240/ijo.2025.07.13

Citation: Tardão GC, Carreira P, Moraes F, Carreira R, Loureiro T, Escada AV, Santos MJ, Cardoso AM, Campos N. Ocular involvement and visual prognosis in juvenile idiopathic arthritis associated uveitis. *Int J Ophthalmol* 2025;18(7):1302-1306

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most prevalent chronic inflammatory rheumatic disease in the pediatric population and the leading cause of anterior uveitis in this age group. According to the American College of Rheumatology, JIA is defined as a heterogenous group of conditions characterized by idiopathic arthritis that begins before the age of 16 and persists for at least six weeks[1-3]. Juvenile idiopathic arthritis-associated uveitis (JIA-U) is the most common extra-articular manifestation of JIA, occurring in approximately 10%-30% of affected patients, with the uveitis being the initial presentation in only 10% of cases[1-5]. In certain cohorts, JIA-U accounts for 20%-40% of uveitis cases and may represent up to 80% of all anterior uveitis in children. Identified risk factors for JIA-U include younger age at onset, recent diagnosis, female gender, oligoarticular subtype of JIA, positivity for anti-nuclear antibodies (ANA), and negativity for rheumatoid factor (RF)[1-2,6-8].

JIA-U typically presents as an insidious and chronic bilateral, non-granulomatous anterior uveitis, often moderate to severe, but lacking classic manifestations such as conjunctival injection, photophobia, or blurred vision. Small keratic precipitates may be present[1-3,9-10]. The uveitis can also exhibit an acute course particularly in cases of enthesitis-related arthritis and, to a lesser extent, in psoriatic arthritis, most commonly observed in older boys who are positive for human leukocyte antigen B27 (HLA-B27)[4,11].

Although JIA-U is often asymptomatic, it can lead to sight-threatening complications in 20%-40% of patients, with some studies reporting rates as high as 67%. These complications include amblyopia, band keratopathy, posterior synechiae, cataract, ocular hypertension or glaucoma, hypotony, vitritis, retinal detachment, cystoid macular edema, epiretinal membrane, optic nerve edema and neovascularization[12-15]. Therefore, early and regular ophthalmological screening for all JIA patients is crucial to enhance visual outcomes. The management of patients whit JIA-U should occur within a multidisciplinary framework, involving shared decision-making between experienced ophthalmologists and pediatric rheumatologists[1-2,16].

The initial management strategy for JIA-U typically includes high-potency steroids and cycloplegics[1-2,17-19]. Immunosuppressive therapies, such as methotrexate (MTX) or biologic agents, should be considered early for certain patients, as they have been associated with improved outcomes[1,19].

While there are established risk factors for ocular involvement, it is essential to conduct ophthalmological screening and follow-up for all patients with JIA-U patients to achieve optimal visual prognosis. Recent evidence suggests additional potential risk factors that may enhance ophthalmological screening in JIA, such as elevated erythrocyte sedimentation rate (ESR), presence of HLA-B27 antigen, and levels of S100A8/A9 and S100A12 proteins[8,20-24]. Tappeiner *et al*[8] described an association between elevated ESR and intraocular inflammation, with analytical measurements every six months. In this line of thought, longer periods of systemic inflammation may relate with an increased risk of ocular involvement even beyond that time frame.

Current evidence regarding the optimal management plan for JIA-U remains limited, and most recommendations are based on expert consensus[1]. This study aims to characterize a Portuguese cohort of patients with JIA in relation to intraocular inflammation and to enhance understanding of potential risk factors.

PARTICIPANTS AND METHODS

Ethical Approval This was a retrospective, observational cross-sectional study that included patients diagnosed with JIA at the Hospital Garcia de Orta over the past 20y, registered in the Portuguese database Reuma.pt. Patients with unrelated ophthalmological disorders or other diseases inconsistent with the diagnosis of JIA (*e.g.,* psoriasis or other rheumatological disorders) were excluded from the study. The ethics committee concluded that this study falls under exempt categories and therefore does not require formal ethics approval. Written informed consent was obtained from all the participants.

Patients were divided into two groups based on the occurrence of at least one documented episode of uveitis (JIA-U and non-JIA-U), and compared regarding demographic (age, sex and race), clinical (type of articular involvement, occurrence of other extra-articular manifestations, administration of immunosuppressive therapy, past medical history, and family history of rheumatic diseases), and laboratory parameters [ANA, anti-cyclic citrullinated peptide (CCP) antibodies, RF, and HLA-B27 status]. Within the JIA-U group, C-reactive protein (CRP), ESR and leucocyte count were evaluated for the 12mo preceding an episode of uveitis, with ESR also assessed outside this timeframe for comparative analysis.

The study noted ocular complications and examined their associations with various factors: age at JIA diagnosis, age at the first episode of JIA-U, time interval from JIA diagnosis to the first episode of JIA-U, biological therapy, JIA subtype, ESR, CRP and leucocyte count.

Descriptive analysis of categorical variables was presented as frequencies and percentages, while continuous variables were reported as means with standard deviations. Continuous variables were evaluated for normality using the Kruskal-wallis test (non-JIA-U group) and the Shapiro-Wilk test (JIA-U group). Comparisons between patients with and without uveitis were performed using the Chi-square test for categorical variables and the Mann-Whitney test for continuous variables. The Wilcoxon test for paired samples was used to assess the temporal association between ESR and ocular inflammation.

Correlations were evaluated using Spearman's correlation coefficient, with statistical significance set at $P<0.05$ (two-sided). IBM® SPSS® Statistics V.23.0 (USA) was used.

RESULTS

This study included 91 patients diagnosed with JIA in the past 20y in Hospital Garcia de Orta, of which 11 had at least one well-defined episode of uveitis evaluated by an experienced ophthalmologist. Patients were regularly followed by Ophthalmology and Rheumatology and were treated according to systemic and ocular disease activity.

Demographic Characteristics JIA-U was observed in 11 JIA patients (12.1%), all of whom presented with bilateral, anterior, non-granulomatous uveitis. The average age at JIA diagnosis was significantly lower in the JIA-U group [mean 4.73y, 95% confidence interval (CI), 1-14] compared to the non-JIA-U group (mean 9.58y, 95%CI, 1-16), resulting in a difference of 4.86y (95%CI, 0.76-8.96; $P=0.008$). The mean age at the first episode of uveitis was 8.45y (95%CI, 3-15), with a mean interval of 3.73y (95% CI, 0-10) between JIA diagnosis and ocular involvement.

There were no significant differences regarding gender between the two groups (45.5% of females in JIA-U *vs* 60% in non-JIA-U group, $P=0.28$). A positive family history of rheumatic disease was reported in 2 (18.2%) JIA-U patients and 12 (15%) non-JIA-U patients, with no significant difference identified

Table 1 Patients demographic and clinical characteristics *n* (%)

Patients caractheristics	JIA-U group	Non-JIA-U group	*P*
Number of patients	11 (12.09)	80 (87.91)	
Age at JIA diagnosis (y), mean (95%CI)	4.73 (1-14)	9.58 (1-16)	*P*=0.008
Female	5 (45.5)	48 (60)	0.28
Oligoarticular subtype	8 (72.7)	32 (40)	0.04
Family history of rheumatic disease	2 (18.2)	12 (15)	0.54
Non-Caucasian	2 (18.2)	6 (7.5)	0.25
Non-uveitis extra-articular manifestations	2 (18.2)	30 (37.5)	0.18
Methotrexate therapy	9 (81.8)	62 (77.5)	0.55
Biological therapy	6 (54.5)	22 (27.5)	0.07
DMARD therapy completion (y), mean (95%CI)	0.9 (0-5)	2.6 (0-16)	0.09
Age at the first episode of uveitis (y), mean (95%CI)	8.45 (3-15)		
Period from JIA diagnosis to uveitis	3.73 (0-10)		

JIA: Juvenile idiopathic arthritis; JIA-U: Juvenile idiopathic arthritis-associated uveitis; DMARD: Disease-modifying antirheumatic drugs.

(*P*=0.54). Furthermore, there were 2 (18.2%) non-Caucasian patients in the JIA-U group compared to 6 (7.5%) in the non-JIA-U group respectively, showing no apparent association between race and ocular inflammation (*P*=0.248).

Patients' demographic characteristics are summarized in Table 1.

Clinical Characteristics Oligoarticular JIA was the most prevalent subtype, and a statistically significant association with ocular inflammation was found [*n*=8 (72.7%) in JIA-U *vs* *n*=32 (40%) in non-JIA-U; *P*=0.04].

Extra-articular manifestations other than uveitis were present in 2 (18.2%) JIA-U patients and 30 (37.5%) non-JIA-U patients. The most frequent extra-articular manifestation in the non-JIA-U group was skin rash (*n*=7, 23%), while enthesopathy was the only extra-articular manifestation in JIA-U (*n*=2, 100%). There were no significant differences between groups regarding the occurrence of extra-articular manifestations other than uveitis (*P*=0.18).

MTX was administered to 9 (81.8%) JIA-U patients and 62 (77.5%) non-JIA-U patients. Biological therapy was utilized in 6 JIA-U patients (54.5%) and 22 (27.5%) non-JIA-U at some point during the disease course. No significant associations were found between ocular inflammation and the use of immunosuppressive therapy (*P*=0.55 for MTX; *P*=0.07 for biological therapy). Additionally, there were no differences between the two groups regarding the timing of disease-modifying antirheumatic drugs (DMARD) therapy completion (mean 0.9y for JIA-U *vs* 2.6y for non-JIA-U; *P*=0.09).

Patients' clinical characteristics are summarized in Table 1.

Laboratory Assessment ANA were positive in 9 (81.8%) patients in the JIA-U group compared to 34 (42.5%) patients in the non-JIA-U group, indicating a statistically significant association with the occurrence of uveitis (*P*=0.01).

RF and anti-CCP antibodies were negative in all JIA-U patients, while they were positive in 8 (10%) and 6 (7.5%) non-JIA-U patients, respectively. HLA-B27 was present in 2 (18.2%) JIA-U patients compared to 8 (10%) non-JIA-U patients (*P*=0.35). All HLA-B27 positive patients belonged to the enthesitis/spondylarthritis-related subtype, with HLA-B27 found in 100% (*n*=2) of JIA-U and 80% (*n*=8) of non-JIA-U patients within this subgroup.

Table 2 Laboratory parameters mean (range)

Laboratory parameters	Values in the 12mo
Erythrocyte sedimentation rate (mm/h)	40.5 (13-83)
C-reactive protein (mg/L)	2.32 (0.05-8.20)
Leucocyte count ($\times10^9$/L)	7.83 (4.5-10.20)

In the JIA-U group, the values of ESR, CRP and leucocyte count were assessed in the 12mo preceding an episode of uveitis. ESR appeared elevated during this period, with a mean value of 40.5 mm/h (13-83 mm/h). In contrast, there were no significant elevations in CRP and leucocyte count, with a mean value of 2.32 mg/L (0.05-8.20) and 7.83×10^9/L [$(4.5\text{-}10.20)\times10^9$/L] respectively. ESR values were also assessed outside this 12-month period, resulting in a mean value of 19.67 mm/h (11.64-24.30 mm/h). A statistically significant association was found between ESR elevation and the occurrence of uveitis (*P*=0.045). Additionally, when comparing ESR values between JIA-U and non-JIA-U patients, a statistically significant difference was noted in the JIA-U during the 12mo prior to an episode of uveitis (*P*=0.017), but not outside this timeframe (*P*=0.71). Laboratory parameters are detailed in Tables 2 and 3.

Disease Features and Ocular Complications Ocular complications occurred in 4 (36.4%) patients with JIA-U. The complications included cataracts (*n*=2), band keratopathy (*n*=1) and posterior synechiae (*n*=1). These complications were associated with a shorter interval between JIA diagnosis and the first occurrence of uveitis (mean 0.67±0.56y *vs* 4.88±2.67y, respectively, *P*=0.012). No significant associations

Table 3 ESR, CRP and leucocyte count in JIA-U group

Laboratory parameters	JIA-U group	Non-JIA-U group	Difference
Anti-nuclear antibodies positivity	9 (81.8%)	34 (42.5%)	*P*=0.01
Rheumatoid factor positivity	0	8 (10%)	
Anti-cyclic citrullinated peptide antibody positivity	0	6 (7.5%)	
HLA-B27	2 (18.2%)	8 (10%)	*P*=0.35

JIA-U: Juvenile idiopathic arthritis-associated uveitis; HLA-B27: Leukocyte antigen B27; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

were found between the occurrence of ocular complications and the following factors: age at JIA diagnosis (*P*=0.38), age at first episode of uveitis (*P*=0.28), JIA subtype (*P*=0.34), immunosuppressive therapy (*P*=0.51 and *P*=0.58 for MTX and biological therapy, respectively), and ESR (*P*=0.14).

DISCUSSION

In this study, we characterized the demographic, clinical and laboratory features of JIA patients from a Portuguese center concerning the occurrence of uveitis. JIA presented an incidence of 4.5 patients per year, meaning approximately 25.7 per 100 000, which aligns with international data[24]. JIA-U was identified in 12.1% of the patients included in this study, consistent with the prevalence reported in the literature (10%-30%)[1-5]. Generally, patients with JIA-U were diagnosed with systemic arthritis at a younger age and exhibited a statistically significant predominance of the oligoarticular JIA subtype. Furthermore, JIA-U patients experienced their first episode of uveitis at a young age, typically less than four years after the diagnosis of systemic arthritis. The majority of JIA-U patients tested positive for ANA, indicating a significant positive association with uveitis. These findings align with existing literature on established risk factors for uveitis in patients with JIA and emphasize the importance of implementing a screening program for ocular involvement based on factors such as age at JIA diagnosis, JIA subtype, ANA positivity, and the duration of systemic disease[1-2,6-7].

There were no statistically relevant associations between the occurrence of uveitis and patients' sex, race, or family history of rheumatic diseases. Additionally, the presence of non-ocular extra-articular manifestations did not appear to influence the risk of developing uveitis.

Ocular complications were observed in 36.4% of JIA-U patients, including cataracts, band keratopathy and posterior synechiae, which are the most common complications described in literature[11-14]. Patients who developed ocular complications tended to experience their first episode of uveitis shortly after their JIA diagnosis, suggesting a possible predictive value for ocular complications and underscoring the importance of ophthalmological screening, particularly in the initial years following JIA diagnosis[1-2].

Despite recent evidence advocating for the early treatment of JIA-U patients with systemic immunosuppressants, such as MTX and biological therapy, to improve of visual prognosis[1,18], our study found no significant differences regarding the occurrence of uveitis or complications. Larger multicenter studies are needed to validate these findings.

RF and anti-CCP antibodies were negative in all JIA-U patients, possibly indicating a negative association with the occurrence of uveitis, as already previously reported [1-2,6-7]. While HLA-B27 did not correlate with ocular involvement, it was only present in the enthesitis/spondylarthritis-related subtype, which was underrepresented in this study and may obscure it's predictive value.

Leucocyte count and CRP levels did not demonstrate predictive utility for uveitis occurrence in JIA patients. However, there was a statistically significant elevation in mean ESR values during the 12mo preceding episode of uveitis compared to values obtained outside that period. This finding is noteworthy, suggesting a potential predictive value of ESR for intraocular inflammation, consistent with recent evidence identifying ESR as a biomarker for ocular involvement[7,19-21]. Thus, ESR could be useful in identifying JIA patients in urgent need of ophthalmological evaluation, potentially enhancing existing screening programs for disease management.

The primary limitations of this study were its retrospective design and small sample size, which may lead to missing data and bias, potentially explaining some discrepancies with current literature. Larger and more comprehensive studies are warranted to assess the role of various risk factors and biomarkers (*e.g.,* S100A8/A9 and S100A12 proteins, differences in ANA titter) in intraocular inflammation and ophthalmological complications. Additionally, evaluating different prognostic factors, such as visual function and comparing various screening programs, could contribute to the development of a more inclusive approach.

In conclusion, uveitis is a common extra-articular manifestation of JIA, underscoring the importance of incorporating an ophthalmological screening program into the comprehensive management of these patients. This study confirmed established risk factors, particularly younger age at diagnosis, positivity for ANA, oligoarticular subtype, and a shorter duration of JIA. These factors should be considered when developing

the ophthalmological management plan for JIA patients. Additionally, ESR may serve as a valuable biomarker for ocular involvement and should be integrated into the criteria for patient selection and prioritization in ophthalmological screening and ongoing monitoring.

ACKNOWLEDGEMENTS

Conflicts of Interest: Tardão GC, None; **Carreira P,** None; **Moraes F,** None; **Carreira R,** None; **Loureiro T,** None; **Escada AV,** None; **Santos MJ,** None; **Cardoso AM,** None; **Campos N,** None.

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