Ocular manifestations in paediatric rheumatic diseases: Experience from a paediatric referral hospital

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Abstract

Background: Rheumatic diseases are characterised by inflammation of the joints, muscles, bones and skin. The musculoskeletal system is commonly involved in rheumatic diseases but ocular involvement, which can lead to loss of vision, may be a clue to the diagnosis or may add to the severity of disease. There is paucity of data regarding ophthalmic findings in children with rheumatic diseases, especially in India.

Objectives: To describe the clinical spectrum of ocular manifestations in paediatric rheumatic diseases in a tertiary level paediatric hospital in South India.

Method: A hospital-based cross-sectional, observational study was conducted in which 220 children diagnosed with rheumatic diseases were subjected to complete ophthalmic evaluation between January 2019 and June 2020 and the different ocular manifestations were documented.

Results: Of the 220 children with rheumatic disease, 29 (13.2%) had ocular involvement. Anterior uveitis was the most common ocular finding occurring in 8 (29.6%) cases. Duration of the disease and HLA B 27 had significant association with abnormal ophthalmic findings.

Conclusions: In this study, ocular involvement was present in 13.2% children with rheumatic diseases. Anterior uveitis was the most common ocular finding. Duration of disease and HLA B 27 positivity were significantly associated with abnormal ophthalmic findings.

(Key words**:** Rheumatic disease, Ocular manifestation, Uveitis, Vaso-occlusive retinopathy)

Introduction

Rheumatic diseases are a group of illnesses characterized by inflammation of the connective tissue, usually of autoimmunological origin[1]. It includes juvenile idiopathic arthritis (JIA), juvenile spondyloarthropathies, reactive arthritis, sarcoidosis, systemic lupus erythematosus (SLE), Behcet disease, antineutrophil cytoplasmic antibody associated vasculitides, Sjogren syndrome, undifferentiated spondyloarthropathy and systemic scleroderma[1]. The ocular involvement in rheumatic diseases may result from the ocular inflammation and can cause blurring of vision and visual loss[2]. Almost all anatomical parts of the eye could be targeted by the inflammatory process depending upon the underlying rheumatic disease[3]. The ocular manifestations could be the only or one of the few clues in a difficult to diagnose patient[4]. Not only could ocular inflammation be a sensitive marker for the severity of the systemic condition, but ocular involvement can also antedate exacerbation of an immune reaction in many systemic diseases[5]. Ocular manifestations include conjunctivitis, episcleritis, cataract, glaucoma, scleritis, keratitis, uveitis, retinal vasculitis and optic neuritis[6]. Of these findings, uveitis is the most common manifestation[6]. Due to this variability in presentation, careful monitoring is vital in preventing ocular complications and preserving vision. The diagnosis of ocular inflammation can be difficult and is frequently delayed in children due to limited history, patient compliance and the chronic and insidious nature of several of these diseases[7]. It has been observed that band keratopathy, cataract, glaucoma, cystoid macular oedema, macular ischaemia and amblyopia lead to significant vision loss in up to one third of children extending up to adulthood[8]. Early screening and diagnosis are imperative as these illnesses not only result in significant visual morbidity in children

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but also can be an indicator of systemic inflammation.

Objectives

To describe the clinical spectrum of ocular manifestations in paediatric rheumatic diseases in a tertiary level paediatric hospital in South India.

Method

We conducted a cross-sectional observational study in a tertiary level paediatric hospital from January 2019 to June 2020.

Inclusion criteria: All children aged less than 18 years, diagnosed to have a rheumatologic disease by a paediatric rheumatologist as per International League of Associations for Rheumatology (ILAR) criteria, attending paediatric rheumatology outpatient and inpatient departments were included.

Exclusion criteria: Children with uveitis, scleritis, glaucoma due to causes other than rheumatologic condition, dry eyes due to chemical injuries, ocular cicatricial pemphigoid, active tuberculosis or any other infective aetiology and with any known predisposing factor that accounts for the ocular manifestation were excluded from the study.

Sample size: Based on a study by El-Shereef RE, *et al*[9] where prevalence of ocular manifestations was found to be 27% in their cohort, a sample size of 220 was calculated.

A detailed ophthalmic examination was done in all children by a senior ophthalmologist with experience of managing rheumatological conditions. Children were reassessed if there was an ocular symptom or worsening/onset of new systemic symptoms and abnormal ophthalmic findings were noted (Figure 1).

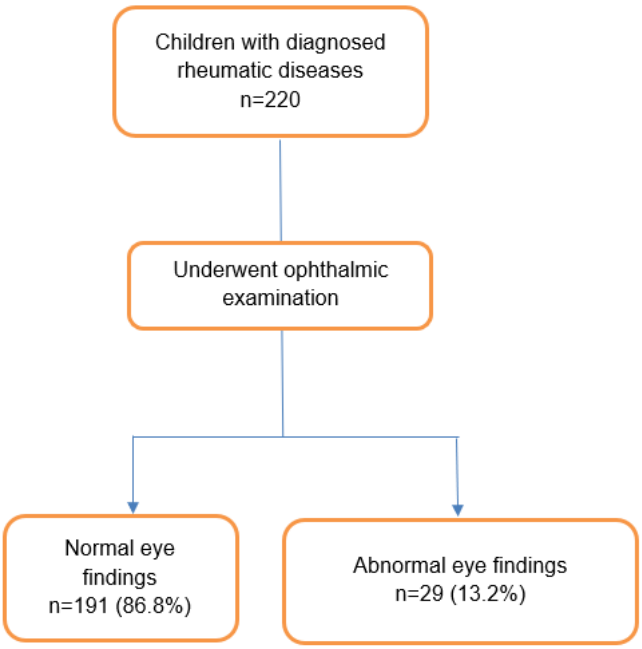

Figure 1: ***Flow diagram of study***

The ophthalmic examination included testing of visual acuity using the Snellen or illiterate E chart (for children below 4 years of age), colour vision testing with pseudo isochromatic Ishihara chart, dry eyes testing with Schimer test using Whatman 41 filter paper or using Tear breakup time test with fluorescein dye. Slit lamp examination for scleritis, episcleritis, keratitis and if required, fluorescein dye were used. Perkins applanation tonometer was used to diagnose glaucoma. Tropicamide drops (0.5%) were used for dilatation of pupils for uveal and retinal examination. Optic coherence tomography (OCT) and fluorescein angiography were performed in evaluation of retinal vasculature. Haematological investigations, complete blood count (CBC) and liver function tests (LFTs) were done. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were done. CRP was done by immunoturbidimetry method and CRP >6mg/dL was considered as elevated. ESR >20mm/hr was considered as elevated. Rheumatoid factor (RF) was done by nephelometry method, antinuclear antibody (ANA) by immunofluorescence assay and human leucocyte antigen (HLA) B-27 was done by microarray deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) method. All investigations were done at the time of initial assessment and diagnosis. CBC, CRP, ESR and

LFTs were repeated at the time of abnormal eye finding documentation. HLA B-27 and RF were done in all cases of suspected JIA, its subtypes, juvenile ankylosing spondylitis, sarcoidosis and suspected Behcet disease.

Ethical issues: The study was approved by the Institutional Ethics Committee of Indira Gandhi Institute of Child Health, Bangalore, India (No. IGICH/ACA/IEC-P-104/2020-21). Written informed parental consent was obtained from all the study participants.

Statistical analysis: Patient information was collected in a predesigned proforma. Data entry and analysis were done using SPSS version 18. The standard statistical tests were applied. Mean (SD) was used for continuous variables. Paired data were analysed using student t-test and proportions were analysed using Chi-square test. The results were considered significant at 5% level of significance ($p< 0.05$).

Results

All children (n=220) underwent ophthalmic examination. Descriptive variables were collected and compared (Table 1).

Table 1: ***Demographic, clinical and laboratory characteristics (n=220)***

Parameters		Normal eye *(n=191)* n (%)	Abnormal eye *(n=29)* n (%)	p-value
Age at onset (years)	0-6	59 (30.8)	11 (38.0)	0.584
	7-12	92 (48.2)	11 (38.0)	
	13-18	40 (21.0)	07 (24.0)	
Duration of the disease (years)	1-3	151 (79.0)	16 (55.0)	0.002
	4-6	36 (19.0)	09 (31.0)	
	7-9	03 (01.6)	02 (06.9)	
	10 or >	01 (0.5)	02 (06.9)	
Presence of	fever	96 (50.3)	10 (34.5)	0.113
	musculoskeletal symptoms	178 (93.2)	24 (82.8)	0.056
	mucocutaneous symptoms	69 (36.1)	17 (58.6)	0.021
	neurological symptoms	08 (04.2)	04 (13.8)	0.034
	cardiovascular symptoms	04 (02.0)	01 (03.4)	0.648
	abdominal symptoms	03 (01.6)	0 (0)	0.772
	hepatosplenomegaly	23 (12.0)	04 (13.8)	0.789
	renal involvement	17 (18.0)	0 (0)	0.094
	CNS involvement	07 (03.7)	01 (03.4)	0.954
	hypertension	09 (04.7)	02 (06.9)	0.615
	anaemia	104 (54.5)	20 (69.0)	0.142
	leucocytosis	67 (35.0)	13 (45.0)	0.309
	thrombocytopenia	08 (04.0)	01 (03.4)	0.851
	elevated ESR	157 (81.2)	24 (82.8)	0.941
	elevated CRP	106 (55.5)	17 (58.6)	0.752
	positive ANA	65 (34.0)	12 (41.4)	0.440
	positive rheumatoid factor	12 (06.3)	0 (0)	0.037
	positive HLA B 27	08 (04.0)	03 (10.3)	0.008
	elevated AST	10 (05.2)	01 (03.4)	0.681
	elevated ALT	10 (05.2)	0 (0)	0.207

CNS: central nervous system, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: antinuclear antibodies, HLA: Human leucocyte antigen, AST: aspartate transaminase, ALT: alanine transaminase

Gender-wise distribution was nearly equal with 115 (51.8%) boys and 105 girls (48.2%) participating in the study. The mean age of the children was 11.21 ± 4.28 years. Mean age of onset of disease was 8.87 ± 4.147 years. Sixty-nine (31.4%) children were symptomatic by the age of 1-6 years and 47 (21.4%) by the age of 13-18 years. The mean duration of disease among the children was 2.45 ± 1.83 years. Only 13 (5.9%) patients reported ocular symptoms. Polyarticular JIA (both RF positive and RF negative) was the most common rheumatological condition observed followed by systemic lupus erythematosus and systemic onset JIA (Table 2).

Table 2: ***Spectrum of rheumatic diseases***

Rheumatological disease	Normal eye *(n=191)* n (%)	Abnormal eye *(n=29)* n (%)	p-value
Systemic lupus erythematosus	34 (17.8)	10 (34.5)	0.036
Juvenile dermatomyositis	12 (06.3)	01 (03.4)	0.546
Polyarticular Juvenile idiopathic arthritis			
Rheumatoid factor +ve	11 (05.7)	0 (0)	0.185
Rheumatoid factor -ve	36 (18.8)	0 (0)	0.011
Systemic onset Juvenile idiopathic arthritis	32 (16.7)	02 (06.9)	0.171
Enthesitis related arthritis	14 (07.3)	02 (06.9)	0.933
Oligoarticular Juvenile idiopathic arthritis	23 (12.0)	05 (17.2)	0.434
Undifferentiated arthritis	01 (0.5)	0 (0)	0.696
Psoriatic arthritis	01 (0.5)	0 (0)	0.696
Sarcoidosis	04 (02.1)	03 (10.3)	0.018
Polyarteritis nodosa	06 (03.1)	0 (0)	0.333
Aorto-arteritis	01 (0.5)	0 (0)	0.696
Behcet disease	0 (0)	04 (13.8)	<0.05
Takayasu arteritis	01 (0.5)	0 (0)	0.696
Juvenile sarcoidosis	0 (0)	01 (03.4)	0.010
Henoch Schonlein Purpura	05 (02.6)	0 (0)	0.378
Reactive arthritis	03 (01.6)	01 (03.4)	0.481
Juvenile ankylosing spondylitis	06 (03.1)	0 (0)	0.378
Linear scleroderma	01 (0.5)	0 (0)	0.696

Twenty-nine (13.2%) children had ophthalmic findings (Table 3). SLE had the most frequent ocular findings followed by oligoarticular JIA (Table 2).

On assessing immunological and haematological parameters, antinuclear antibody (ANA) was positive in 35%, RF was positive in 11.4% and HLA B27 was positive in 9.6% of cases. Elevated ESR was present in 82.3, anaemia in 56.4% and raised CRP in 55.9%. There were combined findings of pan-uveitis and retinal vasculitis, anterior uveitis and cataract, uveitis with posterior synechiae and cataract, ischaemic macular oedema (Figures 2 and 3).

Table 3
Distribution of abnormal ocular findings

Ophthalmic finding	Number (%)
Anterior uveitis	08 (27.6)
Conjunctivitis	02 (06.8)
Pan-uveitis	04 (13.8)
Keratoconjunctivitis sicca	05 (17.2)
Subconjunctival haemorrhage	01 (03.4)
Episcleritis	01 (03.4)
Cataract	01 (03.4)
Proliferative retinopathy	01 (03.4)
Scleritis	01 (03.4)
Uveitis	01 (03.4)
Granulomatous choroiditis	01 (03.4)
Corneal infiltrates	01 (03.4)
Ischaemic macular oedema	01 (03.4)
Pan-uveitis + retinal vasculitis	01 (03.4)
Anterior uveitis + cataract	01 (03.4)

Non granulomatous uveitis in a child with JIA

Uveitis with posterior synechiae and cataract in a child with JIA

granulomatous uveitis in a child with JIA.

Figure 2: ***Uveitis***

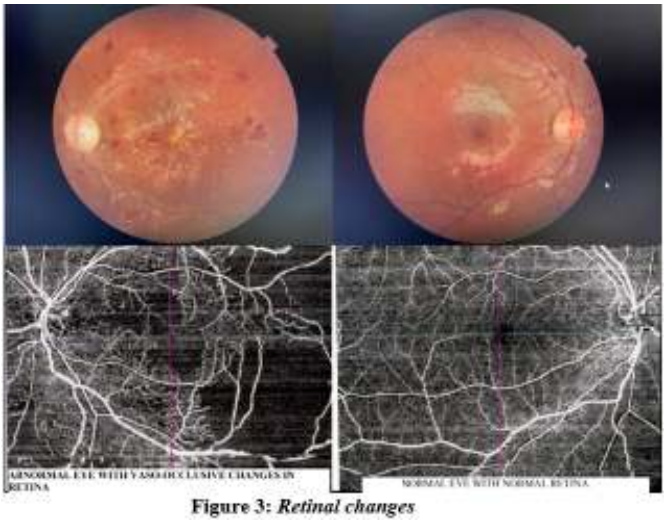

Figure 3: ***Retinal changes***

On correlation of ANA positivity with JIA subsets, we observed that 3 (30%) ANA +ve oligo JIA had ocular involvement; other subsets of JIA with ocular findings were ANA -ve (Table 4).

Table 4: ***Correlation of ANA with JIA and its subtypes***

JIA and subtypes	ANA category	n (%)	Abnormal eye findings *(n=9)*
RF +ve polyarticular JIA	ANA +ve	05 (45.4)	0
	ANA -ve	06 (54.6)	0
RF -ve polyarticular JIA	ANA +ve	10 (27.7)	0
	ANA -ve	26 (72.3)	0
Systemic onset JIA	ANA +ve	02 (6.3)	0
	ANA -ve	32 (93.7)	2
Enthesitis related arthritis	ANA +ve	03 (18.8)	0
	ANA -ve	13 (81.2)	2
Oligoarticular JIA	ANA +ve	09 (32.1)	3
	ANA -ve	19 (67.9)	2
Undifferentiated arthritis	ANA +ve	0 (0)	0
	ANA -ve	01 (100.0)	0
Psoriatic arthritis	ANA +ve	0 (0)	0
	ANA -ve	01 (100.0)	0

ANA: antinuclear antibodies, RF: rheumatoid factor, JIA: Juvenile idiopathic arthritis,

Duration of disease ($p<0.001$) and HLA B27 positivity ($p=0.008$) were found to have statistically significant association with ophthalmic findings (Table 5).

Table 5: ***Factors associated with abnormal ophthalmological findings (n=220)***

Characteristic	Normal eye findings *(n=191)*	Abnormal eye findings *(n=29)*	p value
Female sex – n (%)	98 (51.3)	17 (58.6)	0.297
Duration of disease (years) – Mean ± SD	2.25 ± 1.54	3.79 ± 2.8	<0.001
Elevated ESR – n (%)	157 (82.2)	24 (82.8)	0.94
Elevated CRP – n (%)	106 (55.5)	17 (58.6)	0.75
Positive ANA	65 (34.0)	12 (41.4)	0.28
Positive HLA B27 status	08 (04.2)	03 (10.3)	0.008

Discussion

Majority of the studies of ophthalmic findings in rheumatological conditions were done in adults and there is a paucity of literature regarding ocular manifestation in paediatric rheumatologic conditions in India. The available literature is limited to ophthalmic manifestation in specific conditions[9,10]. Hence this study was done to describe the ocular manifestation in all paediatric rheumatic conditions. In this present study, a total of 220 children diagnosed with rheumatologic conditions were included with a mean age of 11.2 ± 4.28 years. The mean age of children with JIA subsets was 10.6 ± 4.3 years and SLE was 13.5 ± 3.6 years. Similar observations were seen in studies on JIA by El-Shereef RE, *et al*[9] and on SLE by Gawdat G, *et al*[10], though the age group was limited to 6-18 years in study by El-Shereef RE, *et al*[9]. Boys were reported in more numbers in our study (51.8%) whereas 79.3% girls were reported by El-Shereef RE, *et al*[9]. Our study cohort was younger in age distribution, 30% less than 6 years of age, compared to other studies. Early referral to higher centre could be the reason for our younger cohort.

Overall mean age of onset of disease was 8.87 ± 4.147 years. JIA subset of children had a mean age of onset of 8.1 ± 4.1 years and the mean age of onset in the SLE subset was 11.4 ± 3.2 years. Similarly, in a study by El-Shereef RE, *et al*[9] in JIA patients, mean age of onset was 6.9 ± 2.2 years ranging from 4-13 years and in a study by Gawdat G, *et al*[10] mean age of onset of SLE was 8.8 years. The mean duration of rheumatological disease was 2.45 ± 1.8 years whereas El-Shereef RE, *et al*[9] reported a mean duration of disease of 3 ± 3 years. The reason for the shorter mean duration of disease in our cohort could be a combination of all rheumatological diseases contributing to our cohort whereas El-Shereef RE, *et al*[9] reported only JIA cases.

Musculoskeletal symptoms (91.8%) were the most common clinical manifestations complained by our cohort, followed by fever (51.8%) and 5.9% had ocular symptoms. Similarly, El-Shereef RE, *et al*[9] observed musculoskeletal symptoms in 87.5% and fever in 25%, whilst 15% had ocular symptoms.

We found that 29 (13.2%) had ophthalmic findings in our cohort, whereas Hassan KM, *et al*[11] and El-Shereef RE, *et al*[9] had higher frequency of ocular manifestations of 27.6% and 63.7% respectively. This could be due to the subset of disease studied by El-Shereef RE, *et al*[9] (JIA alone) and age group studied as Hassan KM, *et al*[11] was an adult study with a large study population and longer duration of the disease contributing to higher frequency of ocular manifestations. In our study, children with SLE alone contributed to 10 (34%) of ophthalmic findings which is comparable with the study by Gawdat G, *et al*[10] which had 40% of the same in SLE.

In our study, ocular findings were present in 13.2%, more than twice the number of children who complained of ocular symptoms (5.9%). This points towards the unidentified burden of ocular involvement and its complications.

Ravelli A, *et al*[12] observed that ANA +ve oligo arthritis and RF -ve polyarticular JIA have an estimated risk of 30% in developing uveitis. We also found similar observations among the oligoarticular JIA subset, whereas the RF -ve polyarticular JIA subset did not have ocular findings. Regular screening for ocular involvement may be needed in these cases for early detection.

In our study, amongst ocular findings anterior uveitis was the commonest (29.6%) followed by keratoconjunctivitis sicca (18.5%) and pan uveitis (14.8%). Similarly, El-Shereef RE, *et al*[9] found uveitis in 17.3% followed by keratoconjunctivitis sicca in 8.5% and Hassan KM, *et al*[11] found uveitis in 34.3% followed by keratoconjunctivitis sicca in 19.6%. In contrast, Gawdat G, *et al*[10] found that keratoconjunctivitis sicca was the most common finding in the SLE subset alone. A 16-year-old girl with SLE was found to have ischaemic macular oedema with cotton wool spots and tortuous retinal vessels on diagnosis and was found positive for Ku, Sm/RNP antibody in addition to ANA. Workup for APLA in the girl was negative. She underwent optical coherence tomography (OCT) angiography which showed extensive ischaemic areas involving macula and all the quadrants with perivascular leakage. Retinopathy in SLE is a rare finding in children. Similar observations were reported by

Huang G, *et al*[13] and Donnithorne KJ, *et al*[14]. It is observed that 85% of children with arthritis develop uveitis simultaneously or followed by months at the onset and up to 12% of children develop uveitis as the initial presentation of JIA[15].

We found that the duration of the disease had a significant association with the ophthalmic findings ($p<0.001$) comparable with Hassan KM, *et al*[11], El-Shereef RE, *et al*[9] and Gawdat G, *et al*[10]. We also found that there was a significant association between HLA B27 with abnormal ophthalmic findings ($p=0.008$). Behcet disease was found to be have a significant association with abnormal eye findings. We observed that children had ocular findings in the absence of symptoms leading to delay in diagnosis and treatment. Though ACR criteria for SLE do not describe eye involvement[16], ocular manifestation may be an initial feature of SLE in children and delay in diagnosis and subsequent delay in initiation of therapy may lead to vision affecting consequences. Hence inclusion of ocular findings in diagnostic criteria of SLE or on follow up can be advised for early detection and management of ocular complications. Strict adherence to the screening guidelines and a collective approach by paediatrician, paediatric rheumatologist and ophthalmologist will be helpful in management of children with rheumatological diseases and will benefit in preventing disease and treatment related morbidity.

The limitations of this study are that this is an observational study and the outcomes of these conditions, their progression such as remission, recovery, complications are not described. This study can help in planning prospective observational studies to describe the ocular manifestations, their progression and treatment related complications.

Conclusions

In this study 13.2% children with paediatric rheumatic diseases had ocular findings of which anterior uveitis was the commonest (29.6%) followed by keratoconjunctivitis sicca (18.5%) and pan uveitis (14.8%). Duration of disease ($p<0.001$) and HLA B27 positivity ($p=0.008$) were found to have statistically significant association with ophthalmic findings.

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