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Ocular Comorbidities in Juvenile Idiopathic Arthritis

Mayada Khalil[*1], Ali Ibrahim Fouda[1], Abd El Wahab Shams Eldin Elbrashy[1], Ahmed Tabal[2], Lamyaa Mohammed Hashem[1]

Departments of [1]Rheumatology, Rehabilitation and Physical Medicine and [2]Ophthalmology, Faculty of Medicine, Benha University, Egypt

***Corresponding author:** Mayada Khalil, **Mobile:** (+20) 01001659940, **E-Mail:** drmayadakhalil@gmail.com

ABSTRACT

Background: Uveitis is the most widespread and serious extra-articular sign of juvenile idiopathic arthritis (JIA), which is the most prevalent rheumatic condition in children. Despite more effective treatment options, the prevalence of JIA illness remains high, making it so difficult to assess the disease's outcomes—especially if extra-articular symptoms are present. The maintenance of sight and effective care depend on early detection.

Objective: The aim of the current study was to scan the eyes of kids with JIA in order to find any ocular symptoms as soon as possible and stop any problems that could result in blindness and vision loss.

Patients and methods: The study included 97 children who have JIA of both sexes, their age was under 16. All patients were underwent to a clinical examination (general, musculoskeletal, and ophthalmic examination), as well as laboratory testing (ESR, RF, ANA, HLA-B27, and CRP).

Results: Ocular complications of JIA were significant (P<0.05) in uveitis group compared with group without uveitis regarding synechia, macular edema, keratopathy, glaucoma, and mild visual impairment. Correlation showed that disease severity (JDAS 27) is independent risk factors affecting uveitis (r=0.7353, P=0.001). Other risk factors like disease duration, age, JIA subtype and anterior chamber cells as well as CRP and ESR, TLC, and ANA positivity were significantly correlated with uveitis (r=0.976 P=0.032, r=0.728 P=0.014, r=0.932 P=0.042, r=0.963 P=0.026, r=0.854 P=0.045, r=0.768 P=0.036, r=0.697 P=0.057, r=0.719 P=0.019, consecutively). **Conclusion:** JIA-related uveitis might have disastrous consequences. Today, clinical and demographic criteria have been used largely to estimate the risk of developing uveitis in JIA patients. To uncover patient-specific risk variables, recent studies employed molecular proteomic and cellular phenotyping techniques.

Keywords: Juvenile idiopathic arthritis, Uveitis, Slit lamp, JDAS27, Risk factors.

INTRODUCTION

Rheumatic illnesses in children can have an impact on the digestive system, muscles, skin, and eyes. JIA is the most prevalent inflammatory rheumatic condition, occurring in 0.1% of cases. It describes a group of persistent joint issues that can appear before the age of 16 and endure for at least six weeks [1].

Children with JIA are at risk for developing uveitis, an inflammation of the uvea. 15–67% of all pediatric uveitis cases have a JIA connection. The damage to both eyes occurs in 70–80% of instances. It typically presents anteriorly, continues, and shows no symptoms. Oligoarticular patterns, early age at arthritis start, and positive antinuclear antibodies are the most common risk factors in JIA patients for developing uveitis [2].

The HLA-DR5 haplotype and HLA-DRB1*1104 allele have been related with chronic anterior uveitis, particularly the combination of HLA-DRB1*1104 and HLA-DPB1*0201 alleles [3]. Autoimmunity has played a significant role in the development of uveitis. An increased incidence of acute anterior uveitis is linked to HLA-B27, which is frequently observed in ERA patients [4]. This genetic susceptibility was linked to an imbalance between the two allele-regulated lymphocyte subsets (CD20+ B, CD4+ B, Th1 cells, and Th17 cells), which led to a lack of tolerance to self-antigen [5].

In the seven years following the beginning of arthritis, uveitis will strike somewhere between 12% and 38% of JIA patients. Uveitis is largely asymptomatic in the early stages of mild to severe illness. This has led to the current practice of routinely screening all JIA-affected children for uveitis [6].

It has been shown that 10 to 15% of kids with uveitis caused by JIA would lose both of their eyesight, making them legally blind. Therefore, it is essential and required to screen all children with JIA and other rheumatic conditions for visual symptoms in order to prevent further problems that might lead to eventual blindness and severe disability [7].

This study's objective was to scan the eyes of kids with JIA in order to find any ocular symptoms as soon as possible and stop any problems that could result in blindness and vision loss.

PATIENTS AND METHODS

Study participants:

This surveying comparative study was undertaken at multi-centers, including the Rehabilitation and Physical Medicine and Ophthalmology Departments of Benha University Hospitals, New Cairo General hospital from January 2019 to November 2022.

A total of 97 JIA patient diagnosed by expert rheumatologists as regard bases of international league against rheumatism ILAR [8], were classified into two groups; group (1) included 82 children without uveitis (85%) and group (2) included 15 children (15%) with uveitis 12 (80%) were unilateral, 3 (20%) were bilateral. 30/97 were males (31%) while females were

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67/97 (69%), 36 of them were mildly active (37%), 51 were moderately active (52%) and 10 of them came in severe activity (10%) regarding JDAS27. A total of 46 (47%) of them were oligoarthritis (extended, persistent) subtype, followed by 14 (15%) were included in polyarthritis subtype, stills disease 13 (14%), while 6 PSA (6%), 7 (7%) enthesitis related, 11 undifferentiated (11%). A total of 78 (80%) were RF negative and 19 (20%) RF positive. Most of the patients, 55 were ANA (+VE) while, 42 were negative (-VE) ANA. They were on different regimens of treatment (MTX, Anti TNF, local eye steroid drops, systemic steroid), while those had age >16 years, other connective tissue diseases causing arthritis, congenital ocular diseases, ocular trauma, infectious eye diseases and those with lacrimal dysfunction were excluded from this work.

Methodology:

Clinical assessment:

History and clinical evaluation, including (musculoskeletal, ophthalmic examination), intraocular pressure (IOP) measurement, anterior chamber (AC) slit lamp bio-microscopy (**Figure 1**), and classification of specular microscopy (SM) findings using Standardization of Uveitis Nomenclature (SUN) criteria [9]. JDAS 27-based arthritis screening [10].

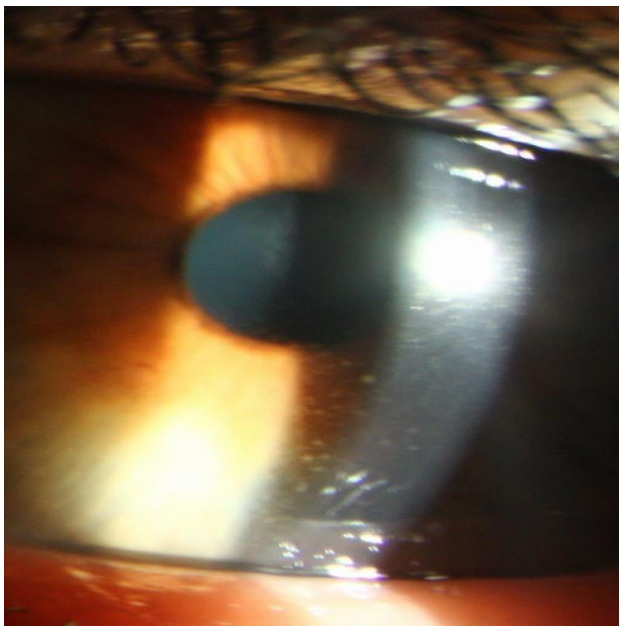

Figure (1): Shows cells in anterior chamber of the RT eye(slit lamp examination of anterior chamber of 9 years old female , diagnosed JIA 3y ago, JDAS27 moderate group , ESR 33, CRP 15, TLC 15000,positive ANA , negative HLAB27).

Laboratory investigation including: Complete blood count (CBC), hemoglobin concentration, platelet count, erythrocyte sedimentation rate (ESR) by Westergren method, rheumatic factor (RF) by latex agglutination slide test, antinuclear antibodies (ANA) by indirect immunofluorescence assays, human leukocyte antigen-B27 (HLA-B27) in major histocompatibility complex (MHC) and C-reactive Protein (CRP) by latex agglutination slide test. Peripheral blood samples were obtained for HLA-B27 typing. Polymerase chain reaction sequence-specific primers were used to type HLA-B27. Genotyping was used to identify HLA-B27 in peripheral lymphocytes (EURO Array, Euroimmun Polska, Wroclaw, Poland). The HLA-B*27 gene's exons 2 and 3 are amplified for the purpose of the test, and the labeled product is then detected via hybridization to immobilize it on the microarray probe.

Ethics consent:

The Research Ethics Committee of the Faculty of Medicine at Benha University in Egypt gave its clearance to this study [Reference Number of approval MS 1-2019]. All of the parents of the study's participants submitted their written, informed consent to take part in the study. Patients older than 16 or patients who were unconscious were excluded from the study. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 23 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD). For parametric data, the two-sided student's t-test and ANOVA tests were utilized; for non-parametric variables, the Mann-Whitney U and Kruskal-Wallis tests were applied. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

30/97 males (31%); 27/82 (33%) had no uveitis and 3/15 (20%) had uveitis and 67/97 females (69%); 55/82 (67%) had no uveitis and 12/15 (80%) had uveitis. The median age of the total sample was 7.8 years, ranged between 5 to 14 years, in **group 1** without uveitis the median age was 7.9 years, ranged between 5.8 to 13 years, in **group 2** with uveitis, a median age of 6.7 years, ranged between 5.1 to 14 years (**Table 1**).

Table (1): Clinical and laboratory characteristics of the JIA studied children.

Characteristics of arthritis	Total (N= 97)	No uveitis (N= 82)	Uveitis (N= 15)	P (KS)
Age (years)	5-14	5.8-13	5.1-14	0.568
Median	7.8	7.9	6.7	
Duration (months)	24 ± 4.2	22.4 ± 5.1	25.7 ± 4.8	**0.0083***
Tender joints:				
Median	8	7	9	
Range	3 – 16	2– 16	4 – 16	**0.034***
Swollen joint:				
Median	4	4	7	
Range	1 – 8	1 – 8	3– 8	**0.04***
Morning stiffness	82 (84%)	73 (89 %)	9 (60 %)	0.787
On therapy	71 (73%)	65 (79%)	6 (40%)	0.545
ANA:				
Positive				
Negative	55 (58%)	44 (53%)	11 (73%)	
HLA-B27:	42 (42%)	38 (46%)	4 (27%)	0.312
Positive				
Negative	28 (29%)	24 (29%)	4 (27%)	
	69 (71%)	58 (71%)	11 (73%)	0.380
Laboratory tests:				
Hb concentration		11.49 ± 0.8	11.4 ± 0.75	0.995
Total leucocytic count		7.91 ± 1.83	7.32 ± 1.76	0.183
Platelet count ($x10^3$)		326.5 ±80.35	336.9 ± 75.75	0.660
C-reactive protein		8.33 ± 1.92	10.53 ± 2.58	0.065
ESR		22.86 ± 3.48	24.68 ± 4.43	0.045

ANA: Antinuclear antibodies, HLA: Human leukocyte antigen. Hb: Hemoglobin , TLC: Total leucocytic count , ESR : Erythrocyte sedimentation rate , CRP: C-Reactive protein m: months, #: mean ± SD, , KS: Kolmogorov–Smirnov test, t: unpaired t-test, χ^2: Chi square test. Bold values are significant at P<0.05.

Clinical presentation of uveitis was illustrated in **(Table 2).** Approximately 68% of the study group was classified as SUN (0), 26% as SUN 1+, and 6% as SUN 2+ (**Table 3**). Ocular complications were prominent in uveitis group as compared with those without uveitis regarding synechia, macular edema, keratopathy, glaucoma and mild visual impairment (P<0.05) (**Table 4**).

Table (2): Clinical presentation of uveitis in JIA studied children.

Clinical Presentation	No.	Percent
Localization	**(15)**	**%**
• Anterior uveitis	13	86
• Intermediate uveitis	2	14
• Posterior uveitis	0	0
• Pan uveitis	0	0
Uveitis symptoms	**(15)**	**%**
• Mostly symptomatic (red eye)	6	40
• Mostly non-symptomatic	9	60
Uveitis course	**(15)**	**%**
• Acute: < 3 months + uveitis with treatment	3	20
• Recurrent: ≥ 3 m without uveitis + treatment	4	27
• Chronic: <3 m without uveitis + treatment	8	53

Table (3): Classification of uveitis according to Standardization of Uveitis Nomenclature (SUN).

SUN classification	No.	Percent
Anterior chamber cells	**(15)**	**%**
• SUN 0 (no cells in field)	10	68
• SUN 1+ (1-15 cells in field)	4	26
• SUN 2+ (16-25 cells in field)	1	6
Anterior chamber flair	**(15)**	**%**
• SUN 0 (no flair)	10	68
• SUN 1+ (faint flair)	4	26
• SUN 2+ (moderate flair)	1	6

Table (4): Ocular complications of JIA in the two studied groups.

Ocular Complications	No uveitis (N=82)		Uveitis (N=15)		P by χ^2
	No.	%	No.	%	
≥ 1 complication	5	6	4	26	**0.001***
Cataract	1	1.2	3	20	**0.002***
Glaucoma	0	0	1	7	0.454
Synechia	0	0	3	20	**0.001***
Macular edema	1	1.2	3	20	**0.001***
Band keratopathy	0	0	1	7	**0.029***
Epiretinal membrane	0	0	0	0	---
Hypotony	0	0	0	0	---
Phthisis	0	0	0	0	---
Best corrected visual acuity (BCVA) Mild impairment Moderate impairment Severe impairment	 1 1 0	 1.2 1.2 0	 3 1 1	 20 7 7	 0.001* 0.354 0.652

Independent risk factors affecting both onset and severity of uveitis in patients with JIA, that were significantly correlated with uveitis were disease duration, age, JIA class, and anterior chamber cells as well as CRP, ESR, TLC and ANA [(r=0.976 P=0.032), (r=0.728 P=0.014), (r=0.932 P=0.042), (r=0.963 P=0.026), (r=0.854 P=0.045), (r=0.768 P=0.036), (r=0.697 P=0.057) (r=0.719 P=0.0.019), respectively]. On the other hand, HLAB27 did not significantly affected uveitis incidence and outcome (r=1.000 P=0.732) (**Table 5**).

Table (5): Correlation coefficient (r) model to study independent risk factors affecting severity of uveitis inpatients with JIA.

Item	R	P value
Disease duration	0.976	**0.032***
Age at onset	0.728	**0.014***
Sex	0.926	**0.028***
ANA	0.719	**0.019***
HLA-B27	1.000	**0.732**
JIA categories	0.923	**0.042***
Anterior chamber cells	0.963	**0.026***
TLC	0.697	**0.057**
CRP	0.854	**0.045***
ESR	0.768	**0.036***
RF-positive	1.112	0.235

Correlation coefficient (r) between JADAS-27 score and severity of uveitis showed statistically highly significant positive connection (r=0.7353, P=0.001) (**Figure 2**).

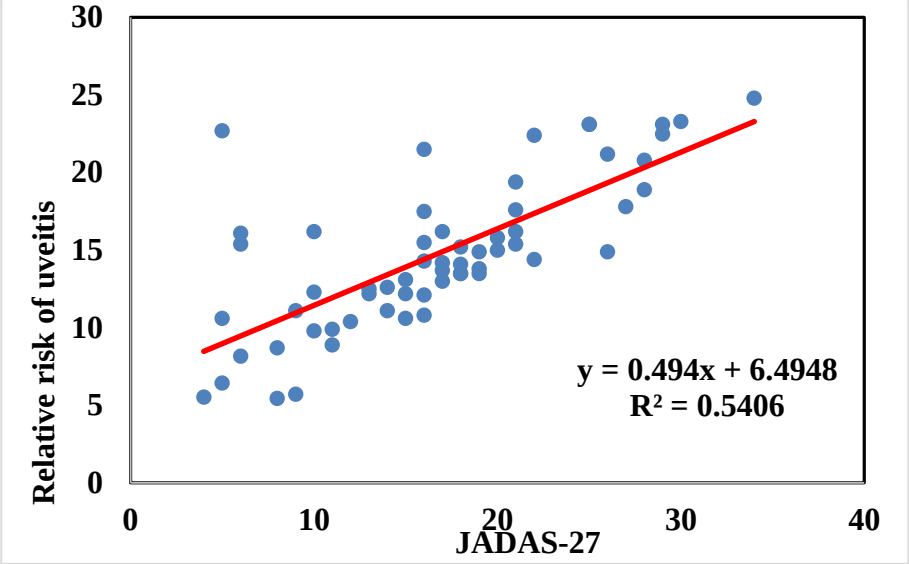

Figure (2): Correlation coefficient (r) between JADAS-27 and relative risk of uveitis.

DISCUSSION

The affected section of the eye (anterior, intermediate, posterior, or pan uveitis), and the chronological pattern of inflammation (acute, subacute, chronic, or recurrent) are used to categorize uveitis; the chronic anterior form is more prevalent in children with uveitis linked to JIA. Although, JIA usually precedes the development of uveitis, a small percentage of patients develop uveitis before JIA. Even though JIA linked uveitis frequently presents with no symptoms at first, it can have major side effects, including irreversible vision loss [11].

The aim of this study is to screen the eyes in children with juvenile idiopathic arthritis in order to detect any ocular alterations earlier and stop any problems that might result in vision loss.

Compared to prior studies, the current investigation found a greater prevalence of uveitis in JIA patients; uveitis developed in almost 16% of the cases.

According to research by **Tappeiner *et al.*** [12], 13.9% of JIA children developed uveitis. Additionally, **Carvounis *et al.*** [13] had shown that JIA had an overall uveitis prevalence of 9-13%. Uveitis rates from Nordic nations, however, were higher, reaching up to 20.5%, according to **Nordal *et al.*** [14]. In contrast to our findings, a cross-sectional investigation by **Kotaniemi *et al.*** [15] including 240 JIA children between 1993 and 2003 discovered a substantial decline in uveitis prevalence. Additionally, there were notable decreases in uveitis complications (P=0.001).

The current screening recommendations call for screening every three to twelve months, depending on the class of JIA, the presence or absence of an ANA, the age of JIA onset, and the length of the disease duration. In order to more precisely classify individuals at risk, it would be preferable to screen the high-risk group with a high rate of uveitis onset and ocular complications using additional demographic, clinical, and laboratory variables. This work has shown that; female sex appeared to be a significant risk factor for uveitis (r=926, P=0.028*).

Similar to our investigations, the study of **Tappeiner *et al.*** [16] indicated that female sex was a significant risk factor for uveitis in the univariate analysis but not in the multivariable analysis.

According to this study, **Angeles-Han *et al.*** [17] found that young girls appear to be more at risk than males for developing early onset arthritis. This may be explained by the larger proportion of ANA-positive females and the gender bias in patients with early-onset oligoarticular JIA [18].

Although females are more likely to develop JIA than boys, sex has not been identified as a separate risk factor for uveitis [19].

In the current study, the median age was 6.7 years in uveitis developing group, young age reported to be a risk factor (r=0.728, P=0.014*), while missing the significance when comparing both groups (P=0.568).

A large cohort research by **Papadopoulou *et al.*** [20] on 299 children with JIA (93 male, 206 female; median age 5.0 years at diagnosis) was retrospectively focused on the development of arthritis/uveitis and had findings that were similar to ours.

In the present work, the mean disease duration was 24±4.2 months. It appears to have a major impact on uveitis appearance, and the longer it lasts, the greater the chance of uveitis development (r=0.976, P=0.032).

According to **Grassi *et al.*** [21], uveitis often appears 4 to 5 months following the beginning of arthritis, with 49% of patients developing it during the first 3 months of JIA and 90% within the first 4 years. Another research by **Zannin *et al.*** [22] claimed that the key indicator of uveitis severity is the length of time between the beginning of arthritis and the commencement of the condition.

In the current study, all JIA categories were the same when examining their influence on the beginning of uveitis (P>0.05), although the oligoarticular subtype

in particular seemed to affect severity (r=0.923, P=0.041*). Additionally, there is no discernible difference between the two groups in terms of the results of the ANA and HLA-B27 testing. Children with uveitis were found to have ANA +ve in more than 70% of uveitis group and HLA-B27 +ve in 27% of cases (r=0.719, P=0.019*, r=1.000 P=0.732).

The JIA classifications with the highest risk for uveitis were determined to be extended oligoarthritis, persistent oligoarthritis, RF-negative polyarthritis, and psoriatic arthritis [23].

Regarding the laboratory findings of JIA, only ESR was significantly higher in patients with uveitis than without uveitis (P<0.05) and showed significant correlation with uveitis severity (r=0.768, P=0.036), while other laboratory findings concerning, ANA and HLA-B27 tests (P=0.312, P=0.380) had insignificant values in comparison between the two groups.

According to the **Haasnoot *et al.*** [24] research, patients with uveitis caused by JIA had increased ESR levels (22.8±21.7 mm/h), whereas patients without uveitis had lower ESR values (13.6±7.79 mm/h), with a statistically significant difference (P<0.05). It's noteworthy to note that ESR has been proven to have a strong correlation with uveitis risk. These findings concurred with those of **Tappeiner *et al.*** [16] 54.2% of JIA kids with uveitis were positive for ANA, while 15.3% of their large cohort of 954 JIA children tested positive for HLA-B27. 133 (13.9%) of these kids had uveitis. These ratios were different depending on the type of JIA category [16].

Up to 60-80% of patients with oligoarticular JIA (oJIA) have ANA. Importantly, oJIA is linked to a significant incidence of uveitis, especially in patients who are ANA positive (ANA+) [25].

Uveitis may be seen in up to 10% of Polyarticular JIA (pJIA) RF-ve patients, and ANA may be found in as many as 40% of them. The MHC class I antigen human leukocyte antigen (HLA)-B27 has a substantial correlation with the diagnosis of this JIA subtype [26].

HLA-B27 positive boys with enthesitis-related arthritis are more likely to develop acute anterior uveitis (AAU). Enthesitis-related arthritis (ERA) is a condition that is linked to HLA-B27 and is associated with AAU [27].

Although prior research has demonstrated that JIA herd appeared to have a higher prevalence of antibodies against the iris and retina, the specificity of the ANAs is unknown [28].

This study revealed that regarding SUN grading, the SUN class (0) is the commonest classification of the study group by more than 60%, which was consistent with the results provided by the Standardization of Uveitis Nomenclature (SUN) Working Group. The most prevalent class was the moderate one [29].

This study speculated that more than one ocular complication was more prevalent in uveitis than group without uveitis with highly significant difference (P<0.001). The most prominent in these complications was synechia, macular edema, cataract with statistically highly significant difference (P<0.001), band keratopathy was less common with P<0.05, while glucoma, hypotony, epiretinal membrane and phthisis were the least frequent (P>0.05) in comparison between the two groups.

Although much lower at 0.04/EY among patients who had no difficulties at baseline, the overall incidence of acquiring a new ocular complication was 0.15/EY.

In the research by **Thorne *et al.*** [30], bilateral uveitis, active uveitis (≥1+ AC cells or ≥0.5 vitreous haze), more protracted uveitis, the appearance of posterior synechiae, and abnormal IOP were all associated with progressive vision loss.

According to **Clarke *et al.*** [2] findings, the most common problems were cataracts, glaucoma, and band keratopathy, which affected 20.5, 18.9, and 15.7% of patients, respectively. A total of 55 JIA-U patients were described by **Skarin *et al.*** [31] in their study. 42% of patients developed cataracts and 5% had glaucoma seven years after the beginning of uveitis. At age 24, 49% of people exhibited symptoms of active uveitis, 22% had glaucoma, and 51% had cataracts.

In the current work, patients with uveitis had more significant mild visual impairment than those without uveitis (P<0.001), while the visual impairment was more in moderate and severe impairment, however it does not reach significance (P>0.05).

In a retrospective analysis with 240 afflicted eyes, **Gregory *et al.*** [32] examined the risk variables for vision loss and found that the incidence of visual loss to 20/50 or worse was 0.18 and 0.09 eye per year.

Cataract is regarded to be the most common problem affecting visual acuity (19–81). Additionally, secondary glaucoma (10-40%) and ocular hypertension (≥22 mmHg), which can result in optic nerve damage and visual field defects, are frequent and usual side effects [33].

LIMITATIONS

The very small number of screening arthritis patients may compromise the precision of statistical analysis and the ability to draw reliable findings. The lack of information on the exact moment when patients started taking topical corticosteroids, the point at which therapy began, or the reason why systemic corticosteroids or DMARDs were prescribed (uveitis or arthritis). Also, this study was intended just for screening, there is no follow-up period. Uveitis may manifest in some trial participants during or after the experiment.

CONCLUSION

Longer follow-up and the development of prediction algorithms for the severe uveitis course should be the focus of future research in order to enable

targeted screening and treatment approaches suited to high-risk populations.

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Competing interests: Nil.

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