The Other Side of the Coin: Uveitis in Patients with Juvenile Idiopathic Arthritis

Madalyonun Diğer Yüzü: Juvenil İdiyopatik Artritli Hastalarda Üveit

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ABSTRACT

Objective: Juvenile idiopathic arthritis (JIA) is a childhood rheumatic disease that causes joint inflammation and tissue damage. Non-infectious uveitis is the most common extra-articular manifestation of JIA.The aim of this study is to evaluate the risk factors that play a role in occurrence and recurrence of uveitis and, to determine the relationship between arthritis and uveitis activity in patients with JIA.

Material and Methods: This retrospective, cross sectional study included JIA patients with/without uveitis from a referral center in Turkey. The Juvenile Arthritis Disease Activity Score was used to evaluate the disease activity and calculated for arthritis and uveitis separately.

Results: Uveitis was seen in 26 (13.3%) of 195 JIA patients. Of 26 JIA associated uveitis (JIA-U) patients, 19 (73%) had an oligoarticular subtype. The median age at diagnosis of JIA with uveitis was younger than without uveitis (p=0.015). Oligoarticular JIA was found to be associated with recurrence of uveitis (p=0.021). The occurrence age of arthritis and uveitis was significantly younger in patients with recurrent uveitis (p=0.041, p=0.002, respectively). The median JADAS27 score at the onset of uveitis was lower in the recurrent group (p=0.038).

Conclusion: Early age is a significant risk factor for occurrence and recurrence of uveitis. It is important to remember that, during the disease course, patients with low disease activity may also develop uveitis.

Key Words: Age, Disease activity, Juvenile idiopathic arthritis, Pediatrics, Recurrence, Uveitis

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ÖZ

Amaç: Juvenil idiyopatik artrit (JİA), eklem iltihabı ve doku hasarına neden olan çocukluk çağı romatizmal bir hastalıktır. Enfeksiyöz olmayan üveit, JİA'nın en sık görülen eklem dışı belirtisidir. Bu çalışmanın amacı, JIA'lı hastalarda üveit oluşumunda ve tekrarlamasında rol oynayan risk faktörlerini değerlendirmek ve artrit ile üveit aktivitesi arasındaki ilişkiyi belirlemektir.

Gereç ve Yöntemler: Bu retrospektif, kesitsel çalışmaya Türkiye'deki bir sevk merkezinden üveiti olan/olmayan JIA hastaları dahil edildi. Hastalık aktivitesini değerlendirmek için Juvenil Artrit Hastalık Aktivite Skoru kullanıldı ve artrit ve üveit için ayrı ayrı hesaplandı.

Bulgular: Üveit 195 JIA hastasının 26'sında (%13.3) görüldü. 26 JIA-U hastasının 19'unda (%73) oligoartiküler alt tip vardı. Üveitli JİA'nın tanı ortanca yaşı üveitsiz JİA'ya göre daha gençti (p=0.015). Oligoartiküler JİA üveit nüksü ile ilişkili bulunmuştur (p=0.021). Tekrarlayan üveiti olan hastalarda artrit ve üveitin ortaya çıkış yaşı anlamlı olarak daha gençti (sırasıyla p=0.041, p=0.002). Üveit başlangıcındaki medyan JADAS27 skoru tekrarlayan grupta daha düşüktü (p=0.038).

Sonuç: Erken yaş, üveit oluşumu ve nüksü için önemli bir risk faktörüdür. Hastalık seyri sırasında, düşük hastalık aktivitesine sahip hastalarda da üveit gelişebileceğini unutmamak önemlidir.

Anahtar Sözcükler: Yaş, Hastalık Aktivitesi, Juvenil Idiyopatik Artrit, Pediatri, Nüks, Üveit

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a childhood rheumatic disease that causes joint inflammation and tissue damage. Non-infectious uveitis is the most common extra-articular manifestation of JIA. Uveitis developed during the disease course due to uveal inflammation. Although the cause of uveal inflammation is not known precisely, several risk factors identified in the occurrence of uveitis. These are JIA-subtype, presence of antinuclear antibody (ANA) and human leukocyte antigen (HLA) B-27, gender, and younger age at disease onset (1,2). Chronic anterior uveitis is the most common JIA associated uveitis (JIA-U) form, and female gender, early age at arthritis onset (<6 years), positive ANA status, and oligoarticular subtype are risk factors that increase its occurrence (3).

JIA-U often has a silent and insidious onset and is most commonly independent of arthritis activity (4). However, recent studies reported relationship between arthritis and uveitis activity (5,6). Zak et al. (7) reported that 20% of patients with JIA who developed uveitis in childhood had ocular complications in adulthood. This result indicates that JIA-U issues such as recurrence persist beyond childhood and highlights the importance of identifying risk factors associated with JIA-U.

The aim of this study is to evaluate the risk factors that play a role in the occurrence and recurrence of uveitis in patients with JIA. Additionally, it is also planned to determine the relationship between arthritis and uveitis activity.

MATERIALS and METHODS

Study design, data collection, definition

This observational study included the patients who were diagnosed and followed up with JIA and JIA-U, between April 2005 and May 2020.

Systemic findings, normal ESR/CRP, and physician's global assessment of disease activity) (11).

The study was approved by Ankara City Hospital, No. 2 Clinical Research Ethics Committee (E2-21-714/ 21.04.2021).

Statistical Analysis

IBM SPSS Statistics for Windows, version 26.0 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Continuous variables that do not have normal distribution were expressed as median (IQR). Categorical variables were summarized as counts (percentages). The Chi-square test was used to compare categorical variables, and Mann-Whitney U-test was used to compare non-normally distributed continuous variables. For the multivariate analysis, the possible factors identified with univariate analyses ($p<0.1$) were further entered into the logistic regression analysis to determine independent predictors of uveitis. Hosmer-Lemeshow goodness of fit statistics were used to assess model fit. The odds ratio (OR) and their 95% confidence interval (CI) obtained in the adjusted regression analysis were calculated. The statistical significance level was accepted as a p-value <0.050.

RESULTS

Characteristics of JIA patients:

A total of 195 patients with JIA were enrolled in the study and 122 patients (62.5%) were female. The median age was 7.8 (4.4-12.2) years. A hundred and seven patients (55%) were oligoarticular JIA, 13 patients (6.6%) were polyarticular JIA, 23 (12%) patients were ERA, and 52 (26.6%) patients were systemic JIA.

Characteristics of JIA-U patients:

Twenty-six patients (13.3%) developed uveitis during the study period. Seventeen (65.4%) of the patients with JIA-U were female. The median duration between JIA diagnosis

and uveitis was 4.5 months. Of 26 JIA-U patients, 19 (73.3%) had oligoarticular, 3 (11.5%) had polyarticular, and 4 (15.3%) had ERA subtype. Presence of ANA was present in 9 patients (34.6%). Uveitis occurred in 2 patients (7.7%) before arthritis and in 10 patients (38.4%) after arthritis. Uveitis and arthritis were coexisting in 10 patients (38.4%) at disease onset. Four patients (15.3%) developed uveitis after withdrawal of treatment. Anterior uveitis was present in 24 patients (92.3%) and granulomatous uveitis in 2 patients. Seven patients (27%) had bilateral, 19 patients (73%) had unilateral disease. The characteristics of the patients were summarized in Table I. Treatment at diagnosis of uveitis was methotrexate (MTX) in 9 patients, NSAID in 1 patients, biological DMARDs in 2 patients, and MTX + biological DMARDs in one patient. Thirteen patients were received only topical therapy for ocular inflammation. Thirteen patients (50%) had uveitis under JIA treatment.

Table I: Characteristics of JIA patients with uveitis

	Uveitis (n=26)
Female gender*	17 (65.4)
Arthritis at the onset of the disease*	24 (92.3)
Uveitis at the onset of the disease*	12 (46.2)
Age at JIA onset, year†	5.1 (3-7.8)
Age at uveitis onset, year†	6.9 (4.4-9.6)
Duration between JIA and uveitis onset, months†	4.5 (0-29.8)
JIA subtype	
Oligoarticular*	19 (73.1)
Others*	7 (26.9)
Active joint count†	2 (1-3)
Uveitis type*	
Anterior uveitis	24 (92.3)
Granulomatous uveitis	2 (7.7)
ESR (mm/hour)†	28.5 (14.8-36)
CRP (mg/dl)†	2.4 (1-12.8)
ANA positivity*	9 (34.6)
HLA-B27 positivity*, n=16	4 (25)
JADAS27 at JIA onset†	19 (14-23)
JADAS27 at uveitis onset†	11 (9-17)
Treatment	
Treatment at uveitis onset*	
No treatment	13 (50)
NSAID	2 (7.6)
MTX	9 (34.6)
Biologic DMARDs	3 (11.5)
Treatment during active uveitis*	
MTX	25 (96.2)
Biologic DMARDs	13 (50)
Total duration of MTX, months†	50.5 (24-72.5)
Duration of MTX before starting biologic DMARDs, months,†, n=12	24 (4-40.5)
Total duration of biologic DMARDs, months†, n=12	33 (23.3-39.5)
Uveitis relapse episode†, n=15	1 (1-3)
Remission on medication, months†	18 (12-37.5)
Remission off medication, months†, n=5	40 (16.5-60)

:** *n (%),* **†**: *median (IQR, %25-75),* ***JIA: *Juvenile idiopathic arthritis,* ***IQR:*** *Interquartile range,* ***ANA:*** *Antinuclear antibody,* ***JADAS:*** *The Juvenile Arthritis Disease Activity Score,* ***HLA:*** *Human Leukocyte Antigen,* ***ESR:*** *Erythrocyte sedimentation rate,* ***MTX:*** *Methotrexate,* ***DMARDs:*** *Disease modifying anti-rheumatic drugs*

Comparison of JIA patients with and without uveitis:

The age of disease onset was significantly younger in patients with uveitis than without uveitis (p=0.015). There was no significant difference between the two groups in sex, JIA subtype, presence of ANA, JADAS27 at diagnosis. Rates of MTX and biologic DMARD use for arthritis were higher in patients with JIA-U than in those without uveitis (p<0.001, p=0.038 respectively). The comparison of JIA patients with and without uveitis was summarized in Table II.

Predicting risk factors of uveitis:

We performed multivariate analysis to determine the risk factors of JIA-U. This model included possible risk factors such as presence of ANA, female gender, and JIA subtype. This present study showed that patients with early age at JIA onset had higher odds of occurring uveitis (Table III).

Comparison of JIA-U patients with none-recurrent and recurrent uveitis:

Of the 26 JIA-U patients, 15 had recurrent episodes, and 11 had a single episode. The median episode during the follow-up period was 1 (1-3). The demographic and baseline characteristics of these two groups were shown in Table IV. There was no significant difference in gender, clinical presentation, positive ANA status, JADAS27 at time of JIA diagnosis between two groups. Oligoarticular JIA was found associated with recurrence of uveitis (p=0.021). Patients with the recurrent uveitis were significantly younger at disease onset than the none-recurrent group (p=0.041, p=0.002, respectively). The median JADAS27 at the onset of uveitis was lower in the recurrent group (p=0.038). Topical cycloplegics and steroids were initially used in all patients with uveitis. The median duration of MTX usage and the median time to initiation of biologic DMARDs after MTX were significantly longer in the relapse group (p=0.013, p=0.045). There was no significant difference in the median duration of biological DMARDs usage between the two groups.

Uveitis-related complications:

Of 26 patients, 15 patients had ocular complications at follow-up. Posterior synechiae (66.6%) was the most frequent complication in our study. Other complications were cataract in two patients, glaucoma in one patient, and iris atrophy in one patient.

Table II: Characteristics of JIA patients with and without uveitis.

	Patients without Uveitis (n=169)	Patients with Uveitis (n=26)	p
Gender, female*	105 (62.1)	17 (65.4)	0.750
Age at JIA onset, year†	8.7 (5.1-12.4)	5.1 (3-7.8)	0.015
Age at uveitis onset, year†		6.9 (4.4-9.6)	
Duration between JIA and uveitis onset, month†		4.5 (0-29.8)	
JIA subtype Oligoarticular* Others*	 100 (59.2) 69 (40.8)	 19 (73.1) 7 (26.9)	0.176
ESR (mm/hour)†	34 (14-62)	28.5 (14.8-36)	0.279
ANA positivity	33 (19.5)	9 (34.6)	0.081
JADAS27 at JIA onset†	19.4 (17-22.2)	19 (14-23)	0.323
JADAS27 at uveitis onset†		11 (9-17)	
Active joint count†	2 (1-3)	2 (1-3)	0.459
MTX treatment*	101 (59.8)	25 (96.2)	<0.001
Biologic DMARDs*	50 (29.6)	13 (50)	0.038

:** *n(%),* **†:** *median (IQR, %25-75),* ***JIA: *Juvenile idiopathic arthritis,* ***IQR:*** *Interquartile range,* ***ANA:*** *Antinuclear antibody,* ***JADAS:*** *The Juvenile Arthritis, Disease Activity Score,* ***ESR:*** *Erythrocyte sedimentation rate,* ***MTX:*** *Methotrexate,* ***DMARDs:*** *Disease modifying anti-rheumatic drugs*

Table III: Risk factors for the development of uveitis

	Patients without Uveitis (n=169)	Patients with Uveitis (n=26)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p	OR (95% CI)	p
Female gender	105 (62.1)	17 (65.4)	1.15 (0.48-2.74)	0.750	1.02 (0.41-2.56)	0.961
Diagnosis age<8	78 (46.2)	20 (76.9)	3.89 (1.49-10.17)	0.006	3.58 (1.35-9.47)	0.010
Oligoarticular JIA	100 (59.2)	19 (73.1)	1.87 (0.75-4.70)	0.181	1.40 (0.52-3.75)	0.501
ANA positivity	33 (19.5)	9 (34.6)	2.18 (0.89-5.33)	0.087	1.82 (0.71-4.65)	0.212

Hosmer and Lemeshow Test p value 0.350, ***JIA:*** *Juvenile idiopathic arthritis,* ***OR:*** *Odds Ratio,* ***ANA:*** *Antinuclear antibody*

Table IV: Characteristics of JIA-U patients with and without recurrent uveitis

	Non-recurrent, n=11	Recurrent, n=15	p
Female gender*	5 (45.5)	12 (80)	0.103
Arthritis at disease onset	10 (90.9)	14 (93.3)	1.000
Uveitis at disease onset	4 (36.4)	8 (53.3)	0.391
Age at JIA onset, year†	6.7 (4.2-13.4)	4.4 (2.8-6)	0.041
Age at uveitis onset, year†	9.3 (7-15.3)	5.6 (3-7.4)	0.002
Duration between JIA and uveitis onset, month†	4 (0-62)	0 (0-12)	0.180
JIA subtype Oligoarticular* Others*	 5 (45.5) 6 (54.5)	 14 (93.3) 1 (6.7)	0.021
ANA positivity*	4 (36.4)	5 (33.3)	1.000
JADAS27 at JIA onset†	15 (14-28)	19 (13-22)	0.357
JADAS27 at uveitis onset†	17 (10-22.3)	9 (2.3-11.5)	0.038
Arthritis relapse episode†	1 (1-2)	1 (0-2)	0.726
Total duration of MTX, month†	24 (18-58)	72 (40-108)	0.013
Duration of MTX before starting biologic DMARDs, month†	3 (3-26.5)	27.5 (12.8-68.3)	0.045
Total duration of biologic DMARDs, month†	35 (17.5-58)	33 (24-34)	0.639

:** *n(%),* **†:** *median (IQR, %25-75),* ***JIA: *Juvenile idiopathic arthritis,* ***IQR:*** *Interquartile range,* ***ANA:*** *Antinuclear antibody,* ***JADAS:*** *The Juvenile Arthritis Disease Activity Score,* ***MTX:*** *Methotrexate,* ***DMARDs:*** *Disease modifying anti-rheumatic drugs*

DISCUSSION

Uveitis is a crucial complication of JIA. Risk factors associated with the occurrence of uveitis should be known to guide specialists in the follow-up of patients. According to our findings, "early onset age at diagnosis" was a risk factor for occurrence and recurrence of uveitis in JIA. However, JADAS27 at uveitis onset was significantly lower in recurrent uveitis than in non-recurrent uveitis.

Ocular inflammation is an insidious condition that affects quality of life. JIA is the most frequent systemic disease that causes noninfectious uveitis. Yalçındağ et al. (12) reported that 25% of non-infectious pediatric uveitis was associated with JIA. In a multicenter study from Turkey, Sahin et al. (13) reported the rate of uveitis development as 6.8% among 500 patients with JIA. In the current study, 26 patients (13.3%) developed JIA-U.

There is a stronger association between inflammatory arthritis and uveitis in childhood than in adults. The various risk factors such as early age at disease onset, female gender, oligoarticular subtype, and positive ANA status increase the odds of developing uveitis (14). In a prospective study that included 1497 Canadian JIA patients, the young age (<7 years) at diagnosis and ANA positivity were independent risk factors for uveitis (15). Calandra et al. (16) reported that JIA-U was strongly related with arthritis at younger age and presence of ANA. However, female gender and oligoarticular subtype were not showed as independent risk factors for uveitis. Similarly, our study showed that there was no difference between JIA and JIA-U groups in parameters gender and oligoarticular subtype. However, the oligoarticular disease was significantly common in recurrent JIA-U group. We observed a higher positive ANA status in the JIA-U group compared to the JIA group, although not statistically significant (34.5% vs. 19.5%). Tappeiner et al. (17) showed that ANA positivity was strongly associated with JIA-U in multivariate analysis .

In a prospective study, uveitis reactivation was associated with age at disease onset (uveitis <5 years, arthritis <4 years) and active disease (18). Similarly, in our study, the median age at arthritis in JIA-U patients was significantly younger than in JIA patients (5.1 years vs 8.7 years). In addition, younger age at onset of the disease increased the recurrence rate of uveitis. The median age at uveitis onset was significantly lower in recurrent patients than in non-recurrent patients (5.6 years vs 9.3 years).

JIA-U is usually of the non-granulomatous type (19). In a retrospective study of 125 JIA-U patients, granulomatous type of uveitis was reported 27.2% (20). Another study reported that, granulomatous subtype could be probably due to the intense inflammation (21). Granulomatous uveitis was defined in two patients in our study. These two patients had uncontrolled inflammation due to treatment non-compliance.

The disease activity of JIA is variable due to its heterogeneous nature. Optimal control of inflammation prevents long-term disability. Many authors reported that arthritis and uveitis activity might parallel each other (6,22,23). In a recent multicenter study, the JADAS27 at disease onset was significantly higher in patients with uveitis than those without uveitis (24). Heiligenhaus et al. found the disease activity of JIA to be similar in the group with and without uveitis. In addition, moderate and high disease activity was associated with reactivation of uveitis (18). According to our findings, JADAS27 was not different between patients with JIA-U and JIA without uveitis. However, the JADAS27 was significantly lower in the recurrent uveitis group than the non-recurrent group. These critical findings highlight that the JADAS27 is may be insufficient in evaluating the disease activity in the presence of uveitis. Otherwise, it can be considered that arthritis activation and uveitis recurrence in JIA may be independent of each other, and in this case, due to the insidious course of uveitis, eye examinations should be performed regularly in patients who are in remission for arthritis.

Patients diagnosed with JIA in the last 15 years in our center were included in our study. In 15 years there have been significant advances in the treatment approach of JIA-U. In addition to MTX and topical corticosteroids, the use of biological DMARDs has become widespread over the years. Papadopoulou et al. (25) reported that JIA patients treated with MTX had a lower rate of developing uveitis during the disease than those who were not treated. Heiligenhaus et al. (18) showed that topical corticosteroid use was associated with a significantly higher risk of uveitis recurrence. In our study, the median duration of MTX usage was longer in the recurrent group. Furthermore, the median time interval before initiating biological DMARDs after the MTX usage was longer in the recurrent group. Early and effective treatment prevents recurrence of uveitis. In recent years, biological DMARDs are recommended to achieve clinical remission in a short time interval (26).

The major limitations of our study were the retrospective design, the small number of patients. In addition, the outcomes of JIA patients in the last 15 years were evaluated in this study. During this period, the use of biologic agents has increased with updates in the treatment approach. It is inevitable that this change will have an effect on uveitis recurrence over the years, but the effect of the changing treatment modality over the years was not analyzed in this study.

In conclusion, the treatment of JIA should be planned according to both joint and ocular involvement. Sometimes uveitis can be more difficult to treat than arthritis. We emphasize that "early age" is a significant risk factor for developing and recurrence of uveitis. However, it is to keep in mind that patients with low disease activity may also develop uveitis. Since the risk of recurrence of uveitis is increased in oligoarticular JIA, these patients should be carefully follow-up for uveitis. Therefore, treatment and follow-up should be planned with a multi-

disciplinary approach, including a pediatric rheumatologist and ophthalmologist.

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