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Original Article

Prevalence, Risk Factors, and Expression of Human Leukocyte Antigen-DRB1 in Juvenile Idiopathic Arthritis-associated Uveitis

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Objective. This study investigated the prevalence and risk factors of juvenile idiopathic arthritis (JIA)-associated uveitis (JIA-U) in a pediatric tertiary center in Korea. In addition, this study examined whether a specific HLA-DRB1 allele could be a predictive risk factor of uveitis in JIA. **Methods.** The pediatric rheumatology and ophthalmology medical records for JIA between March 2006 and March 2016 were analyzed retrospectively. A total of 233 were enrolled in this study. **Results.** Of 233 patients, 31 developed uveitis (13.3%): 14 oligoarticular, three polyarticular, six systemic, seven enthesitis-related, and one undifferentiated-type JIA. In oligoarticular JIA, 26.4% developed uveitis. The percentage of females with JIA-U was 54.8%, and the median age of the onset of JIA was 7.02 years in JIA-U. Antinuclear antibody (ANA) positivity in oligoarticular JIA-U was 57.1%. Of the 31 JIA-U cases, 26 (83.9%) were clinically asymptomatic when diagnosed. The allele frequency of HLA-DRB1*09 of the total JIA-U was higher than that of JIA without uveitis. HLA-DRB1*09 and HLA-DRB1*12 were higher in oligoarticular JIA-U than in JIA without uveitis. **Conclusion.** Korean JIA-U has different features from JIA-U in Western countries. The sex ratio and age of JIA onset showed no significant differences in Korean JIA-U. The ANA positivity was more common in JIA-U than in JIA without uveitis only in oligoarticular type JIA. These differences might be due to genetic factors, particularly HLA-DRB1. These results suggest HLA-DRB1*09 and HLA-DRB1*12 in oligoarticular JIA to be risk factors for JIA-U in Korea. This is the first study to analyze the association between HLA-DRB1 and JIA-U in Korea. **(J Rheum Dis 2018;25:58-64)**

Key Words. Juvenile idiopathic arthritis, Uveitis, Prevalence, Risk factor, HLA-DRB1

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a joint disorder whose symptoms persist for more than six weeks in children under the age of 16. JIA has several extra-articular manifestations, such as high fever, skin rash, serositis, and uveitis. Among these, uveitis is the most critical complication, because it can cause severe vision loss even if it is asymptomatic when diagnosed [1].

The frequency of JIA-associated uveitis (JIA-U) in JIA is about 10%～20% in each country [2-7]. Uveitis occurs most frequently in children with oligoarticular-type JIA, about 20%～30% in Western data [3,8]. About 60.4%～84.2% of JIA-U sufferers are female; however, ocular symptoms, signs, and complications are more severe in males in Western studies [8-11]. Most cases of uveitis develop around four years after JIA onset [2,8]. Ocular complications have been reported in about 24%～70% of JIA-U cases. Common complications include synechiae, band keratopathy, cataracts, and glaucoma [8,9,12-15].

The known risk factors for JIA-U include antinuclear antibody (ANA) positivity, JIA subtype (especially oligoarticular JIA), and young age of JIA onset. However, genetic associations of JIA-U are relatively less investigated due to the current lack of understanding of the pathogenic mechanisms of JIA-U [16].

Studies on the genetic risk factors for JIA and JIA-U have been focused on the human leukocyte antigen (HLA)

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Class II DR alleles on chromosome 6. HLA-DRB1*11 of oligoarticular JIA was confirmed as a risk allele for uveitis in a study [17]. Similarly, a recent Italy study found that HLA-DRB1*11 was a good predictor of uveitis [8]. In Norwegian study, HLA-DRB1*01 and HLA-DRB1*02 were thought to be risk alleles for JIA-U [18]. It has also been reported that HLA-DRB1*13 was associated with JIA-U in a Caucasoid population [19].

The aim of this study is to investigate the prevalence and risk factors of JIA-U in a Pediatric tertiary center in Korea. We tried to demonstrate the different features of JIA-U between our data and Western studies. To find the etiology for differences, we retrospectively analyzed the association between HLA-DRB1 and JIA-U in Korea.

MATERIALS AND METHODS

Patients

We analyzed pediatric rheumatology and ophthalmology medical records for JIA between March 2006 and March 2016. Patients were diagnosed using International League of Associations for Rheumatology (ILAR) classification criteria. All patients enrolled in this study were followed up at the Department of Pediatrics, Hallym University Sacred Heart Hospital. A total of 233 patients were included in this study. This study is approved by the Institutional Review Board (IRB) at Hallym University Sacred Heart Hospital (IRB no. 2017-I058).

Data collection

Patient information included age at onset of arthritis, gender, ANA, and HLA-DRB1 typing. Moreover, we included information on the signs, symptoms, complications, and the onset time of uveitis in JIA-U patients. All JIA patients had initial eye examination by ophthalmologists from Hallym University Sacred Heart Hospital when diagnosed JIA. Ophthalmologic follow-up was done every 6 months regardless of JIA subtypes. The examinations involved visual acuity, ocular pressure, fundus examination, and biomicroscopy. We analyzed DNA to genotype HLA-DRB1 from peripheral blood mononuclear cells using a polymerase chain reaction sequence-specific oligonucleotide probe. HLA-DRB1 analysis was performed routinely in all JIA patients when initially diagnosed.

Statistics

Statistical analyses were performed using IBM SPSS statistics 20.0 (IBM Co., Armonk, NY, USA). HLA-DRB1, subtypes of JIA, and ANA positivity were compared between JIA-U and JIA without uveitis, which were analyzed by the chi-squared test or Fisher's exact ratio. The Mann–Whitney U-test was used to analyze the differences in gender predominance and age at disease onset. In this analysis, p-values <0.05 were considered significant. The risk factors that are known to develop uveitis such as subtypes of JIA, ANA positivity, female gender, and age of JIA onset (<6 years) were analyzed in a Cox proportional hazard multiple regression model.

RESULTS

Prevalence

A total of 233 JIA cases were categorized as follows by ILAR criteria: oligoarticular (n=53), polyarticular (n=49), systemic (n=64), psoriatic (n=1), enthesitis-related (n=50), and undifferentiated type (n=16) JIA. Among the 233 JIA patients, 31 developed uveitis (13.3%): 14 oligoarticular, three polyarticular, six systemic, seven enthesitis-related JIA, and one undifferentiated type JIA. There were no uveitis cases in psoriatic JIA (Table 1). Gender differences were not significant in total JIA-U (male:female=1.0:1.2). In age <6 years at diagnosis of JIA, female predominance of JIA-U (73.3%) was higher than that of JIA without uveitis (61.6%), however, it was not statistically meaningful.

Table 1. Subtypes of JIA-U and JIA without uveitis

JIA subtype	JIA-U (n=31)	JIA without uveitis (n=202)	Total JIA (n=233)	p-value
Oligoarticular	14 (45.2)	39 (19.3)	53 (22.7)	0.001*
Polyarticular	3 (9.7)	46 (22.8)	49 (21.0)	0.096
Systemic	6 (19.4)	58 (28.7)	64 (27.5)	0.277
Psoriatic	0 (0)	1 (0.5)	1 (0.4)	1.0
Enthesitis-related	7 (22.6)	43 (21.3)	50 (21.5)	0.870
Undifferentiated	1 (3.2)	15 (7.4)	16 (6.9)	0.702

Values are presented as number (%). JIA-U: juvenile idiopathic arthritis-associated uveitis, JIA: juvenile idiopathic arthritis. *$p<0.05$.

Oligoarticular and polyarticular JIA-U showed 71.4%～100% of female predominance, however, there were no meaningful difference compared with JIA without uveitis group. There were more boys than girls in systemic JIA-U and enthesitis-related JIA-U (Table 2). In this study, The median age at diagnosis of JIA was 7.02 years in total JIA patients and the distribution of age at JIA onset is summarized in Figure 1. The median age of uveitis onset was 11.2 years, and the median interval of diagnosis between JIA and uveitis was 4 years. Oligoarticular JIA showed the shortest median interval of diagnosis between JIA and JIA-U (3.3 years).

Risk factors

In univariate analysis, a comparison of ANA positivity in JIA-U and JIA without uveitis did not yield statistically meaningful results (p=0.602). However, in oligoarticular-type JIA (n=53), ANA positivity was higher in JIA-U than in JIA without uveitis (p=0.033) (Table 2). The frequency of uveitis was relatively high in oligoarticular JIA (p=0.001) (Table 1). The median age at JIA diagnosis was similar between JIA-U (7.02 years) and JIA without uveitis (7.25 years). Inflammatory markers such as erythrocyte sedimentation rate and c-reactive protein showed

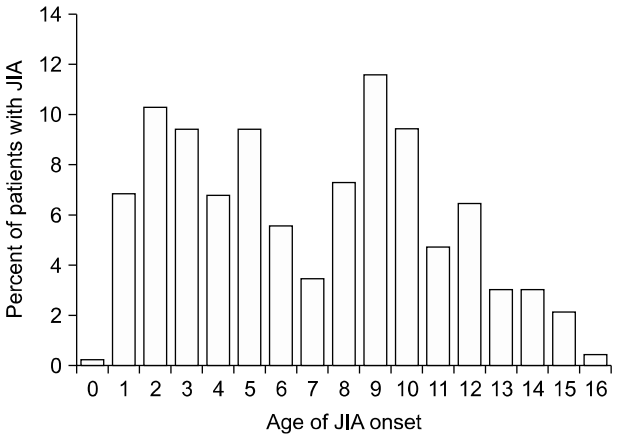

Figure 1. Distribution of age at time of diagnosis of arthritis in 233 patients with juvenile idiopathic arthritis (JIA).

Table 2. Characteristics of JIA-U and JIA without uveitis

Characteristic	JIA-U (n=31)	JIA without uveitis (n=202)	p-value
Oligoarticular (n)	14	39	
Female	10 (71.4)	28 (71.8)	1.000
Age at JIA diagnosis (yr)	3.4 (0.5～13.6)	4.3 (0.8～14.3)	0.262
Interval of diagnosis between JIA and JIA-U	3.3 (0.8～10.2)	NA	NA
ANA positivity	8 (57.1)	10 (25.6)	0.033*
Polyarticular (n)	3	46	
Female	3 (100.0)	32 (69.6)	0.548
Age at JIA diagnosis	10.2 (10.0～11)	6.7 (1.3～14.2)	0.094
Interval of diagnosis between JIA and JIA-U	3.8 (0.9-8.7)	NA	NA
ANA positivity	2 (66.7)	22 (47.8)	0.609
Systemic (n)	6	58	
Female	2 (33.3)	26 (44.8)	0.688
Age at JIA diagnosis (yr)	6.0 (1.4～9.1)	5.3 (1.0～15.3)	0.440
Interval of diagnosis between JIA and JIA-U	6.3 (0.3～11.3)	NA	NA
ANA positivity	0 (0)	9 (15.5)	NA
Enthesitis-related (n)	7	43	
Female	1 (14.2)	4 (9.3)	0.546
Age at JIA diagnosis (yr)	9.6 (6.2～15.7)	9.8 (3.5～15.8)	0.722
Interval of diagnosis between JIA and JIA-U	8.1 (1.0～12.7)	NA	NA
ANA positivity	0 (0)	7 (16.3)	NA
Total JIA (n)	31	202	
Female	17 (54.8)	101 (50.0)	0.616
Age at JIA diagnosis (yr)	7.02 (0.5～15.7)	7.25 (0.8～15.8)	0.440
Interval of diagnosis between JIA and JIA-U	4.0 (0.3～12.7)	NA	NA
ANA positivity in JIA	10 (32.2)	56 (27.7)	0.602

Values are presented as number (%) or median (range). JIA-U: juvenile idiopathic arthritis-associated uveitis, JIA: juvenile idiopathic arthritis, ANA: antinuclear antibody, NA: not available. *p<0.05.

no statistical difference between the JIA-U and JIA without uveitis groups. The risk factors that are known to develop uveitis were analyzed in a Cox proportional hazard multiple regression model. Subtype of JIA (p=0.020) and ANA positivity in oligoarticular JIA (p=0.032) were significant risk factors, but age <6 years at diagnosis of JIA (p=0.991) and female sex (p=0.987) were not.

Ocular signs, symptoms, and complications

Of the 31 uveitis patients, 26 (83.9%) were clinically asymptomatic when diagnosed, while the most common symptom for uveitis was ocular pain and/or redness (16.1%) (Table 3). Among the 31 JIA-U patients, eight developed ocular complications (Table 4): four had posterior synechiae, five had band keratopathy, two had cataracts, and one had glaucoma. Among them, two patients suffered near blindness.

Association between HLA-DRB1 and uveitis

We performed genotype of HLA-DRB1 in enrolled JIA patients including the 31 JIA-U. According to our study, the phenotype frequency of HLA-DRB1*09 in total JIA-U was higher than that in JIA without uveitis ($p<0.05$) (Figure 2). In the 53 patients with oligoarticular-type JIA, which is thought to be a crucial risk factor in developing uveitis, the phenotype frequencies of HLA-DRB1*09 and HLA-DRB1*12 were higher in JIA-U than in JIA without uveitis ($p<0.05$) (Figure 3).

Table 3. Initial ocular signs and symptom in JIA-U

Characteristic	JIA-U (n=31)
Signs and symptoms (n=5)	
Ocular pain and/or redness	5
Change in vision	2
Photophobia	2
Asymptomatic (n=26)	

JIA-U: juvenile idiopathic arthritis-associated uveitis.

Table 4. Frequency of complications of JIA-U

Complication	JIA-U (n=8)
Synechiae	4
Band keratopathy	5
Cataract	2
Glaucoma	1
Hypopyon	2
Near blindness	2

JIA-U: juvenile idiopathic arthritis-associated uveitis.

DISCUSSION

JIA is a multifactorial disorder. The pathogenesis of JIA involves a genetic predisposition to autoimmune/autoinflammatory conditions combined with environmental factors or infections. However, the relationship between joint inflammation and eye involvement is not well established. The current hypothesis of JIA-U pathogenesis is based on autoimmune and genetic-based mechanisms. Both JIA and uveitis share a common inflammatory process; CD4+, CD8+, and regulatory T cells serve as effectors and regulators of the adaptive and innative immune

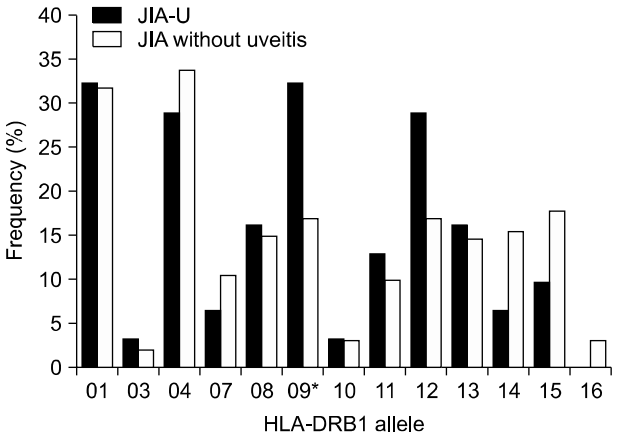

Figure 2. Human leukocyte antigen (HLA)-DRB1 phenotype frequencies in juvenile idiopathic arthritis-associated uveitis (JIA-U) and juvenile idiopathic arthritis (JIA) without uveitis. *p-value<0.05.

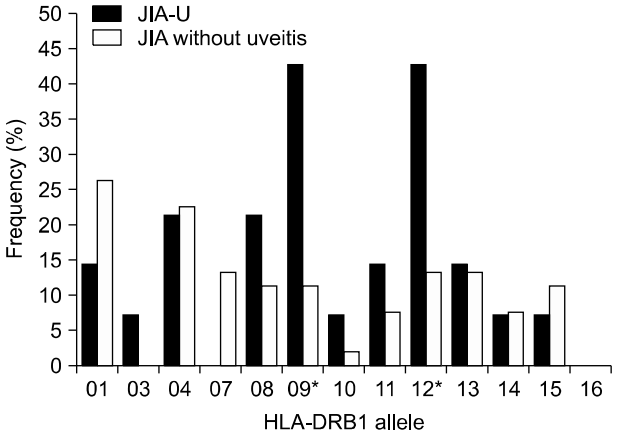

Figure 3. Human leukocyte antigen (HLA)-DRB1 phenotype frequencies of oligoarticular juvenile idiopathic arthritis (JIA) in juvenile idiopathic arthritis-associated uveitis (JIA-U) and JIA without uveitis. *p-value<0.05.

response. Moreover, the genetic bases of both JIA and uveitis are similar, and they are focused mainly on HLA genes [20].

In our study, 233 patients were followed up in a single center, and the age distribution showed biphasic peak that frequency of JIA was high in 3 years and 9 years of JIA onset (Figure 1). Systemic JIA (27.5%) was the most common subtype and oligoarticular JIA (22.7%), enthesitis-related JIA (21.5%), and polyarticular JIA (21.0%) were similarly common in our study (Table 1). In Western study, age of onset shows monophasic pattern which peaks at 2～4 years, and most common JIA subtype is oligoarticular JIA (30%～60%). Female predominance (60%～70%), younger age of JIA onset, and lower frequency of enthesitis-related JIA (7%～13%) are characteristic in Western studies [6,9,21,22].

In our study, the frequency of JIA-U in JIA was 13.3%. Previously reported frequencies of uveitis have varied from 10%～20% in Western studies [2-7]. These diversity in frequency seem to be due to patient selection, especially inherent differences in the development of uveitis. A female predominance of about 60.4%～84.2% in JIA-U has been reported in Western studies. Moreover, it has been suggested that increased frequency of JIA-U in girls is an outcome of the female predominance in young age of JIA onset (＜6 years) [8-11]. However, males and females showed no difference in the incidence of uveitis in JIA in our study (male:female=1.0:1.2). In age ＜6 years at diagnosis of JIA, the female predominance was higher in JIA-U than in JIA without uveitis, which however showed no statistically meaningful results. In previous Western data, JIA-U patients had an earlier onset compared to those without uveitis [2,4,23]. However, our data showed no significant difference in the median age of onset between the JIA-U (7.02 years) and JIA without uveitis groups (7.25 years). These epidemiologic differences according to race and ethnicity suggest that genetic factors are crucial in the development of uveitis in JIA.

According to Cassidy's *Textbook of Pediatric Rheumatology* (7th ed. 2016), the prevalence of bilateral uveitis and asymptomatic uveitis ranges from 25%～89% and 51%～97%, respectively [24]. In our study, the prevalence of bilateral uveitis was 25.8% (n=8), and the prevalence of asymptomatic uveitis was 83.9% (n=26). As the most common presentation of uveitis is asymptomatic, it is crucial to perform accurate and proper eye screening for all types of JIA. The frequencies of other symptoms such as ocular pain and/or redness (n=5, 16.1%) were relatively low in our data. Several studies have reported rates of ocular complications that range from 24%～70% for JIA-U cases [8,9,12-15]. These include band keratopathy, posterior synechiae, cataracts, glaucoma, hypotony, macular edema, optic disc swelling, etc. Our report showed a lower complication rate (n=8, 25.8%) than Western studies. This might be because of genetic difference of JIA-U or the relatively short follow-up period (every 6 months) regardless of JIA subtypes in our study.

In previous studies, ANA positivity, oligoarticular-type JIA, and young age of JIA onset were considered the main risk factors for developing uveitis in JIA [16,25]. According to these risk factors for JIA-U, regular ophthalmologic screening examinations were recommended for all children diagnosed with JIA. ANA-positive oligoarticular or polyarticular JIA patients whose age of onset is below 6 years should have eye examinations every 3 to 6 months. ANA-positive oligoarticular or polyarticular patients whose age of JIA onset is over 6 years should be followed up every 6 to 12 months. ANA-negative oligoarticular or polyarticular JIA patients can have eye screenings every 6 to 12 months. Systemic JIA patients, regardless of ANA positivity or age of JIA onset, can screen their eyes every 12 months [26-28]. In our study, oligoarticular JIA with ANA-positive patients seemed to be related with uveitis (p=0.033). However, a younger age of JIA onset did not raise the risk of uveitis.

The relationship between sex and age of JIA onset are proved In Western study. As discussed earlier, Increased frequency of JIA-U in girls was thought to be an outcome of the female predominance in young age of JIA onset (＜6 years) [22]. In our study, there was no difference in sex ratio between JIA-U and JIA without uveitis. Moreover, there was no difference in age of JIA onset between JIA-U and JIA without uveitis. We could not prove the correlation between sex and age of JIA-onset. However, we could think that no difference in female ratio is probably due to no difference in age of JIA onset between JIA-U and JIA without uveitis.

The genetic factors for predicting uveitis are yet not established due to diverse results on each different country, ethnic group, and race. Many sibling pair and twin studies were performed to show the genetic predisposition in JIA-U. In monozygotic twins, the concordance rate for JIA-U was about 25%, and the concordance rate for arthritis was 20%～40% [29-32]. Among several genes essential to the immune system, HLA, which is located in chromosome 6p, is expected to be highly related with JIA

and JIA-U. Moreover, HLA-A, HLA-B and HLA-DRB1 have been thought to be associated with the disease, and HLA-DRB1 has attracted particular interest due to its potential association with JIA and JIA-U [33]. As discussed earlier, HLA-DRB1*11, HLA-DRB1*01, and HLA-DRB1*13 were thought to be risk allele for uveitis in Western studies [8,17-19]. In Korea, there have been no studies on the relationship between HLA-DRB1 and JIA-U. Only a study on HLA-DRB1*01 as a risk factor for developing JIA compared with normal healthy controls has been reported [34]. As our study was the first investigation in Korea searching for a specific risk allele related to developing uveitis in JIA patients, we suggest that HLA-DRB1*09 and HLA-DRB1*12 in oligoarticular JIA might be risk alleles for developing uveitis. Thus, clinicians should carefully follow-up of oligoarticular JIA patients carrying HLA-DRB1*09 and HLA-DRB1*12 in Korea.

CONCLUSION

In our study, the prevalence of uveitis in JIA was 13.3%. In oligoarticular JIA, 26.4% developed uveitis. In JIA-U patients, the percentage of female was 54.8% and median age of JIA onset was 7.02 years. ANA positivity in oligoarticular JIA-U was 57.1%. Of this group, 83.9% were asymptomatic when diagnosed with uveitis, and eight uveitis patients had complications. The epidemiologic features in our study differed from those of Western countries, perhaps due to genetic factors. We suggest that HLA-DRB1*09 and HLA-DRB1*12 in oligoarticular JIA might be risk alleles for uveitis in Korea.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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