Evaluation of Patients with Juvenile Idiopathic Arthritis-Associated Uveitis from Rheumatology Perspective

Juvenil İdiyopatik Artrit ile İlişkili Üveitli Hastaların Romatolojik Açıdan Değerlendirilmesi

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ABSTRACT

Objective: Uveitis, the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA), is most commonly found in children with oligoarticular type and polyarticular rheumatoid factor (-) JIA. Close follow-up of these children by pediatric rheumatologists and ophthalmologists is important because of the risk of blindness if these cases are untreated. This study aims to evaluate the frequency of uveitis, demographic characteristics, and complications in children with JIA.

Material and Methods: Among the patients with JIA who were followed up at the Pediatric Rheumatology Clinic of Dr Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital between January 2017 and July 2021, those with uveitis were included in the study. Location of uveitis, laterality, age at onset of uveitis, complications of uveitis, duration of follow up, laboratory findings, medications used, and status of uveitis at the time of data collection were obtained from the patients' files.

Results: Uveitis was observed in 34 (7.1%) of the 473 children with JIA included in the present study. Twenty three patients were female (67.6%). The age at diagnosis of JIA was 5.9±5.1 years, and the age at diagnosis of uveitis was 7.5±4.2 years. The most common form of JIA was the persistent oligoarticular form. Compared with the age of onset of arthritis in all JIA patients, the age of onset of arthritis was lower in patients with JIA-associated uveitis (7.8±4.6 years vs. 5.9±5.1 years). Anatomically, all patients had anterior uveitis. Antinuclear antibody positivity was more common in children with JIA-associated uveitis (47.1%) than all of our patients with JIA (19%). In one of the patients, arthritis and uveitis were diagnosed simultaneously. Posterior synechia was found in three patients (8.8%). Arthritis was the first symptom in 27 patients (79.4%) and uveitis in six patients (17.6%), cataract in five patients (14.7%), glaucoma in two patients (5.9%), and blindness in one eye (2.9%).

Conclusion: Uveitis is the most common extra-articular complication of JIA and has sight-threatening complications which may lead to irreversible visual loss. The findings of this study suggest that the joint effort of pediatric rheumatologists and ophthalmologists is needed to diagnose these children promptly and treat them appropriately.

Key Words: Eye diseases, Juvenile Idiopathic Arthritis, Uveitis

ÖZ

Amaç: Jüvenil idiyopatik artritin (JİA) en yaygın eklem dışı bulgusu olan üveit, en sık olarak oligoartiküler tip ve poliartiküler romatoid faktör (RF) negatif JİA'lı çocuklarda bulunur. Bu çocukların pediatrik romatologlar ve oftalmologlar tarafından

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yakın takibi, tedavisiz kalan vakalarda körlük riski nedeniyle önemlidir. Bu çalışmanın amacı JİA'lı çocuklarda üveit sıklığını, demografik özelliklerini ve komplikasyonlarını değerlendirmektir.

Gereç ve Yöntemler: Ocak 2017-Temmuz 2021 tarihleri arasında SBÜ Dr Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi hastane bilgi veri tabanından elde edilen hastaların demografik, klinik ve sonuç verileri geriye dönük olarak incelendi. Çocukların yaşı ve cinsiyeti, takip süresi, artrit başlangıç yaşı, JİA alt tiplerinin dağılımı, üveit başlangıç yaşı, tanı yaşı, üveit lokalizasyonu, özellikleri, semptomları, laboratuvar parametreleri ve kullanılan ilaçlar değerlendirildi.

Bulgular: Çalışmaya alınan 473 JİA'lı çocuğun 34'ünde (%7.1) üveit görüldü. JIA'nın en yaygın formu, kalıcı oligoartiküler formdu. Tüm JIA hastalarında artrit başlangıç yaşı ile karşılaştırıldığında, JIA ile ilişkili üveiti olan hastalarda artrit başlangıç yaşı daha düşüktü (5.94±5.143 ve 7.83±4.62 yıl). Antinükleer antikor pozitifliği, JIA ile ilişkili üveiti olan çocuklarda tüm JIA hastalarımıza kıyasla daha yaygındı (%19'a karşı %47.1). Bir hastada artrit ve üveit aynı anda teşhis edildi. 3 hastada (%8.8) posterior sineşi, 5 hastada (%14.7) katarakt, 2 hastada (%5.9) glokom ve bir gözde (%2.9) körlük saptandı.

Sonuç: Üveit, JİA'nın en sık görülen eklem dışı komplikasyonudur ve geri dönüşü olmayan görme kaybına yol açabilen komplikasyonlara sahiptir. Bu çalışmada JİA hasta popülasyonumuzda üveit tanısı alan hastalarımızı değerlendirmeyi amaçladık. Bu çocuklara bir an önce teşhis koymak ve uygun şekilde tedavi etmek; hem pediatrik romatologların hem de oftalmologların ortak çabasını gerektirmektedir.

Anahtar Sözcükler: Göz bozuklukları, Jüvenil idiopatik artriti, Üveiti

INTRODUCTION

Uveitis is the most common extra-articular manifestation of juvenile idiopathic arthritis (JIA). The incidence of uveitis in children with JIA is between 12-38%. Chronic anterior uveitis, which is usually asymptomatic, is the most common type of JIA-associated uveitis. Acute anterior uveitis usually presents with a painful, red eye. It is generally associated with enthesitis-related arthritis (ERA) and HLA-B27 positivity (1).

If JIA-associated uveitis is treated inadequately, it may lead to ocular complications, such as cataracts, glaucoma, band keratopathy and persistent macular edema, ultimately resulting in visual impairment and blindness (2). According to the 2019 American College of Rheumatology (ACR) recommendations, patients with JIA should be screened regularly (every 3-12 months) for uveitis depending on the risk factors (3) (Figure 1). It is more commonly observed in girls with oligoarticular JIA who have positive antinuclear antibodies (ANA) (2).

In approximately 10% of children, uveitis may be present before the onset of arthritis, while in nearly half of affected children, it occurs at the time of or soon after the diagnosis of arthritis. In a significant number of children, it develops within seven years of onset (2,4,5). Treatment of JIA-associated uveitis includes the use of both topical and systemic medications. In resistant cases, the use of biological agents may be required. Approximately 51% develop synechia and 34% develop band keratopathy. Cataract is found in 20% of affected children, while glaucoma develops in approximately 17% of children (4,6,7). In some children, some of the structural complications are already present at the time of uveitis (1,6-8). This study aims to evaluate the frequency and complications of JIA- associated uveitis.

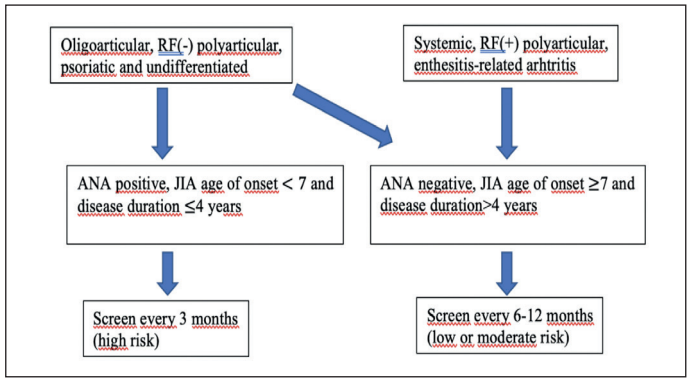

Figure 1: 2019 American College of Rheumatology/Arthritis Foundation Guideline for Juvenile Idiopathic Arthritis-Associated Uveitis opthamologic screening examination.

RF:*Rheumatoid factor,* ***ANA:*** *Antinuclear antibody,* ***JIA****: juvenile idiopathic arthritis.*

MATERIAL and METHODS

This retrospective study was conducted by analyzing the medical records of 473 children with JIA who were followed up for at least three months in the Pediatric Rheumatology Clinic of Dr Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital between January 2017 and July 2021. Diagnosis and classification of subtypes of JIA were made in accordance with the International League of Associations for Rheumatology (ILAR). In the present study, demographic, clinical and outcome data of the patients from the hospital information database were examined retrospectively. Child's age and sex, duration of follow-up, age of onset of arthritis, distribution of subtypes of JIA, age of onset of uveitis, localization, symptoms (eye redness and pain, photophobia, vision changes), laboratory parameters at the time of diagnosis, rheumatoid factor (RF), ANA, HLA-B27 results and the drugs they used were evaluated. An ANA titer of ≥1:80 by fluorescent antibody testing was designated positive. This study was approved by Ankara Keçiören Training and Research Hospital, Clinical Research Ethics Committee, numbered 22.07.2020/15-2153.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). The

Shapiro-Wilk test was used to determine the variables whether or not they are normally distributed. Results are given as mean ±SD. Categorical variables were evaluated using the chi-square test. Comparisons of continuous variables between the two grupsa were performed using the T-test. The level of statistical significance was set at $p < 0.05$.

RESULTS

Of the 473 patients with JIA who were followed up at Dr Sami Ulus Maternity, Child Health and Diseases Training and Research Hospital between 2017-2021, 34 patients with JIA-associated uveitis were included in the present study. Twenty three patients were female (67.6%). The female/male ratio was 2:1. At the time the patient data were collected, their age was 12.8±5.4 years. The age at first diagnosis of uveitis was 7.5±4.2 years, and the age at first diagnosis of arthritis was 5.9±5.1 years. Arthritis was the first symptom in 27 patients (79.4%) and uveitis in six patients (17.6%). In one patient, uveitis and arthritis were diagnosed at the same time. Compared with the age of onset of arthritis in all our patients with JIA, the age of onset of arthritis was lower in patients with JIA-associated uveitis (13.3±5.1 years vs. 5.9±5.1 years) ($p<0.05$). Considering the subtypes of JIA, persistent oligoarticular JIA was the most common type associated with JIA-associated uveitis in 19 patients (55.9%). Eleven patients (32.4%) had ERA, 3 patients (8.8%) had RF (-) polyarticular JIA and 1 patient (2.9%) had extended oligoarticular JIA. Anatomically, all patients had anterior uveitis. Considering the laterality of uveitis, 5 patients (14.7%) had right, 3 patients (8.8%) had left, and 26 patients (76.5%) had bilateral involvement. Although not statistically significant, bilateral involvement was more frequent in female patients (76.9%) than males (23.1%) ($p= 0.11$). While ANA positivity was 19% in our JIA patients, it was 47.1% with JIA-associated uveitis. ($p<0.05$). Although ANA positivity was higher in girls (52.2%) than in boys (36.4%), it was not statistically significant ($p= 0.38$).

Topical treatment was administered to all patients with uveitis. Systemic steroid treatment was administered to 25 patients (73.5%) and methotrexate treatment was administered to 29 (85.2%) patients. Biological agent treatment was administered to 24 patients (70.5%) who were resistant to systemic steroid and methotrexate treatment. Twenty patients (58.8%) received adalimumab, 3 patients (8.8%) received infliximab after adalimumab. Tocilizumab treatment was administered in one patient after adalimumab and infliximab (2.9%). The need for biological therapy for ocular complications was higher in our female patients, but it was not statistically significant ($p=0.53$). No patient received intraocular steroid injection. Considering the eye complications, posterior synechia were observed in 3 patients (8.8%), cataracts in 5 patients (14.7%), glaucoma in 2 patients (5.9%), and blindness in one patient (2.9%). Ocular complications were higher in female patients, but they were not statistically significant ($p= 0.92$). The main characteristics of patients are given in Table I.

Table I: Main characteristics of patients.

Number of patients	34
Gender (girls %)*	23 (67.6)
Arthritis onset age	5.9± 5.1years
Age of onset of uveitis	7.5± 4.2 years
Bilateral uveitis*	26 (76.5)
Antinuclear antibody positivity*	16 (47.1)
Number of patients given biologic therapy*	24 (70.5)

***** *n(%)*

DISCUSSION

Uveitis is the most common extra-articular manifestation of JIA, with a potential risk of visual impairment. We aimed to evaluate the frequency of uveitis in our patient population with JIA, the demographic data of our patients with uveitis, and eye complications. The prevalence of uveitis in children with JIA varies widely between 10-38% (8-10). The frequency of uveitis in JIA was reported as 12% by Heiligenhaus et al (8). In our patient cohort, uveitis was detected in 7.1% of JIA patients.

The previous studies have shown that frequency of uveitis in JIA varies with the JIA subtype. According to Paroli et al. (10) reported that 87.3% of joint involvement in patients with JIA-associated uveitis was compatible with oligoarticular JIA. Angeles-Han et al. (11) reported that 41% JIA patients had a persistent oligoarticular form of JIA. They concluded that having oligoarticular type of JIA is one of the most important determinants in the development of uveitis. Oligoarticular JIA was the most common JIA category (38.8%) in the JUPITER study cohort, which included four centers from Turkey. Other JIA subgroups and percentages in the JUPITER study were ERA, 23.2%; RF (-) polyarthritis, 15.6%; systemic arthritis, 12.2%; juvenile psoriatic arthritis, 5.2%; undifferentiated arthritis, 2.8%; and RF-positive polyarthritis, 2.2% (12). In our report, the most common type of JIA associated with uveitis was the persistent oligoarticular JIA with a rate of 55.9% and ERA was the second most common JIA subtype category with 32.4%.

Another important risk factor for JIA-associated uveitis is the age at onset of JIA. In early-onset disease, the risk of accompanying uveitis increases accordingly (5). Paroli et al. (10) reported that the mean age of children with JIA-associated uveitis was 3 years in their study. The age at first diagnosis of uveitis was older (7.5±4.2 years) in our study. The high mean age of our ERA patients may have increased the mean age of uveitis.

The role of ANA in the pathogenesis remains unclear. Angeles-Han et al. (11) found ANA positivity more frequently in children with JIA-associated uveitis than in children without uveitis (16.7% vs. 66.7%). Kasapçopur et al.(13) found ANA positivity in 25 of 37 children with oligoarticular JIA and reported that

uveitis developed in 10 of them. A study conducted in Italy revealed that ANA positivity was the biggest risk factor for the development of uveitis and that 30% of ANA-positive JIA patients develop uveitis regardless of the age and gender of the child (14). In 2017, Çakan et al. (15). found the frequency of uveitis to be 4.5% in 265 JIA patients. ANA positivity was present in 27.2% of these patients. In our JIA cohort, ANA positivity was 19%.

Uveitis may develop before the diagnosis of JIA, so eye-related inflammatory conditions may progress in the meantime, remain undetected for a while and cause complications. Studies show that 50% to 70% of eyes have at least one complication at the initial ophthalmology exam. The biggest risk of having all these complications is blindness (1,2,5). Angeles- Han et al. (11) reported that cataracts and synechiae were frequently present in 31% of children, while keratopathy was less common in 25% and glaucoma in 17%. Ocular complications were found in 32.3% of our cohort. This rate is similar to the complication risk in JIA-associated uveitis in the literature. We think that the close cooperation between the ophthalmology and the pediatric rheumatology clinics will reduce the risks of these complications. In this respect, a multidisciplinary team approach is essential.

In Angeles- Hans' report the need for methotrexate treatment was 76.8%, and the need for biological treatment was 55.7% in JIA-associated uveitis (11). These were 85.2% and 70.5%, respectively, in our patient cohort. The reason for the high number of patients using biological agents in our study is the early detection of treatment-resistant cases and early initiation of biological treatments for complicated cases.

The limitations of the study are that it is retrospective and the number of patients is small. The asymptomatic course of the disease may complicate the diagnosis and cause the number of patients to appear less.

CONCLUSION

Uveitis is one of the most important long-term complications of patients with JIA. In this respect, a multidisciplinary team approach is essential. Also families should be warned about the risks of JIA uveitis and to take their children for eye check-ups even if they do not have any complaints.

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