Outcome of uveitis in juvenile idiopathic arthritis and spondyloarthritis patients – a 5-year follow-up study

Oliveira Pinheiro F[1*], Leuzinger-Dias M[2], Fernandes BM[1], Fonseca D[3], Vilaça J[4], Figueira L[2], Brito I[5]

[1] Rheumatology Department, Centro Hospitalar Universitário de São João
* ORCID: https://orcid.org/0000-0002-3162-9018

[2] Ophthalmology Department, Centro Hospitalar Universitário de São João

[3] Rheumatology Department, Centro Hospitalar Vila Nova de Gaia/Espinho

[4] Pediatrics Department, Hospital de Braga

[5] Pediatric and Young Adult Rheumatology Unit, Centro Hospitalar Universitário de São João

Correspondence to

Filipe Oliveira Pinheiro

E-mail: filipe.pinheiro92@gmail.com

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Abstract

Objective: Uveitis is a frequent complication of juvenile idiopathic arthritis (JIA) and spondyloarthritis (SpA). The aim of this study is to evaluate the prevalence and risk factors for complications associated with uveitis in patients with JIA and SpA.

Methods: A longitudinal, monocentric cohort study that included patients diagnosed with JIA and SpA who developed uveitis. Demographic, laboratory, and clinical data were collected including complications of uveitis, HLA-B27, antinuclear antibodies, erythrocyte sedimentation rate, C-reactive protein, visual acuity and DMARD treatment. Comparison between groups (complicated versus uncomplicated uveitis) was evaluated using chi-square, t test and Mann-Whitney U test. Logistic regression was performed to determine predictors of complications.

Results: A total of 270 patients were evaluated, of which 37 patients (13.7%) had uveitis and were included in this study. Twenty patients were female (54.1%), aged 11.9±8.7 years at diagnosis of SpA/JIA and 15.3±9.9 years at diagnosis of uveitis. Twenty-seven patients (73.0%) had a diagnosis of JIA (23 with oligoarticular disease) and in 12 patients (32.4%) uveitis was the first manifestation. Fifteen (40.5%) patients exhibited complications during follow-up period. Eleven patients (29.7%) underwent ophthalmologic surgery. Complications were significantly higher in patients with JIA (51.9% vs 10.0% in SpA, p=0.03), as was the need for surgery (40.7% vs 0%, p=0.02). Complications in JIA were significantly more frequent in patients who had uveitis as the initial presentation (50.0% vs 7.7%, p=0.03); no significant differences were found between the groups in the other variables studied. Univariate logistic regression analysis showed that uveitis as the first manifestation of JIA (OR 12.0, confidence interval 95% 1.21-118.89, p=0.03) is a significant predictor of complications.

Conclusion: We found higher rates of complications and need for ophthalmologic surgery in patients with JIA-associated uveitis. The initial presentation of JIA as uveitis is significantly associated with the occurrence of uveitis complications, so it is essential that there is a collaboration between ophthalmologist and rheumatologist in the diagnosis and treatment of these patients.

Keywords: Juvenile idiopathic arthritis; Paediatric/Juvenile rheumatology; Spondylarthritis; Ophthalmic; Spondyloarthropathies (including psoriatic arthritis).

Key messages:

- Uveitis is a frequent complication of juvenile idiopathic arthritis and spondyloarthritis.
- Complications of uveitis occurred in 40.5% of patients with uveitis after 5 years of onset of uveitis.
- The initial presentation of juvenile idiopathic arthritis as uveitis is significantly associated with the occurrence of complications.

Introduction

Uveitis is a frequent manifestation of juvenile idiopathic arthritis (JIA) and spondyloarthritis (SpA)[1-3]. There are significant differences between JIA-associated and SpA-associated uveitis. SpA uveitis is typically unilateral, presents with acute ocular symptoms, and responds adequately to therapy, with a tendency to recur, but an overall good prognosis[4, 5]. JIA-associated uveitis usually presents insidiously, as a chronic bilateral uveitis, and complications, such as band keratopathy, posterior synechiae, cataract formation and glaucoma, are more frequent than in SpA-associated uveitis[6, 7]. Early involvement is often not evident by direct examination and the role of slit-lamp examination is crucial to reveal the presence of inflammatory cells and increased protein within the anterior chamber of the eye[8]. As prognosis is dependent on early recognition and treatment[9], recommendations have been made regarding the screening for uveitis in patients with JIA, including from the Portuguese Societies of Ophthalmology and Pediatric Rheumatology[10]. In SpA-associated uveitis, if there is a delay in diagnosis or multiple recurrences, complications also occurred more frequently, justifying a special need for physician attention to this topic[4].

The incidence, course and outcome of uveitis vary widely between different countries[7,11]. To date, to the knowledge of the authors, no study has described and investigated the outcome of JIA and SpA in Portugal. The aim of this study is to describe the outcome of uveitis in these patients, as well as to evaluate the prevalence and risk factors for complications associated with uveitis in patients with JIA and SpA.

Materials and Methods

Patient Selection and Design: We designed a retrospective monocentric study that included all patients diagnosed with JIA and SpA followed at the Pediatric and Young Adult Rheumatology Clinic and the Ocular Inflammation Clinic, responsible for the care of patients aged 25 years or less, who developed uveitis, in a tertiary university hospital (Centro Hospitalar Universitário de São João, Porto, Portugal). Demographic, laboratory, and clinical data were collected at the time of diagnosis of uveitis and after 5 years of follow-up. JIA was classified according International League of Associations for Rheumatology (ILAR)[12], and uveitis classification followed Standardization of Uveitis Nomenclature (SUN) group classification[13].

Data: Data were collected including gender, age, form of presentation of the disease (uveitis versus rheumatologic), uveitis and JIA classifications, HLA-B27 status, antinuclear antibodies (ANA), erythrocyte sedimentation rate, C-reactive protein, visual acuity, complications of uveitis and DMARD treatment.

Statistical analysis: Statistical analysis was conducted by using SPSS version 25. We used Shapiro-Wilk test and histogram analysis to look for normality. Comparisons between groups were evaluated using chi-square (categorical variables), t test (continuous variables with normal distribution) and Mann-Whitney U test (continuous variables with non-normal distribution). Logistic regression was performed to determine predictors of complications. A 2-tailed probability value of $p < 0.05$ was considered statistically significant.

Ethics: The protocol was approved by the Ethics Committee of Centro Hospitalar Universitário de São João. The study was run in accordance with the principles of the Declaration of Helsinki as amended in Fortaleza (2013).

Results

A total of 270 patients were evaluated, of which 37 patients (13.7%) had uveitis and were included in this study. There were 27 patients diagnosed with JIA (73.0%), of which 16 were females (59.3%), aged 6.5±4.6 years at diagnosis of JIA and 10.1±6.9 years at diagnosis of uveitis; of the 10 patients included with SpA, 4 (40.0%) were females, aged 22.0±3.0 years at diagnosis

of SpA and 24.4±4.7 years at diagnosis of uveitis. Patients with JIA-associated uveitis had mostly oligoarticular disease (n=23, 85.2%), with 2 cases classified as psoriatic arthritis, 1 as polyarticular disease and 1 as enthesitis-related arthritis). In 12 patients (32.4%) uveitis was the first manifestation of the rheumatic disease, 8 (29.6%) in JIA and 4 (40.0%) in SpA. In patients with JIA, HLA-B27 was present in 71.4% and ANA in 46.2% of the patients who were tested, while in SpA HLA-B27 was positive in 100% and ANA in 42.9% patients. At the time of the diagnosis of uveitis, 13 patients (35.1%) were under conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), namely methotrexate (n=11) and sulfasalazine (n=2), and 3 (8.1%) under biological DMARDs (bDMARDs), 2 on etanercept and 1 on adalimumab. Clinical and demographic data can be viewed in Table I. There was a statistically significant difference in age between SpA and JIA, with no other statistically significant differences found.

Table II describes the initial features and outcome of uveitis for each disease. Most patients had anterior uveitis (n=26, 70.3%), of which 19 (73.0%) presented with acute recurrent episodes, with the other diagnoses observed being chronic uveitis (n=7, 18.9%), posterior uveitis and panuveitis (each with n=2, 5.4%). We did not find any statistically significant differences between SpA and JIA, although there were no cases of chronic uveitis and posterior uveitis in patients diagnosed with SpA. Regarding laterality, most patients had an alternating unilateral pattern (n=13, 35.1%), 10 patients had only involvement of the left eye (27.0%), 8 of the right eye (21.6%), and 6 presented simultaneous involvement of both eyes (16.2%). There were no statistically significant differences between JIA and SpA. After 5 years of follow-up, 15 (40.5%) patients exhibited complications, namely cataract (n=11), synechiae and ocular hypertension (n=7), band keratopathy (n=6), retinal detachment (n=2), vitreous hemorrhage and glaucoma (n=1). There was a significantly higher proportion of complications in patients with JIA (51.9% vs 10.0%, p=0.03), but we did not find any statistically significant differences regarding any individual complication. Eleven patients (29.7%) underwent ophthalmic surgery, all patients with JIA. Twenty-three patients (62.2%) had decreased visual acuity at presentation; in those patients, median (interquartile range, IQR) visual acuity at the diagnosis of uveitis was 7 (3.8-9)/10. At the end of follow-up, 10 of them (43.5%) had irreversible decreased visual acuity, with median (IQR) visual acuity of 8 (1.5-8.5)/10, all patients with JIA; there was a significant association between irreversible decreased visual acuity and ocular hypertension (71.4% vs 16.7%, p=0.01), synechiae (71.4% vs 16.7%, p=0.01) and cataract (63.6% vs 11.5%, p<0.01).

Comparisons between complicated versus uncomplicated uveitis in JIA can be found in Table III. Only one patient with SpA suffered from complications (cataract), so we opted to

further analyze complications in JIA patients only. Complications were significantly more frequent in those who had uveitis as the initial presentation of JIA (50.0% vs 7,7%, p=0.03). We found a non-significant trend towards higher rates of complications in patients with younger age at diagnosis of uveitis and younger age at the diagnosis of JIA, as well as in patients withchronic uveitis. All 3 patients with non-recurrent acute anterior uveitis had no complications. No significant differences were found between groups in the other variables studied, including in different ILAR categories of JIA.

Through univariate logistic regression analysis, we found that uveitis as first manifestation of JIA is a significant predictor of complications (OR 12.0, CI 1.21-118.89, p=0.03).

Discussion

The aim of our study was to provide a descriptive analysis of patients with JIA or SpA and uveitis, and to assess the outcome of uveitis in these patients, in a Portuguese cohort from a tertiary hospital setting. We chose SpA patients diagnosed until the age of 25 years to lessen the age differences between both groups. Approximately a third (32.4%) of patients presented first with uveitis, prior to the development of musculoskeletal symptoms. Most patients with JIA-associated uveitis had oligoarticular disease. There was a high prevalence of complications of uveitis after a 5-year follow-up, and frequently patients needed eye surgery and developed impairment of visual acuity, which was associated with ocular hypertension, synechiae and cataract. We identified most cases of complications in patients with JIA in those who had uveitis as the first manifestation of the disease, which significantly increases the odds of developing a complication in patients with JIA.

Uveitis was observed in 13.7% of the patients followed at our Pediatric and Young Adult Rheumatology Clinic, a number similar to what is reported in major studies[6,11,14]. The predominance of the oligoarticular JIA subtype is also similar to what is described in the literature[6, 11]. The diagnosis of JIA was more frequently associated with complications of uveitis, in 51.9% of patients, which was also reported in other studies, which showed a prevalence of uveitis complications in 37-56% of patients with JIA[6,11]. Similarly, most commonly reported complications include cataracts, synechia and band keratopathy, as we detailed in this study[6,15]. The rate of visual acuity impairment in our study, 27%, was higher than reported in other studies, 5.6-17.6%, which is likely related to the small sample[7,16]. This study demonstrated that the initial

presentation as uveitis is significantly associated with complications after 5 years, as had been demonstrated in other studies[11]. In this study, the risk of complications was not associated with any particular ILAR category in JIA, the subtype of uveitis or the presence of ANA, which we postulate is likely related to small sample size as well.

There are several limitations in our study. First, it is a retrospective study, without a control group, which precludes a more global assessment, namely of the risk factors for uveitis, described in other studies. Second, even though it is original as a descriptive study in Portugal and provides a detailed assessment of complications, the small sample size makes it difficult to obtain more accurate predictors of uveitis complications.

A larger, nation-wide study is necessary to confirm the findings from our center, especially if a control group without uveitis is included, to further explore predictors of uveitis and of complications of uveitis.

Conclusion

In conclusion, ophthalmologic complications of uveitis occur in a significant percentage of patients with JIA and SpA. We found higher rates of complications and need for ophthalmologic surgery in patients with JIA-associated uveitis. The initial presentation of rheumatic disease as uveitis is significantly associated with the occurrence of uveitis complications in JIA, so a close collaboration is essential between the ophthalmologist and the rheumatologist in the diagnosis and treatment of these patients. Early referral and implementation of a validated screening program can have a marked impact on patients' prognosis.

Tables and Figures

Table I. Demographic and clinical features at the diagnosis of uveitis

Variables	Total (n=37)	JIA (n=27)	SpA (n=10)	p-value
Female gender – n (%)	20 (54.1)	16 (59.3)	4 (40.0)	0.46
Age at diagnosis, years – mean (SD)	11.9 (8.7)	6.5 (4.6)	22.0 (3.0)	<0.01
Age of uveitis, years – mean (SD)	15.3 (9.9)	10.1 (6.9)	24.4 (4.7)	<0.01
Uveitis as first manifestation – n (%)	12 (32.4)	8 (29.6)	4 (40.0)	0.70
csDMARD – n (%)	13 (35.1)	11 (40.7)	2 (20.0)	0.44
bDMARD – n (%)	3 (8.1)	1 (3.7)	2 (20.0)	0.17

bDMARD – biological disease-modifying antirheumatic drugs; csDMARD – conventional synthetic disease-modifying antirheumatic drugs; JIA – Juvenile idiopathic arthritis; SD – Standard deviation; SpA – Spondyloarthritis.

Table II. Presentation and complications of uveitis

Variables	Total (n=37)	JIA (n=27)	SpA (n=10)	p-value
Uveitis subtype – n (%)				
- Recurrent anterior uveitis	19 (51.4)	14 (51.9)	5 (50.0)	0.61
- Chronic uveitis	7 (18.9)	7 (25.9)	0 (0)	0.16
- Acute anterior uveitis	7 (18.9)	3 (11.1)	4 (40.0)	0.07
- Posterior uveitis	2 (5.4)	2 (7.4)	0 (0)	0.53
- Panuveitis	2 (5.4)	1 (3.7)	1 (10.0)	0.47
Laterality – n (%)				
- Alternating unilateral	13 (35.1)	9 (33.3)	4 (40.0)	0.72
- Left eye	10 (27.0)	8 (29.6)	2 (20.0)	0.69
- Right eye	8 (21.6)	5 (18.5)	3 (30.0)	0.66
- Both eyes simultaneously	6 (16.2)	5 (18.5)	1 (10.0)	0.48
Complications* – n (%)	15 (40.5)	14 (51.9)	1 (10.0)	0.03
- Cataract	11 (29.7)	10 (37.0)	1 (10.0)	0.22
- Synechiae	7 (18.9)	7 (25.9)	0 (0)	0.16
- Ocular hypertension	7 (18.9)	7 (25.9)	0 (0)	0.16
- Keratopathy	6 (16.2)	6 (22.2)	0 (0)	0.16
- Retinal detachment	2 (5.4)	2 (7.4)	0 (0)	0.53
- Hemovitreous	1 (2.7)	1 (3.7)	0 (0)	0.73
- Glaucoma	1 (2.7)	1 (3.7)	0 (0)	0.73
Surgery – n (%)	11 (29.7)	11 (40.7)	0 (0)	0.02

*Note: The sum of individual complications exceeds the number of patients with complications because some patients had more than one complication simultaneously.

Table III. Comparison between complicated vs uncomplicated uveitis in juvenile idiopathic arthritis.

Variables	Uncomplicated (n=13)	Complicated (n=14)	P-value
Female gender – n (%)	8 (61.5)	8 (57.1)	0.82
Uveitis as first manifestation – n (%)	1 (7.7)	7 (50.0)	0.03
JIA subtype – n (%)			
- Oligoarticular	10 (76.9)	13 (92.9)	0.33
- Psoriatic arthritis	2 (15.4)	0 (0)	0.22
- Poliarticular	0 (0)	1 (7.1)	0.52
- Enthesitis-related arthritis	1 (7.7)	0 (0)	0.48
Uveitis subtype – n (%)			
- Recurrent anterior uveitis	9 (69.2)	5 (35.7)	0.08
- Chronic uveitis	1 (7.7)	6 (42.9)	0.08
- Acute anterior uveitis	3 (23.1)	0 (0)	0.10
- Posterior uveitis	0 (0)	2 (14.3)	0.48
- Panuveitis	0 (0)	1 (7.1)	0.52
Age at diagnosis of JIA, years – mean (SD)	7.2 (5.4)	5.9 (3.9)	0.50
Age at diagnosis of uveitis, years – mean (SD)	11.1 (8.3)	9.1 (5.3)	0.48

JIA – Juvenile idiopathic arthritis; SD – Standard deviation.

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