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Frequency of Uveitis among Juvenile Idiopathic Arthritis Patients in a Tertiary Care Hospital of Bangladesh: A Retrospective Study

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most frequently encountered pediatric rheumatologic disorder with an unknown etiology. At present there is no published data regarding the frequency of uveitis in patients with JIA in Bangladesh. This study aimed to observe the frequency of JIA-associated uveitis (JIAU) and distribution of uveitis among different sub-categories of JIA at the Pediatric Rheumatology division, both outdoor and indoor patients, Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) in Bangladesh. **Methods:** This was a retrospective study of 1784 JIA patients at the Pediatric Rheumatology division, BSMMU from July 2010 to March 2023. **Results:** Among the 1784 enrolled JIA patients, we observed that 0.73% of cases had uveitis. Here, 61.5% of JIAU cases were male. Most of the cases (92.3%) had bilateral uveitis and only 7.7% cases had unilateral uveitis. Among JIAU patients, the majority were Oligo JIA (53.8%), followed by ERA 30.8%, Poly JIA RF(−) 7.7% and Systemic JIA 7.7% cases respectively. This study also revealed that 15.4% of JIAU patients had ANA positivity and 23% had HLA B-27 positivity. Here we also found ocular complications associated with uveitis such as band keratopathy (23.1%), posterior synechiae (15.4%) and cataract (15.4%). **Conclusions:** In this study, we observed only 0.73% of patients of JIA had developed uveitis which is lower than the frequency observed in other European studies. This study also showed various ocular complications amongst JIA-associated uveitis patients which signifies the importance of adherence to periodic ophthalmological follow-up to prevent these ocular complications.

Keywords

JIA, Uveitis, HLA-B27, ANA, BSMMU

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most frequent rheumatological disorder among children [1]. It is a heterogeneous, chronic, childhood arthritis that persists for ≥6 weeks, with disease onset before 16 years of age [2]. The incidence and prevalence of JIA vary widely across the world, partly due to its heterogeneous nature and multi-factorial pathogenesis of the disease, which is also influenced by genetic characteristics and environmental triggers [3]. In several studies, the incidence of JIA was 2 - 20 per 100,000 individuals and prevalence was 7 - 400 per 100,000 individuals [4] [5].

Morbidities and disabilities are commonly associated with JIA, including both articular and extra-articular complications [6]. The most frequent extra-articular complication of JIA is uveitis. The intra-ocular inflammation usually affects the iris and ciliary body. Uveitis is found in 5.6% - 24.4% of patients with JIA, more frequently with the oligoarticular JIA (10% - 30%) [7] [8]. Chronic, asymptomatic, and insidious onset uveitis is commonly found in oligoarticular JIA. Risk factors of uveitis associated with JIA include positive anti-nuclear antibody (ANA), disease onset at a younger age (≤6 years), female sex and oligoarthritis [9]. On the other hand, acute symptomatic anterior uveitis is commonly found in enthesitis-related arthritis (ERA) and carries a better prognosis [7]. Patients with systemic JIA, Rheumatoid factor (RF) positive polyarthritis, and psoriatic arthritis rarely develop uveitis. Ocular complications of JIA-associated uveitis include synechiae, cataracts, glaucoma, band keratopathy, and loss of vision [1] [10]. Outcome has improved over the past 20 years, but 5% - 81.5% of pediatric uveitis associated with JIA cases remains a serious cause of morbidity and loss of vision [11]. Strict adherence to meticulous ophthalmologic screening programs and interdisciplinary management appear to be the best approach to prevent complications and decrease the risk of visual impairment [12].

Until now there has been no previous study regarding the occurrence of JIA-associated uveitis in Bangladesh. The objective of this study was to provide demographic, clinical and therapeutic findings of patients with JIA-associated uveitis, to compare the frequency of uveitis and the uveitis-related complications between different categories of JIA and documentation of comorbidities in a pediatric rheumatology referral center in a tertiary hospital of Bangladesh.

2. Materials and Methods

This retrospective study was performed at the Pediatric Rheumatology division, department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh from July 2010 to March 2023. A total of 1784 JIA patients who were regularly followed up with complete medical records were included in this retrospective study. The study was performed by the ethical standards stated in the 1964 Declaration of Helsinki and its later amendments. Because of the study's retrospective nature, obtaining written informed consent from the patients was not required. The study protocol was reviewed and ap-

proved by the ethical committee of Bangabandhu Sheikh Mujib Medical University.

Inclusion criteria included male and female patients ≤16 years of age diagnosed with JIA between July 2010 to March 2023, based on the 2001 revised International League of Associations for Rheumatology (ILAR) criteria. Patients who had arthritis due to other than JIA and had incomplete medical data were excluded.

The diagnosis of JIA was made by a pediatric rheumatologist on a clinical picture of arthritis in one or more joints occurring for 6 weeks or more in a child aged 16 years or younger, with negative etiological investigation and after ruling out all differential diagnoses.

Pediatric rheumatologists diagnosed these patients according to the International League of Associations for Rheumatology (ILAR) classification criteria and after initiating treatment, these patients were regularly followed up. All JIA patients were classified initially at the time of diagnosis and then reclassified after completing the first six months. A total of 2058 JIA patients were enrolled and subsequently 274 children were excluded due to incomplete follow-up. So, 1784 JIA patients were finally included in this study. Follow-ups were done initially at 4 - 6 weeks intervals and then 3 monthly. All the data were recorded both electronically (web-based) and documented in files. Some patients (depending on disease severity and complications) needed more frequent follow-up. All the relevant data were collected from the electronic database and written records of patient's profile of Pediatric Rheumatology division, Department of Pediatrics, BSMMU. History and clinical examination findings regarding musculoskeletal system, and other systemic examinations, including eye examination done by slit lamp examination were recorded. Relevant laboratory findings including complete blood count with ESR, SGPT, serum creatinine, rheumatoid factor (RF), anti-nuclear antibodies (ANA) and human leukocyte antigen (HLA-B27) status were also recorded at the time of diagnosis. RF was tested twice, at least three months apart during the first 6 months of the disease. HLA-B27 was tested in all male patients with arthritis or enthesitis over 6 years of age and in all patients (male or female) with ERA like presentation. Eye examination was done by ophthalmologist at the Department of Ophthalmology of BSMMU for assessment of uveitis. Ophthalmological screening was done following the schedule given in Textbook of Pediatric Rheumatology (8th edition) based on ILAR classification of JIA given below in **Table 1** [13] [14]. Treatment of JIA was given following the new 2019 ACR guideline that included NSAIDs, corticosteroids, DMARDs, e.g., methotrexate (MTX), sulfasalazine, leflunomide and biological DMARDs (etanercept, infliximab, tocilizumab, adalimumab), thalidomide and tofacitinib were also recorded. Uveitis treatment was given by the ophthalmogy department of BSMMU which included topical corticosteroids, methotrexate, sulfasalzine and adalimumab. Patients who had incomplete follow-up were excluded from the study. There were some missing data which were collected by communicating with the patient's parents via phone or email as

much as possible. Missing values were not imputed via any assumptions, and statistical analyses were conducted with all available data.

Data were checked, verified, and analysed by IBM SPSS (statistical program for social science) for Windows, Version 22.0. IBM Corp. (2013), Armonk, New York. Categorical variables were presented as frequency and percentage, while continuous variables were presented as mean ± standard deviation (SD).

Table 1. Recommendations for ophthalmological screening based on ILAR classification of JIAdations for screening based on the ILAR classification of JIA [13] [14].

JIA subgroup	ANA	Age at onset at JIA	Duration of JIA	Screening
Oligoarthritis, RF− polyarthritis, Psoriatic arthritis, Undifferentiated arthritis	+	<7 years	<5 years	3 months
	+	<7 years	>4 years	6 months
	+	<7 years	>7 years	12 months
	+	>6 years	<3 years	6 months
	+	>6 years	>2 years	12 months
	−	<7 years	<5 years	6 months
	−	<7 years	>4 years	12 months
	−	>6 years	Not applicable	12 months
Enthesitis-related arthritis		Not applicable	Not applicable	12 months
RF+ polyarthritis		Not applicable	Not applicable	12 months
Systemic arthritis		Not applicable	Not applicable	12 months
Patients in any category with uveitis		Not applicable	Not applicable	According to uveitis course

3. Results

Among the 1784 enrolled JIA patients in this retrospective study from Paediatric Rheumatology clinic of BSMMU, ERA (39.4%) was found to be the commonest subtype of JIA followed by 17.8% Oligo JIA, 16.6% Systemic JIA, 14.7% Poly JIA RF(−), 6.2% Poly JIA RF(+), 5.2% Unclassified JIA and 0.1% Psoriatic arthritis (Table 2). In our study, 58.3% were male and 41.7% were female, with a male: female ratio being 1.39:1. Here, we found that among the subtypes of JIA ERA, systemic JIA were male predominant whereas in other subtypes cases were female predominant. This study showed in Table 2 that the mean age at diagnosis was 8.31 years and mean disease duration at last follow-up visit was 3.23 years. Here we observed RF and ANA positivity in 6.2% and 7.3% cases respectively. HLAB27 was found positive in 31.5 % of patients, of which 89.1 % had ERA (Table 2).

Table 3 demonstrated that among the patients of JIA associated uveitis, majority of the cases were oligo JIA (53.8%), followed by ERA 30.8%, Poly JIA RF(−) 7.7% and systemic JIA 7.7% in this study.

Table 2. Baseline characteristics of JIA patients (n= 1784).

Item		Overall JIA	ERA	Oligo JIA	Poly JIA (RF−)	Poly JIA (RF+)	Psoriatic arthritis	Systemic JIA	Unclassified JIA
All subjects n, (%)		1784 (100%)	703 (39.4%)	317 (17.8%)	262 (14.7%)	111 (6.2%)	2 (0.1%)	296 (16.6%)	93 (5.2%)
Sex	Male n, (%)	1040 (58.3%)	611 (34.3%)	103 (5.8%)	106 (5.9%)	18 (1%)	1 (0.05%)	169 (9.5%)	32 (1.8%)
	Female n, (%)	744 (41.7%)	92 (5.1%)	214 (12%)	156 (8.8%)	93 (5.2%)	1 (0.05%)	127 (7.1%)	61 (3.4%)
Age at diagnosis, years (mean ± SD)		8.31 ± 4.6	12.4 ± 3.1	6.1 ± 4.2	8.3 ± 4.6	11.8 ± 4.5	10.1 ± 3.3	3.7 ± 3.4	11.2 ± 2.9
Disease duration, years (mean ± SD)		3.23 ± 0.9	3.9 ± 1.7	4.1 ± 1.8	4.3 ± 1.9	5.3 ± 2.5	3.6 ± 1.9	4.1 ± 2.7	2.2 ± 1.3
ANA (IF) positive		129 (7.3%)	2 (0.1%)	89 (5%)	26 (1.5%)	8 (0.5%)	1 (0.05%)	0 (0%)	3 (0.1%)
HLA B-27 positive		562 (31.5%)	631 (35.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RF positive		111 (6.2%)	0 (0%)	0 (0%)	0 (0%)	111(6.2%)	0 (0%)	0 (0%)	0 (0%)

Table 3. Uveitis frequency in different categories of JIA patients (n= 13).

Types of JIA	Number	Percentage
Oligo JIA (persistent)	4	30.8%
Oligo JIA (extended)	3	23%
Poly JIA RF (+)	0	0%
Poly JIA RF (−)	1	7.7%
ERA	4	30.8%
Systemic JIA	1	7.7%
Psoriatic arthritis	0	0%
Unclassified JIA	0	0%

In this retrospective study, we observed 13 (0.73%) cases of uveitis amongst overall 1784 JIA patients (Table 4). Here, we found a male predominance (61.5%) amongst JIA with uveitis patients. Mean duration between onset of arthritis and uveitis was 1.9 years in this retrospective study. Our study revealed that majority of the patients had uveitis in both eyes 92.3% and only 7.7% cases had unilateral uveitis. Here we observed that 15.4% JIA associated uveitis patients had ANA positivity and 23% had HLA B-27 positivity. In this study, all JIA with uveitis patients were treated with topical steroid as a first line therapy with or without mydriatics, 92.3% cases were treated with methotrexate as a second line therapy and 7.7% cases were managed with adalimumab as a third line therapy (Table 4). According to interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with JIA, all the cases were initially treated with topical corticosteroid with or

without mydriatics is to be started and continued for up to 3 months provided inflammation is controlled, before gradually tapering frequency of eye drops [13] [15]. If disease activity increases, does not respond or requires >2 drops daily or new inflammation-related complications, a second-line agent methotrexate (10 to 15 mg/m^2 by mouth or by subcutaneous injection once a week) was added. Also systemic corticosteroids would have been given if there were any prognostic factors for impending visual deterioration. If inflammation was controlled with methotrexate, then it was continued further and topical corticosteroids were tapered. After 16 weeks (or earlier if required), if disease control is unsatisfactory or disease worsens, a third-line therapy in the form of TNF-α blocker adalimumab (20 mg if <30 kg body weight and 40 mg if ≥30 kg subcutaneously every 2 weekly) were added. Similarly if after 16 weeks (or earlier if required) disease control is unsatisfactory or disease worsens, a fourth-line therapy (infliximab, tocilizumab, abatacept or rituximab) would have been considered [15]. In this study, we observed 23.1% band keratopathy, 15.4% posterior synechiae and 15.4% cataract amongst cases of uveitis associated with JIA (**Table 4**). Outcome measures such as visual acuity improvements and quality of life assessments after treatment were not recorded in our paediatric rheumatology department electronic database.

Table 4. Characteristics of patients with JIA-associated uveitis (n = 13).

Patient Characteristics		Number	Percentage
Number of uveitis associated with JIA cases among 1784 study participant JIA cases		13	0.73%
Sex	Male	8	61.5%
	Female	5	38.5%
Duration between onset of arthritis and uveitis, years, mean ± SD		1.9 ± 1.7	
Affected eye	Right eye only	1	7.7%
	Left eye only	0	0%
	Both eyes	12	92.3%
Localization of uveitis	Anterior	13	100%
	Posterior	0	0%
ANA positivity		2	15.4%
HLA B-27 positivity		3	23%
Treatment of uveitis	Topical steroid	13	100%
	Methotrexate	12	92.3%
	Adalimumab	1	7.7%
Complications	Cataract	2	15.4%
	Band keratopathy	3	23.1%
	Posterior synechiae	2	15.4%

4. Discussion

This retrospective study was carried out to assess the frequency of uveitis among JIA patients at any period of disease at the Division of Pediatric Rheumatology in BSMMU, Bangladesh. In the present study, ERA was found to be the commonest subtype of JIA followed by oligo JIA and systemic JIA. This finding was similar to the studies conducted among the children from Taiwan region [16]. Kunjir V *et al*. (2010) in their study in India and Tanya M *et al*. (2020) in their study in Singapore also reported ERA as the main subtype where 36% and 32.8% cases respectively had ERA in their series [17] [18]. But studies done in Europe, North America and Africa showed that oligoarthritis represented the largest JIA subtypes [19]-[22]. Similar to other studies conducted in the South and Southeast Asian region, the frequency of oligoarthritis was low in the present study [17] [23].

Similar to previous Bangladeshi studies, this study also found male predominance with a male:female ratio of 1.39:1 among overall JIA patients [23] [24]. Indian studies also reported similar results [17] [26] [27]. Females were predominant in European and North American studies [28]. Socio-cultural context could be the factor behind this male predominance [29]. Here, we found that among the subtypes of JIA ERA, systemic JIA was male predominant whereas in other subtypes cases were female predominant. These findings were also consistent with another study done in Türkiye [6].

Our study showed, the mean age at diagnosis was 8.31 ± 4.6 years which was similar to the previous studies from this center [24] [25]. The age at presentation and age at onset in the Bangladeshi cohorts appeared comparatively higher in all the subtypes of JIA which were comparable to the reports from India and Singapore [17] [18]. Median age of onset was lower in the European and American cohorts compared to the present study [30]. Lack of awareness, wrong or delayed diagnosis and ethnicity could be the reasons for the late presentations [29]. The mean age at diagnosis for different subtypes of JIA was almost similar in another study reported by Sahin *et al*. in 2021 [6].

In this study, we observed mean disease duration at the last follow-up visit was 3.23 years. It was also consistent with previous studies on JIA patients in this institute [29]. We also described the mean disease duration of disease at follow-up of different subtypes of JIA which is also adjacent to the data observed in a multicentered study done at Türkiye [6].

Our study showed RF and ANA positivity were found in 6.2% and 7.3% of cases respectively. HLA B27 was found positive in 31.5% of patients, of which 89.1% had ERA. These findings were almost similar to the previous studies performed in our country [29]. A study done by Sahin *et al*. (2021) observed HLA B27 positive patients among overall JIA was 33.3% which was close to our findings, but they also found 48.2% ANA positivity which was almost 7.8 times more than that of our study. They also showed a lower frequency of RF+ of 2.2%, whereas we observed a higher percentage of RF+ of 6.2%. These factors vary considerably throughout the world, probably due to ethnic differences as well as

immunogenetic and environmental factors [6].

In this retrospective study, we observed 13 (0.73%) cases of uveitis amongst overall 1784 JIA patients. The prevalence rates of uveitis in patients with JIA are highly variable throughout the world, ranging from 3.4 to 16% [9] [14] [17] [20] [23] [31]-[38]. In a large multiracial Canadian cohort of patients with JIA observed that, those of European descent had a 3- to 4-fold increased risk of developing uveitis compared with those of non-European origin [9]. The highest prevalence is reported in Northern (19.1%) and Southern Europe (18.8%), the lowest in and Latin America (6.4%), Africa, the Middle East (5.9%), and Southeast Asia (5.0%) [39]. A recent study from Japan reported a uveitis prevalence of 6.1% among JIA patients [35]. Lower rates of uveitis have been reported in Southeast Asian countries, where oligo JIA has been less commonly recognized (18.5% - 37.1% of overall JIA) which has been historically associated with the higher frequency of uveitis than other JIA subtypes [17] [18] [23] [36] [37]. Accordingly, higher rates of JIA-associated uveitis have been observed in Europe and North America, where oligo JIA (30% - 60% of overall JIA) predominates over other categories [1] [14] [20] [22] [31] [32] [39]. It is still unclear whether the increased risk of developing uveitis in those of European ancestry could be attributable to ethnicity per se or to higher rates of oligo JIA categories, female sex, ANA positivity or any combination of these in European JIA patients [40]. Low vitamin D may also contribute to the aforementioned differences in uveitis prevalence between geographic regions with Northern countries having the highest uveitis rates among JIA patients because of lack of sun exposure in these areas [41]. Vitamin D deficiency is associated with multiple autoimmune/inflammatory diseases which may increase the risk of an inflammatory condition like uveitis [42].

In this study, we observed male predominance of 61.5% amongst JIA with uveitis patients, whereas a Turkish study found a female predominance of 58.8% [6]. This variation of sexual predominance may be due to ethnic differences, immunogenetic, environmental factors or sociocultural contexts where the male child gets more attention and care [6] [29].

Our study revealed that the mean duration between the onset of arthritis and uveitis was 1.9 years. This finding was similar to the study done by Sahin *et al*. (2021) where the mean duration between onset of arthritis and uveitis was 1.8 years. This study observed that the majority of the patients had uveitis in both eyes 92.3% and only 7.7% cases had unilateral uveitis. Turkish multicentered study done in 2021 also observed predominantly bilateral uveitis 55.2% and 44.8% unilateral uveitis [6]. We found that all the cases with uveitis were anterior uveitis. Sahin *et al*. (2021) also observed that anterior uveitis was present in the majority (76%) of cases [6].

In this retrospective study, we observed that among patients of JIA-associated uveitis, the majority of the cases were oligo JIA (53.8%), followed by ERA 30.8%, Poly JIA RF(−) 7.7% and systemic JIA 7.7%. Saurenmann RK *et al*. (2007) and Angeles-Han ST *et al*. (2013) reported that oligo JIA had the highest rate of uveitis, followed by those with ERA and RF-negative polyarticular JIA [9] [38]. A

multicentered study recently done in Türkiye in 2021 also showed that oligo JIA patients had the highest frequency of uveitis followed by ERA and poly JIA RF(−) patients [6]. The frequency of uveitis in any JIA cohort seems to correlate with the incidence of the oligo JIA category in that cohort and is rare in patients with polyarticular JIA RF(+) and systemic JIA [14].

Our study revealed that 15.4% JIA associated uveitis patients had ANA positivity and 23% had HLA B-27 positivity. Sahin *et al*. 2021 demonstrated that 48.2% of JIA patients with uveitis had ANA positivity and 33.3% had HLA B-27 positivity. This high frequency of ANA positivity among Turkish patients could be associated with their higher frequency of Uveitis 6.8% among JIA patients. There is a possibility that higher frequency of ANA positivity resulted in higher incidence of uveitis in European JIA patients [6]. Although another population-based Nordic cohort study showed that there was no significant difference in ANA positivity among JIA associated with uveitis group and JIA without uveitis group, but they observed a significant difference in HLA B-27 positivity between the two groups [43]. The exact relation between ANA positivity and uveitis is still unknown. However, B-cells and fully differentiated plasma cells are characteristic of the inflammatory ocular cellular infiltrate in JIA-associated uveitis. The high prevalence of ANA positivity in these patients suggests a role of B-cell dysregulation in disease pathophysiology [41].

In our study, we found that all JIA with uveitis patients were treated with topical steroid, 92.3% of cases were treated with methotrexate, 30.8% of patients with sulfasalazine and 7.7% of cases were managed with adalimumab. Sahin *et al*. (2021) described that most of the uveitis patients (38.2%) were treated with TNF-α inhibitors, 17.6% methotrexate, 11.8% patients with azathioprine & sulfasalazine and lastly 8.8% patients were treated with tocilizumab [6].

In this retrospective study, ocular complications following uveitis associated with JIA were band keratopathy 23.1%, posterior synechiae 15.4% and cataract 15.4%. Rypdal *et al*. (2020) in a Nordic study observed cataract 23.7%, glaucoma 22.2%, synechiae 14.1%, macular edema 6.7%, band keratopathy 6.7%, epiretinal membrane 3%, hypotony 3%, phthisis 3% [43]. Turkish study on uveitis associated with JIA found cataract 11.8% and band keratopathy 2.9% of cases [6]. These differences in ocular complications in various regions could be due to variations in frequency and severity of uveitis amongst JIA cases, ethnicity, genetic inheritance, delay in diagnosis and beginning of treatment of JIA and uveitis and lack of ophthalmological follow-up in due time.

We are aware of the possible limitations associated with the retrospective design of this cohort study and because the data were collected from the perspective of paediatric rheumatologists, complications and characteristics of uveitis flares may have been under-represented in this study. Outcome measures such as visual acuity improvements and quality of life assessments after treatment were also not recorded in our paediatric rheumatology department electronic database. Further prospective cohort studies in the future in collaboration with ophthalmologists might mitigate these limitations inherent to this retrospective study.

5. Conclusion

In this study, we observed that JIA patients developed uveitis at a lower frequency compared to other European studies. Uveitis was associated with other ocular complications, highlighting the importance of strict adherence to periodic ophthalmological follow-up.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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