Research Article
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Juvenile idiopathic arthritis-associated uveitis: the experience in Libya

Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease. The development of associated uveitis represents a significant risk for serious complications, including permanent loss of vision. Initiation of early treatment is important for controlling JIA-uveitis, but the disease can appear asymptomatically, making frequent screening procedures necessary for patients at risk. As our understanding of pathogenic drivers is currently incomplete, it is difficult to assess which JIA patients are at risk of developing uveitis. In the present study, we described the prevalence and clinical profile of JIA-associated uveitis and out come among children in the Libyan clinical settings.

Methods: A total of 90 JIA patients who fulfilled International League of Associations for Rheumatology (ILAR) diagnostic criteria were included in this retrospective study. The data collected were age, gender, age at disease onset and at diagnosis, and follow-up duration. Duration from JIA diagnosis to uveitis diagnosis. Antinuclear antibody (ANA), rheumatoid factor (RF), and human leukocyte antigen B-27 were evaluated for each patient.

Results: A total of eight uveitis cases were identified among the 90 JIA cases, which gives a prevalence of 8.9%. All cases were females (100.0%), the majority were Libyans (87.5%), and their mean age was 12.3 (SD=4.3) years old. The mean age at JIA onset for this group was 5.3(SD=2.3) years old and that for JIA diagnosis 6.2 (SD=2.6) years old, with an average duration of JIA of 6.8 (SD=3.7) years. The most common JIA subtype in this group was oligoarthritis (50%), followed by poly arthritis (37.5%). The majority of the cases had a negative rheumatoid factor test (75%), and ANA was positive only in 1 of 7 valid cases (14.3%).

Conclusion: Better recognition of uveitis in JIA is required to improve its outcome and avoid serious complications.

Keywords: libya, north africa, jia, children, uveitis

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Introduction

Juvenile idiopathic arthritis is a common rheumatic disorder in children, with a prevalence of 16–150 per 100,000 annually. With varying clinical characteristics, disease course, and associated outcomes. The occurrence of uveitis in JIA accounts ~75% of all pediatric anterior uveitis cases.[1]

Uveitis is the most extraarticular involvement seen overall in JIA patients. It can be a chronic anterior, recurrent anterior, acute anterior, or anterior uveitis with vitritis.[2,3] Chronic anterior uveitis is usually silent, most frequently associated with oligoarticular and rheumatoid factor (RF) negative polyarticular categories of JIA; Patients with systemic JIA or RF-positive juvenile arthritis rarely develop uveitis. It is reported that it exists in the group of ANA positive oligoarticular JIA patients and 80% are girls. Girls more frequently develop JIA-associated uveitis as compared with boys.[2,3] However, due to the chronic course of this disease may lead to severe sight threatening complications such as synechiae, cataracts, and glaucoma when not successfully controlled by therapy. [1]

The management of uveitis in JIA is based on controlling the symptoms and preventing ocular complications, typically includes topical glucocorticoids. In those who are refractory to or dependent on topical glucocorticoids, they can be used immunosuppressive drugs, as the usual first-line systemic immunosuppressive agent is Methotrexate, followed by tumor necrosis factor inhibitor (TNF) biologics, particularly the monoclonal antibodies infliximab and adalimumab.[1,2,4–9]

Since the introduction of biologic agents may include anti-TNF' agents revealed a great advance in patients with a high risk of developing ocular complications and rapid control of ocular inflammation.[1,10–12]

An ophthalmologist should routinely screen all children with JIA, including new diagnosis of uveitis and new diagnosis of uveitis with any ocular complication. Early recognition and rapid therapeutic intervention of uveitis could prevent any complication.[1,2] Therefore; the Purpose of this current study is to describe the clinical, serological characteristics, treatment and outcomes of children diagnosed by JIA associated with uveitis. Since no current data are available in JIA associated uveitis in Libya.

Objectives

To identify the demographic, clinical pattern, serological and therapeutic for uvietis among children diagnosed with JIA in Tripoli-Libya, also to compare the clinical characteristics of children who developed uveitis with those who did not develop uveitis in JIA diagnosed children, and determine the association between these characteristics and having uveitis.

Methods

Current study is a part of another research that was designed to identify subtype patterns of Juvenile idiopathic Arthritis (JIA) in the Libyan clinical settings, focusing on phenotypes of JIA. The study was conducted at a pediatrics rheumatology clinic in Tripoli Children's

Hospital, whereby the medical files of all JIA cases presented in the period from January 2009 to January 2020 were retrospectively reviewed and were extracted. In this present paper, we focused on JIA associated uveitis, and thus data relevant to the clinical characteristics of uveitis of all confirmed uveitis cases were considered. The uveitis in JIA is the outcome variable, and was defined as a dichotomous variable (uveitis and no uveitis), and it was based on having at least one episode of uveitis after being diagnosed with JIA based on ophthalmic examination of all JIA cases every 3 months.

Data analysis paragraph

We used (SPSS), version 26 to run the analysis, descriptive analysis was done and statistics were presented as numbers and percentages for the categorical data and mean and standard deviation (SD) for continuous data, or median and interquartile range were used to summarize the numerical variables as appropriate to their distribution. Because the Chi-square test assumptions were violated, Fisher's exact test, or the maximum likelihood ratio Chi-square test were used as appropriate to size of the contingency table to test the association between the outcome variable; uveitis in JIA status (uveitis and no uveitis), and the categorical independent variables. The difference in each numerical variable between JIA cases who have uveitis and those who do not have uveitis was tested using the independent t test or Mann Whitney test as appropriate to the distribution of that numerical variable. The statistical significance of the findings was based on a p value of less than 0.05.

Results

Ninety children suffering of JIA were considered in the analysis. Table 1 summarizes their most relevant characteristics. The mean age of the patients was 11.9 (SD=4.3) years old, and female comprised 73.3% of the sample. The average duration of JIA was 6.2 years (SD=3.5). Polyarthritis was the most common JIA subtype (38.9%), followed by oligoarthritis (31.1%), and systemic arthritis (21.1%). Out of 83 valid cases, 78 (94.0%) were RF negative, and of 87 cases, 78 (89.7%) were ANA negative.

Table 1 Characteristics of the studied subjects (n=90)

Variable	**f**	**(%)**
Age (years) †	11.9	±4.3
Sex		
Males	24	(26.7)
Females	66	(73.3)
Duration of JIA (years) †	6.2	±3.5
JIA Subtype		
Polyarthritis	35	(38.9)
Oligo-arthritis	28	(31.1)
Systemic arthritis	19	(21.1)
Psoriatic arthritis	6	(6.7)
Enthesitis related arthritis	2	(2.2)
RF (n=83)*		
+ve	5	(6.0)
-ve	78	(94.0)
ANA (n=87)*		
+ve	9	(10.3)
-ve	78	(89.7)

† (Mean± SD), * valid cases (all presented percentages were the valid percentages)

Uveitis was present in eight cases of 90 JIA cases, with the prevalence of 8.9%. Table 2 displays the demographic and clinical characteristics of those cases. All cases of uveitis were females (100.0%), the majority were Libyans (87.5%), and their mean age was 12.3 (SD=4.3) years old. The mean age at JIA onset for this group was 5.3(SD=2.3) years old and that for JIA diagnosis 6.2 (SD=2.6) years old, with an average duration of JIA of 6.8 (SD=3.7) years.

The mean age at uveitis diagnosis was 8.2 (SD=3.7) years old. The median duration from time at diagnosis of JIA till uveitis diagnosis was 1 (IQR=1-1.7) year. 6 patients out of 8 developed a symptomatic uveitis. The course of uveitis was acute in 3 out of 6 cases (50.0%). Anterior uveitis constituted 62.5% of all uveitis types. Two patients presented with unilateral uveitis, while 4 cases presented with bilateral uveitis. Over half of the patients were on follow-up for uveitis for duration of at least 3 months, while the remaining cases (37.5%) had a follow-up duration shorter than one month. Half of the cases had impaired visual acuity. However, it was complicated by cataract and synechiae in 3 cases, band keratopathy in 2 cases.

Treatment profile of the identified uveitis cases is shown in Table 3. All cases were on systematic therapy; and the majority had received it combined with biological therapy (87.5%). All uveitis cases were receiving topical treatments. The majority of the patients were on more than one topical medication, where by 25% were on mydriatics and topical non-steroidal anti-inflammatory drugs (NSAID), and 25% received mydriatics and steroid eye injections. Systemic steroids and methotraxte had been used in 7 children (87.5%), Etanercept was the most popular onetreatment (25%), then Infliximab (12.5%), and Adalimumab (12.5%).

Table 4 compares the demographic and clinical characteristics, of JIA cases who have uveitis and those who did not develop uveitis. None of the studied characteristics showed to be significantly associated with having uveitis in this bivariate analysis. All uveitis cases were among females, however no statistically significant association found between sex and having uveitis in JIA (p=0.103). JIA patients who developed uveitis had a lower mean age at JIA onset (mean=5.3, SD= 2.3) than those who did not have uveitis (mean=5.8, SD= 3.5), but the mean age at onset difference was not significant (p=0.562). Patients with uveitis had been diagnosed as JIA at a younger age (mean=6.2, SD= 2.6) than those who did not develop uveitis (mean=7.0, SD= 3.8), and again the mean difference of the age at JIA diagnosis between the two groups was not statistically significant (p=0.567). The mean duration of JIA in patients with uveitis was longer (mean=6.8, SD=

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3.7) than that in non-uveitis patients (mean=6.2, SD= 3.5), but this mean difference was not statistically significant (p=0.621). Parallelly, the median duration of JIA follow-up in uveitis patients was longer (Mdn=5.8, IQR= 3.2-9.2) than that in in non-uveitis group (Mdn=4.1, IQR= 3-7.0), but the median difference was not statistically significant (p=0.215).

Table 2 Demographic and clinical profiles of JIA-Uveitis cases (n=8)

Variable	f	(%)	Range
Age (years) †	12.3	±4.6	(6-20)
Sex			
Females	8	(100.0)	
Males	0	(0.0)	
Nationality			
Libyan	7	(87.5)	
Non-Libyan	1	(12.5)	
Age of onset of JIA (years) †	5.3	±2.3	(2.6-10)
Age at JIA diagnosis (years) †	6.2	±2.6	(3-11)
Time from age of onset to age of diagnosis (years)‡	0.75	(0.3-1.7)	(0.2-20)
Duration of JIA (years) †	6.8	±3.7	(3-13)
Duration of JIA follow-up (years) ‡	5.8	(3.2-9.2)	(3-10)
JIA Type			
Oligo-arthritis	4	(50.0)	
Polyarthritis	3	(37.5)	
Psoriatic arthritis	1	(12.5)	
Systemic arthritis	0	(0.0)	
Enthesitis related arthritis	0	(0.0)	
ANA (n=7)*			
+ve	1	(14.3)	
-ve	6	(85.0)	
RF			
+ve	2	(25.0)	
-ve	6	(75.0)	
Age at diagnosis of uveitis†	8.2	±3.7	(5-15)
Duration from JIA diagnosis to uveitis diagnosis	1	(1-1.7)	(0.8-8)
Uveitis Characteristic (n=7)			
Symptomatic	1	(14.3	
Asymptomatic	6	(85.7	
Uveitis course (n=6) *			
Acute uveitis	3	(50.0	
Chronic uveitis	2	(33.3	
Recurrent uveitis	1	(16.6	
Types of Uveitis			
Anterior	5	(62.5	
Posterior	2	(25.0)	
Not classified	1	(12.5)	
Site of Uveitis (n=6)*			
Bilateral	2	(33.3)	
Unilateral	4	(66.6)	
Duration of follow-up for uveitis			
No follow-up	0	(0.0)	
≤ 1month	3	(37.5)	
1 to <3 months	0	(0.0)	
≥3 months	5	(62.5)	
Visual outcome (Visual Acuity)			
Good visual acuity	4	(50.0)	
Impaired vision	4	(50.0)	
Uveitis complications			
Yes	5	(62.5)	
Cataract +synechiae	3	(37.5)	
Cataract +synechiae +band keratopathy	2	(25.0)	
Blindness	0	(0.0)	
No	3	(37.5)	

*Valid cases, † (mean, SD), ‡ (Median, IQR)

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Table 3 Medications profiles of JIA-Uveitis cases (n=8)

Type of Medication	**f**	**(%)**
Systematic therapy	8	(100.0)
Systemic therapy only	1	(12.5)
Systemic and Biological therapies	7	(87.5)
Systematic therapy profile (Alone or combined with biological) (n=8)		
Systemic steroid and Methotrexate	7	(87.5)
All (Systemic steroids, Methotrexate, Leflunomide, Hydroxychloroquine, sulfasalazine)	1	(12.5)
Biological therapy profile (all combined with systemic) (n=7)		
Etanercept	2	(25.0)
Infliximab	1	(12.5)
Remsima	1	(12.5)
Etanercept and Infliximab	1	(12.5)
Tocilizumab and Adalimumab (Humira)	1	(12.5)
Etanercept, Infliximab and Adalimumab	1	(12.5)
Topical medications profile	8	(100.0)
Mydriatics	1	(12.5)
Mydriatics+ Topical non steroid (NSAID)	2	(25.0)
Mydriatics+ Steroid eye injections	2	(25.0)
Mydriatics+ Topical non steroid (NSAID)+ Steroid eye injections	1	(12.5)
Unknown / Others	2	(25.0)

Table 4 Comparison of demographic and clinical characteristics of JIA cases with and with no uveitis (n=90)

Variable	**Uveitis**		**No uveitis**		**P**
	F	**(%)**	**f**	**(%)**	
All	8	(8.9)	82	(91.1)	
Age (years)	12.3	±4.6	11.8	±4.3	0.478[a]
Sex					
Males	0	(0.0)	24	(100.0)	0.103[†]
Females	8	(12.1)	58	(87.9)	
Nationality					
Libyan	7	(8.0)	80	(92.0)	0.246[†]
Non-Libyan	1	(33.3)	2	(66.7)	
Age of onset of JIA (years)	5.3	±2.3	5.8	±3.5	0.562[a a]
Age at JIA diagnosis (years)	6.2	±2.6	7.0	±3.8	0.567[aa]
Time from JIA onset to JIA diagnosis	0.7	(0.3-1.7)	0.5	(0-2)	0.454[b]
Duration of JIA (years)	6.8	±3.7	6.2	±3.5	0.621[a]
Duration of JIA follow-up (years)	5.8	(3.2-9.2)	4.1	(2.9-7)	0.215[b]
JIA Type*					
Oligo-arthritis	4	(14.3)	24	(85.7)	0.297[‡]
Polyarthritis	3	(8.6)	32	(91.4)	
Systemic arthritis	0	(0.0)	19	(100.0)	
Psoriatic arthritis	1	(16.7)	5	(83.3)	
Enthesitis related arthritis	0	(0.0)	2	(100.0)	
ANA (n=87)					
+ve *	1	(11.1)	8	(88.9)	0.548[†]
-ve	6	(7.7)	72	(92.3)	
RF (n=83)					
+ve *	2	(40.0)	3	(60.0)	0.071[†]
-ve	6	(7.7)	72	(92.3)	
JIA Medications profile					
Systemic therapy only	1	(2.7)	36	(97.3)	0.154[‡]
Systemic and biological	7	(13.7)	44	(86.3)	
No medications	0	(0.0)	2	(100.0)	

* p<0.25, † Fischer Exact Test, ‡ Exact likelihood ratio Chi-square test, a independent- t test, b Mann Whitney test

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Discussion

This retrospective study was conducted in the Pediatric Rheumatology department at Tripoli Children's Hospital, Tripoli-Libya, which is the only center in Libya dedicated to Pediatric rheumatology diseases in west region. No current data available on uveitis in JIA, in the current study describing the clinical patterns of uveitis in JIA in Libya.

We aimed at this study to identify clinical pattern and outcome of uveitis in JIA and found an overall prevalence of 8.9%% Half of the cases had impaired visual acuity. Regarding complications, cataract and synechiae were the commonest (37.5%), followed by cataract, synechiae and band keratopathy in a quarter of cases with no of blindness.

in our study uveitis was diagnosed in 8 patients with low frequency (8.9%), were similar to other studies in India and Costa Rica with low rate 2-3% and contrast to reports in Australia with a high of 38%.[12–16] While in US, the frequency has varied from a low of 3.4% to a high of 17.2%, in the percentage of patients with oligoarticular JIA compared with other subtypes of JIA.[12,17–20]

We found that patients with oligoarticular JIA had the highest rate of uveitis 4 cases (50%), followed by patients with RF- negative polyarticular JIA 3 case (37.5%). The lowest rate of uveitis one case (1%) was seen in patients with psoriatic or RF-positive JIA, which were similar to other reports.[21–24]

In our study, univariate analysis demonstrated that uveitis was all were females and associated with ANA negativity not like other studies. However. The laboratory profile was found to be the most common serological findings among children with JIA associated uveitis. ANA was negative among 85% of cases, which was almost not like other studies.[22–26] However. There was no correlation between uveitis and ANA positive and confirmed that in our study, but there was female predominance similar to previous studies that uveitis develops more in females than males.[25,27–29]

Topical glucocorticoids used in our study as initial treatment. Methotrexate.Anti-TNF-agents adalimumab, infliximab, etenrecpt were used when is needed for the management of uveitis.were used in7 cases out of 8 patients (86.3%). The great benefits of anti-TNF agents have been reported elsewhere.[29,30]

Immunosuppressive treatment should be considered for children with JIA-related uveitis who have uncontrolled uveitis despite prolonged high-dose topical treatment, especially if they already have synechiae.[31,32] Methotrexate is our first-line systemic treatment in these situations, and if that fails we turn to biological treatment TNF' blockers, preferably infliximab. [31]

The most common complications that occurred in our study were cataracts (62.5% of patients) synechiae and band keratopathy. While in other studies found band keratopathy, a complication seen in only 14% of our patients, to be the most common.[33] Overall, the rate of complications was rather low in our cohort compared with other reports showing complication rates of up to 90%.[3,27,34] We confirmed that the reasons of lower complication rates and better visual outcome in our study may be the more frequent use of systemic immunosuppressive agents (particularly methotrexate and anti- TNF' agents), as well as biological treatment (Etanercept, Infliximab and Adalimumab) and routinely screened by an ophthalmologis in children who are at risk of vision problems.

Conclusion

The low rate of uveitis in JIA, more female predominance with ANA negativity in young onset oligoarticular JIA, not ANA positivity. Treatment with biological agents is important for decreasing the number of uveitis and ocular complications.

Recommendations

Firstly it was a single center retrospective cohort study that subjected to bias. Secondly, Future studies are necessary to clarify the risk factors and the role of other therapeutic alternatives in treatment.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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