INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

PREVALENCE AND COMPARISON OF UVEITIS IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS WITH POSITIVE AND NEGATIVE ANTI-NUCLEAR ANTIBODIES AT A TERTIARY CARE HOSPITAL

Original Research

Ayesha Murtaza[1], Shafiqur Rehman[1], Faiza Ghuman[1], Tabe Rasool[2], Wajid Ali[1], Arshad Ali Bhutto[1], Rabia Yamin[3], Erum Ahmad[2], Sajid Atif Aleem[4]
[1]Jinnah Postgraduate Medical Centre (JPMC)
[2]Dow University of Health Sciences (DUHS)
[3]National Institute of Child Health (NICH)
[4]Jinnah Sindh Medical University (JSMU)
Corresponding Author: Sajid Atif Aleem, Jinnah Sindh Medical University Karachi, Pakistan, sajid.aleem@jsmu.edu.pk

Conflict of Interest: None
Grant Support & Financial Support: None
Date Submitted: 07-10-24
Date Published: 21-10-24

Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is the most common pediatrics rheumatic disease, with uveitis as a masquerading and severe extra-articular manifestation causing major incidence of ocular morbidity if left untreated. JIA patients with ANA (Anti-Nuclear Antibodies) positivity have an elevated likelihood of uveitis. Recognizing this relationship is important, to prevent complications in early life. The aim of this study was to compare the prevalence of uveitis in JIA patients with positive and negative ANA as a reminder for screening timely detection, and intervention.

Methods: A cross-sectional study conducted at the Department of Rheumatology at JPMC Karachi over a period of six months. The study population consisted of children younger than 16 years age, suffering from Juvenile Idiopathic Arthritis (JIA) were included in the study. ANA levels were measured using immunofluorescence. Uveitis was diagnosed when slit lamp examination showed inflammation of the anterior and posterior uveal layers (iris, ciliary body, vitreous, retina, and choroide). Uveitis laterality was reported as right, left, or bilateral. Clinical parameters determine uveitis type (anterior, middle, or posterior). SPSS version 26.0 was used to analyze the data. Descriptive statistics in terms of Mean± SD and frequency were calculated.

Results: The mean age of the patients was 10.31 ± 3.46 years among them 37 patients (56.9%) being male, and 28 patients (43.1%) are female. The most frequent symptom was joint pain, present in 96.9% of the patients, followed by joint swelling (73.8%). Morning stiffness was reported by 69.2%, and fever in the past from 35.4 %. Rash was seen in only 9.2% of patients, and weight loss was reported by 15.4%. Among 65 individuals, 27 (41.53%) tested positive for ANA, with uveitis present in 15 (23.1%). In contrast, only 3 (4.6%) of the 38 (58.46%) ANA-negative patients had uveitis (p=0.0001).

Conclusion: It is to be concluded that the strong relationship between ANA and uveitis in JIA was noted. Moreover, the results emphasize the importance of screening, especially with ANA positivity as untreated uveitis can cause considerable morbidity. Further studies of other potential risk factors, e.g., sex and genetic background, are needed for establishing screening and treatment protocols for JIA-associated uveitis.

Keywords: Anti-Nuclear Antibodies, Autoimmune Diseases, Juvenile Idiopathic Arthritis, Pediatric Rheumatology, Risk Factors, Screening Protocols, Systemic Inflammation, Uveitis Development, Visual Complications, Youth Arthritis.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most frequent pediatric rheumatic disorder affecting 1.6–23 per 100,000 children (1). It is described as arthritis of unknown etiology with inflammation of at least one joint for a duration exceeding 6 weeks prior to synovial fluid is explored (2). The International League Against Rheumatism (ILAR) Classification (3) indicates that there are seven mutually exclusive categories of JIA manifestations. The most common is oligoarthritis, defined by chronic arthritis involving four or fewer joints during the first 6 months of disease (4). The most common extra-articular complication of JIA is uveitis, which is manifested in 11.6–30% of patients (5). Based on the layers of inflammation, it can be categorized as anterior uveitis (iris and ciliary body), intermediate uveitis (vitreous), posterior uveitis (choroid and retina) or panuveitis involving all three layers of the uveal tract (6).

The principal manifestations of uveitis are pain, tearing, redness due to vascular dilation in the white part of the eye (sclera), photophobia and blurred vision. If left untreated, uveitis can lead to serious complications, including permanent vision loss. The most consistent predictor of uveitis development in JIA patients is the presence of Anti-Nuclear Antibodies (ANA), with B-cell dysregulation frequently suspected in ANA-positive cases (7). This is because an ocular inflammatory infiltrate in these patients contains B cells and plasma cells. The involvement of antinuclear antibody (ANA) and the uveitis features in JIA-associated uveitis have been widely studied.

ANA positivity in patients with JIA was 64.7% and their rate of uveitis development was found to be 6.8%, according to a study by Sahin et al. Further, 47% of enrolled patients exhibited bilateral eye involvement and anterior uveitis (76%) was the most common clinical form seen in these cases (8). Noves et al. studied the incidence of Uveitis in patients with JIA and discovered a prevalence rate for uveitis at all stages. Observational Study on ANA-positive and Negative JIA (OSNAJ) showed that uveitis is more common in ANA positive than negative patients with 20% vs.9.09%, respectively (9). Ali et al. reported that uveitis in JIA patients was more common in males (61.5%), affected both eyes in 92.3% of cases, was localized as anterior uveitis in 100% of cases, and had a mean onset duration of 1.9 ± 1.7 years (10). Kim et al. assessed JIA-associated uveitis and found that 9.8% of JIA patients had uveitis, 46.7% were ANA-positive, and the mean visual acuity (logMAR) at presentation was 0.149 ± 0.355 (11). The literature clearly indicates that uveitis is a common extra-articular manifestation of JIA, and ocular examination must be an essential component of the diagnostic workup for JIA. Since the disease often appears asymptomatically, frequent screening is crucial, particularly for high-risk patients (12-15).

METHODOLOGY

A cross-sectional study conducted at the Department of Rheumatology at JPMC Karachi over a period of six months. The study population consisted of children younger than 16 years, either gender suffering from Juvenile Idiopathic Arthritis (JIA), characterized by the presence of arthritis in one or more joints for at least six weeks with other causes being ruled out were included in the study. Participants were selected through nonprobability consecutive sampling technique. Patients with secondary causes of arthritis including septic arthritis, rheumatic disease, reactive arthritis or history of hemophilia, recent joint trauma autoimmune conditions like SLE and active malignancies like Leukemia were excluded from the study.

Informed consent was obtained from the parents or guardians, and baseline demographic and clinical information—including age, gender, and symptom duration—was recorded using a predefined form. Anti-Nuclear Antibody (ANA) levels were assessed using the immunofluorescence technique. A positive ANA result was defined as a titer of ≥ 1:160 on at least two occasions, three months apart.

All patients underwent ophthalmological assessment in order to detect uveitis. Slit lamp examination revealed intraocular inflammation of the anterior and posterior uveal layers (iris, ciliary body, vitreous, retina and choroid), which confirmed a diagnosis of Uveitis. The laterality of the uveitis was recorded and categorized into right eye, left eye or bilateral involvement. The type of uveitis (anterior, intermediate or posterior) was defined according to established clinical criteria.

Visual acuity was assessed at the time of presentation using Snellen's chart, and the results were converted to logMAR equivalents for analysis. All data were securely recorded in a predesigned proforma and analyzed using SPSS version 26.0. Descriptive statistics were calculated for all study variables. The frequency of uveitis in ANA-positive and ANA-negative JIA patients was determined, and comparisons were made between the two groups regarding uveitis characteristics—including laterality, location, duration of onset, and visual acuity—using the Chi-square test or Fisher's exact test. A p-value of ≤ 0.05 was considered statistically significant.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

RESULTS

Table I Demographic Characteristics of the Patients (n=65)

Variable	Frequency%
Gender	
Male	37 (56.9)
Female	28 (43.1)
Age, Mean ± SD= 10.31 ± 3.46 years	
3-10 Years	35 (53.8)
>10 Years	30 (46.2)
Body Mass Index, Mean ± SD= 20.24 ± 4.19 kg/m^2	
13-20 Kg/m^2	37 (56.9)
>20 Kg/m^2	28 (43.1)

The demographic profile of 65 patients is shown in Table I. While 37 patients (56.9%) being male and 28 patients (43.1%) are female. The mean age of the patients were 10.31 ± 3.46 years and divide into two age categories, consisting of 35 patients (53.8%) with an age between 3 to 10 years and the other group constituted from different ages > 10 years accounting for total 30 (46.2%) patients. The Body Mass Index (BMI) is also presented with a mean of 20.24 ± 4.19 kg/m².

Table 2 Clinical Parameters of the Patients (n=65)

Duration of Drug History, Mean ± SD= 24.13 ± 29.21 weeks	
2-25 weeks	44 (67.7)
>25 weeks	21 (32.3)
Joints Pain	
Yes	63 (96.9)
No	2 (3.1)
Joints Swelling	
Yes	48 (73.8)
No	17 (26.2)
Morning Stiffness	
Yes	45 (69.2)
No	20 (30.8)
Fever	
Yes	23 (35.4)
No	42 (64.6)
Rash	
Yes	6 (9.2)
No	59 (90.8)
Weight Loss	
Yes	10 (15.4)

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Duration of Drug History, Mean ± SD= 24.13 ± 29.21 weeks	
No	55 (84.6)
Pedal Edema	
Yes	8 (12.3)
No	57 (87.7)
Decrease Vision	
Yes	7 (10.8)
No	58 (89.2)
Red Eye	
Yes	3 (4.6)
No	62 (95.4)
Enthesitis	
Yes	9 (13.8)
No	56 (86.2)
Anorexia	
Yes	8 (12.3)
No	57 (87.7)
Lymphadenopathy	
Yes	12 (18.5)
No	53 (81.5)
Hepatomegaly	
Yes	7 (10.8)
No	58 (89.2)
Splenomegaly	
Yes	19 (29.2)
No	46 (70.8)
ANA Profile	
Positive	27 (41.5)
Negative	38 (58.5)
RA Factor	
Positive	23 (35.4)
Negative	42 (64.6)
Anti CCP	
Positive	22 (33.8)
Negative	43 (66.2)

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Table 2 summarizes clinical parameters of the 65 patients, including drug history, symptoms, and serological findings. Mean time of drug history was 24.13 ± 29.21 weeks; range, 2–130 weeks. There was a drug history of 2-25 weeks in the majority of patients (67.7%). The most frequent symptom was joint pain, present in 96.9% of the patients, followed by joint swelling (73.8%). Morning stiffness was reported by 69.2%, and fever in the past from 35.4 %. Rash was seen in only 9.2% of patients, and weight loss was reported by 15.4%.

Table 3 Laboratory Findings of Patients with or without Uveitis (n=65)

Variables	**Uveitis**		**P-Value**
	Yes, (n=18)	**No**, (n=47)	
Hb, g/dl	11.81 ± 2.08	11.87 ± 1.84	0.899
MCV, fl	85.56 ± 10.37	77.95 ± 11.76	0.019*
TLC, 10^3/L	11.56 ± 2.92	12.53 ± 4.25	0.375
PLT, 10^3/L	379.67 ± 110.79	367.64 ± 89.60	0.652
ESR, mm/hour	66.38 ± 21.60	52.13 ± 25.33	0.039*
CRP, mg/dL	14.19 ± 19.39	13.89 ± 15.24	0.949
SGPT, IU/L	15.22 ± 7.51	16.72 ± 8.23	0.503
B. Urea, mg/dl	39.94 ± 7.84	36.41 ± 10.49	0.201
Creatinine, mg/dl	0.92 ± 0.34	0.76 ± 0.33	0.092

Table 3 reported the laboratory findings in patients with and without uveitis. Among uveitis patients, MCV was significantly higher (85.56 ± 10.37 fl) compared to those without uveitis (77.95 ± 11.76 fl, p=0.019). Furthermore, uveitis patients had a higher ESR (66.38 ± 21.60 mm/hour) than non-uveitis patients (52.13 ± 25.33 mm/hour, p = 0.039). While Hb, TLC, PLT, CRP and creatinine and other parameters did not show significant differences between the two groups.

Table 4 Comparison of Uveitis in Juvenile Idiopathic Arthritis Patients with Positive and Negative Anti-Nuclear Antibodies (n=65)

Uveitis	**ANA Profile**		**O. R (95% C. I)**	**P-Value**
	Positive (n=27)	**Negative** (n=38)		
Yes, (n=18)	15 (23.1)	3 (4.6)	14.583 (3.588 ---- 59.275)	0.0001
No, (n=47)	12 (18.5)	35 (53.8)		

Table 4 compares the incidence of uveitis in JIA patients based on ANA profiles. Of these 65, a total of 27 (41.53%) patients were ANA positive, with uveitis found in 15 (23.1%), compared to only 3 (4.6%) of the 38 (58.46%) ANA-negative patients who had uveitis (p=0.0001). This difference was statistically significant, with an OR of 14.583 (95 % C.I.:3.588–59.275). This high odd ratio indicated that ANA positivity was strongly associated with the risk of uveitis development in JIA.

DISCUSSION

Our research analyzed the relationship between antinuclear antibody (ANA) status and uveitis development in children with juvenile idiopathic arthritis (JIA), observing results consistent with prior literature. Studies continually identify a clear relationship between ANA positivity and increased risk of uveitis, with one study reporting that over 64.7% of ANA-positive patients develop uveitis (8). Another examination indicated a higher incidence of uveitis in ANA-positive patients (20%) compared to ANA-negative patients (9.09%) (9). Kim and associates also confirmed this correlation, emphasizing the importance of ANA testing for monitoring patients and anticipating ocular complications, highlighting the necessity of regular screening to prevent irreversible harm from unseen uveitis (11). Additionally, Ravelli and colleagues presented evidence that ANA positivity predicts uveitis, particularly in younger patients who have a 25% higher risk than older patients (12). Walker and associates echoed this, suggesting that early evaluation and consistent monitoring in ANA-positive patients could prevent sight-threatening uveitis and complications such as cataracts or glaucoma (13).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

In our cohort, ANA positivity was strongly correlated with the development of uveitis (23.1% vs. 4.6% in ANA-negative patients). Noves et al. also established a strong association between ANA positivity and uveitis (9). Furthermore, Carlsson et al. recommended consistent slit-lamp assessments, especially for ANA-positive instances, as an integral part of JIA management (7,16). Among our JIA patients with uveitis, we observed elevated mean corpuscular volume (MCV) and erythrocyte sedimentation rate (ESR) levels, suggesting systemic inflammation involvement. Prior studies have reported similar findings, supporting the theory that such laboratory markers could help identify at-risk groups for extra-articular complications like uveitis (14). However, our results showed that other markers like C-reactive protein (CRP) did not significantly differ between groups, implying that uveitis may develop independently of systemic inflammation.

The consequences of delayed uveitis diagnosis are serious, with potential outcomes including cataracts, glaucoma, or vision loss leading to blindness if left untreated. Research by Carlsson et al. (2021) and Sen & Ramanan (2020) emphasized the importance of frequent and thorough eye exams for ANA-positive patients to prevent such complications (5,7,17). Our findings are in line with these recommendations, stressing the critical need for regular and comprehensive eye evaluations in JIA management. Consistent with Ali and colleagues' 2024 findings, our study also identified anterior uveitis as the most common condition among JIA cases, even though our results indicated a slightly lower frequency compared to previous studies (10).

CONCLUSION

It is to be concluded that the strong relationship between ANA and uveitis in JIA was noted. Moreover, the results emphasize the importance of screening, especially with ANA positivity as untreated uveitis can cause considerable morbidity. Further studies of other potential risk factors, e.g., sex and genetic background, are needed for establishing screening and treatment protocols for JIA-associated uveitis.

REFERENCES

1. Costello R, McDonagh J, Hyrich KL, Humphreys JH. Incidence and prevalence of juvenile idiopathic arthritis in the United Kingdom, 2000–2018: results from the Clinical Practice Research Datalink. Rheumatology. 2022;61(6):2548-54.

2. Al-Mayouf SM, Al Mutairi M, Bouayed K, Habjoka S, Hadef D, Lotfy HM, et al. Epidemiology and demographics of juvenile idiopathic arthritis in Africa and Middle East. Pediatr Rheumatol. 2021;19(166):1-30.

3. Martini A, Lovell DJ, Albani S, Brunner HI, Hyrich KL, Thompson SD, et al. Juvenile idiopathic arthritis. Nat Rev Dis Prim. 2022;8(1):5.

4. Thatayatikom A, De Leucio A. Juvenile idiopathic arthritis (JIA). StatPearls, National Library of Medicine (NLM): Bethesda, MD, USA. 2020.

5. Sen ES, Ramanan A. Juvenile idiopathic arthritis-associated uveitis. Clin Immunol. 2020; 211:108322.

6. Gezgin Yıldırım D, Hasanreisoğlu M, Bakkaloğlu SA. Comparison of pediatric patients with idiopathic uveitis, and uveitis due to juvenile idiopathic arthritis and Behçet's disease. Postgrad Med. 2023;135(1):79-85.

7. Carlsson E, Beresford MW, Ramanan AV, Dick AD, Hedrich CM. Juvenile idiopathic arthritis associated uveitis. Children. 2021;8(8):646.

8. Sahin S, Acari C, Sonmez HE, Kilic FZ, Sag E, Dundar HA, et al. Frequency of juvenile idiopathic arthritis and associated uveitis in pediatric rheumatology clinics in Turkey: a retrospective study, JUPITER. Pediatr Rheumatol. 2021;19:1-10.

9. Noves AT, Cortés JI, García EG, Castro DR, Sanchez LM, Barcena CR, et al. AB1424 clinical variability in patients diagnosed of juvenile idiopathic arthritis with positive and negative antinuclear antibodies (ANA). Ann Rheum Dis. 2023;82(Suppl 1):1940-

10. Ali MA, Haque M, Laila K, Al-Mamun MH, Islam MM, Islam MI, et al. Frequency of uveitis among juvenile idiopathic arthritis patients in a tertiary care hospital of Bangladesh: a retrospective study. Open J Rheumatol Autoimmune Dis. 2024;14(3):144-56.

11. Kim J, Kwon S, Kim KN, Kim HW, Park IW, Cho B-J. Clinical Features and risk factors of uveitis in Korean children with juvenile idiopathic arthritis. 2022.

12. Ramos FO, Zinterl C, Fonseca JE. A lifelong journey: Long-term perspectives on Juvenile Idiopathic Arthritis. Best Practice & Research Clinical Rheumatology. 2024;101984.

13. Angeles-Han ST, Ringold S, Beukelman T, Lovell D, Cuello CA, Becker ML, Colbert RA, Feldman BM, Holland GN, Ferguson PJ, Gewanter H. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis–associated uveitis. Arthritis Care Res (Hoboken). 2019 Jun;71(6):703-16.

14. Rodríguez-García A. The importance of an ophthalmologic examination in patients with juvenile idiopathic arthritis. Reumatología Clínica (English Edition). 2015;11(3):133-8.

15. Wu SR, Kuo HC, Wei CY, Nong BR. The ophthalmologic examination of children with juvenile idiopathic arthritis should be emphasized in Taiwan. Kaohsiung J Med Sci. 2018 Aug;34(8):475-6.

16. Ede K, Shishov M, Wershba E, Goswami N, Gorry S, Joseph M, Mirea L, O'Neil J. Screening for juvenile idiopathic arthritis associated uveitis with laser flare photometry in the pediatric rheumatology office: a prospective observational study. Pediatr Rheumatol. 2024;22(1):22.

17. EL-Shereef RR, Lofty G, Shawkat A. Ocular manifestation of Juvenile Idiopathic Arthritis and its relation to disease activity. J Arthritis. 2014;3(3):137.