Ocular manifestations of rheumatic diseases: A hospital based study

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Abstract

Background: Changes in the organ of sight in rheumatic diseases may result from the inflammatory process because of immune-mediated ocular inflammation which causes severe debilitation and visual loss. Therefore by understanding the various ocular presentations of these systemic inflammatory diseases is vital so as to arrive expeditiously at the correct diagnosis and treatment plan with the goal of preserving visual function.

Methods: A cross sectional study was done on patients over a period from November 2014 to September 2015. A total of 102 patients with rheumatic disease were investigated for any ocular manifestations after obtaining informed written consent. ACR(American College of Rheumatology) criteria was used for the diagnosis of Rheumatic Diseases. Ocular investigation for dry eye included Schirmer's test, Tear film break up time test (TBUT) and 1% Rose Bengal test. Positivity for Immunological factors and their association to ocular manifestations statistically analyzed.

Results: The overall incidence of ocular manifestations of the rheumatic disease process in the study was 63.7% (65 cases). Uveitis incidence was 34.3%(35 cases) being the commonest ocular abnormality detected followed by KCS of 19.6%(20cases). The total number of cases with ANA positivity in Rheumatic disease is 22 as in Table 4, those with ocular manifestations and ANA positivity is 16 out of 20 (80%) as in Table 5. Six (50%) of the twelve patients with Keratoconjunctivitis sicca had high Rheumatoid factor titer values by slide agglutination ($\geq$ 1:128). Conversely of the seven patients with high Rheumatoid factor titer values ($\geq$ 1:128), six (85.7%) had Keratoconjunctivitis sicca.

Conclusion: Therefore, following a multidisciplinary approach by ophthalmologists, rheumatologists, physicians and pediatrician would help for an early intervention to preserve vision where possible.

Keywords: Anti-Nuclear Antibody (ANA), Keratoconjunctivitis sicca, Ocular Manifestations, Rheumatic Diseases, Rheumatoid Factor (RF), Uveitis.

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Introduction

Rheumatic diseases constitutes different types of illnesses characterized by the inflammation of the connective tissue, usually an autoimmune disease. It affects people of both sexes, all ethnic groups and ages. Since most of the symptoms of the rheumatic diseases concern primarily the musculoskeletal system[(1)], but ocular involvement in the rheumatic diseases may result from the inflammatory process because of immune-mediated ocular inflammation which causes severe debilitation and visual loss[(2)]. Patients with rheumatological disease have poor follow up with a rheumatologist. Almost all the anatomical parts of the eye could be a target for an immunological reaction depending upon the underlying etiological disease[(3)]. Many ocular complications are indicators of active systemic disease process and some of them are markers of severe and potentially life-threatening systemic involvement[(2)]. Therefore by understanding the various presentations of these systemic inflammatory diseases with regard to the eye is important in order to be able to arrive expeditiously at the correct diagnosis and treatment plan with the goal of preserving visual function.

Materials and Methods

A cross sectional study was done on patients referred from Rheumatology O.P.D. to the Ophthalmology department, of SRM Medical College Hospital and Research Centre, Kattankulatur, Chennai. The study was done irrespective of age, sex, duration of severity of the disease, the presence or absence of ocular symptoms and examined for any ocular manifestations. The study was carried over a period from November 2014 to September 2015. A total of 102 patients with rheumatic disease were investigated for any ocular manifestations after informed written consent. Clearance from the institute ethical committee was obtained. ACR[(4)] (American College of Rheumatology) criteria was used for the diagnosis of the Rheumatic disease.

Inclusion Criteria: All Diagnosed patients of Rheumatic diseases referred by the Rheumatology department.

Exclusion Criteria: Patients with uncontrolled diabetes, hypertension, patients with active tuberculosis or any other infective etiology and with any known

predisposing factor that account for the detected ocular manifestation.

A complete history with regard to the rheumatic and ocular symptoms were obtained from each patient and a detailed systemic and ocular examination was done. Information regarding age and sex was recorded. Ocular examinations included documentation of best-corrected visual acuity, orbital & external eye disease examination, checking of extraocular movements, pupil reflexes, anterior segment examinations with slit lamp biomicroscopy, fundus examination after pupil dilation (with 1% Tropicamide) with indirect ophthalmoscopy & fundus fluorescein angiography were done when needed. Intraocular pressure measurements by Goldmann applanation tonometer and visual field testing by HFA 30-2 was done where required. Further, ocular investigations involved to test dry eye included the tear film adequacy using Schirmer's test, its integrity was analyzed using Tear film break up time test (TBUT) and finally 1% Rose Bengal test was done for ocular surface staining. Also B-scan ultrasonography was done for patients with defective vision secondary to complicated cataract in JRA patients where fundus cannot be seen.

The following investigations were done for all the patients in association with the Rheumatology Department. A complete hematological profile, a steroid work up to rule out conditions (like uncontrolled diabetes, hypertension, active tuberculosis) that could be aggravated by the institution of steroids as a treatment for the ocular condition, assay of immunological parameters like Rheumatoid factor by slide agglutination and Anti-nuclear antibody by FANA (fluorescent anti-nuclear antibody test) was done[5,6]. Therefore, firstly the general objective of this study was to identify different types of ocular involvement in cases of Rheumatic diseases in a rural tertiary care hospital. Secondly, to study age and sex distribution of the patients and to establish a source of comparison for the prevalence of the ocular findings in these Rheumatic diseases in these settings. All data were analyzed using statistical software package SPSS version 21.0. Variables of interest were summarized using descriptive statistics. For categorical variables, frequencies and percentages were used.

Results

Table 1: Ocular Manifestations in Rheumatic Diseases

Ocular Findings	**RA**=31cases	**AS**=30cases	**SLE**=11cases	**PA**=10cases	**RS/ReA**=8cases	**SD**=2cases
Uveitis	6	14 (11 cases ant.uveitis)		6 (4 cases ant.uveitis)	4 (ant.uveitis)	
KCS	12		7			1
Scleritis	5					
Episcleritis	3					
Sclerosing Keratitis	2					
SLE-Retinopathy			3			
SLE-associated Optic Neuritis			1			
PUK	2					
Keratitis	1					
Conjunctivitis				1	1	
Lids						2

RA = Rheumatoid Arthritis**, AS =**Ankylosing Spondylitis**, SLE =** Systemic Lupus Erythematosus**, PA =** Psoriatic Arthritis**, RS/ReA =** Reiter's Syndrome/ Reactive Arthritis**, SD =** Scleroderma, KCS= Keratoconjunctivitis sicca, PUK = Peripheral ulcerative keratitis.

Of 102 patients enrolled in the study, 31 had Rheumatoid arthritis, 30 had Ankylosing Spondylitis, 11 had Systemic Lupus Erythematosus (SLE), 10 had Psoriatic arthritis, 10 had Juvenile Rheumatoid Arthritis, 8 had Reactive arthritis and 2 had Scleroderma. Ocular involvement was seen in 65 patients (63.7%). The demographic pattern of sex and age distribution is shown in Table 2 and Table 3 respectively for different rheumatic diseases examined. The different types of ocular manifestations seen in rheumatic diseases is shown in Table 1, the commonest being Uveitis, 35 cases {(34.3%) 30 as in Table 1 & 5 JRA} followed by KCS, 20 cases(19.6%). The mean IOP was normal. Individual eye presentations of different rheumatic diseases is elaborated in the tables below.

Table 2: Gender Profile of each Rheumatic Disease

Disease Entity	Number of Patients	%	Number of Patients (Male)	Number of Patients (Female)
Rheumatoid Arthritis (RA)	31	30.4	3 (9.7%)	28(90.3%)
Ankylosing Spondylitis (AS)	30	29.4	30(100%)	_
Systemic Lupus Erythematosus (SLE)	11	10.9	1(9.1%)	10(90.9%)
Psoriatic Arthritis (PA)	10	9.8	7(70%)	3(30%)
Juvenile Rheumatoid Arthritis (JRA)	10	9.8	6(60%)	4(40%)
Reactive Arthritis(RS/Re)	8	7.9	8 (100%)	_
Scleroderma (SD)	2	1.8	_	2(100%)
Total	102	100		

Table 3: Age wise distribution of Rheumatic disease

Age Group	Number of Patients						
In Years	RA	SLE	PA	RS/ReA	AS	JRA <16yrs.	SD
01-10	-	-	-	-	-	7(70%)	-
11-20	-	4 (36.3%)	-	-	6 (20%)	3(30%)	-
21-30	2 (6.5%)	5 (45.5%)	3 (30%)	8 (100%)	17 (56.6%)	-	-
31-40	18(58.1%)	2(18.2%)	7(70%)	-	7 (23.3%)	-	2 (100%)
41-50	8 (25.7%)	-	-	-	-	-	-
51-60	2 (6.5%)	-	-	-	-	-	-
> 61	1 (3.2%)	-	-	-	-	-	-

Further, the total number of cases with ANA positivity in Rheumatic disease is 22 as in Table 4, those with ocular manifestations and ANA positivity is 16 out of 20 (80%) as in Table 5. Number of patients without ocular manifestations and ANA positivity is 4. There was a greater incidence of ANA positivity in patients having ocular manifestations of the Rheumatic disease process, than those without them, as in Table 5.

Table 4: Anti-Nuclear Antibody (ANA) Positivity among Rheumatic Disease patients

Rheumatic Disease	Number of patients	Incidence of ANA positivity *Ref 5.*
Rheumatoid Arthritis	31	22.5%(7 cases)
Systemic Lupus Erythematosus, SLE	11	90.9%(10cases)
Scleroderma	2	50% (1 case)
Pauciarticular Type 1 JRA	5	80% (4 cases)
Pauciarticular Type 2 JRA	2	_
Polyarticular JRA	3	_

There was a high incidence of ANA positivity in SLE, Scleroderma and Pauciarticular Type 1 of JRA in the study, Table 4.

Table 5: Anti-Nuclear Antibody (ANA) Positivity with Ocular Manifestations

Ocular Disorder	Number of Patients	Proportion of ANA Positivity
Uveitis	35	22.9%(8 cases)
KCS	20	25%(5 cases)
Retinopathy	3	66.7%(2 cases)
SLE-associated optic neuritis	1	100%(1case)
No abnormality detected	34	11.8%(4 cases)

Juvenile Rheumatoid Arthritis (JRA): In Pauciarticular type 1 JRA patients, there were 5 cases(mean age 7.6yrs) out of which 4 had ANA positivity as in Table 4. The ocular presentations were mixed i.e., 4 had chronic uveitis, 3 had complicated cataract and 2 with band keratopathy. In Pauciarticular type 2 JRA patient, 1 had acute uveitis out of 2 cases(mean age 9.5yrs). There was no ocular involvement in 3 of the cases with Polyarticular JRA patients(mean age 11.3yrs). Among JRA patients, uveitis was seen in 5 cases.

Rheumatoid Arthritis (RA) patients had mixed ocular findings. The commonest ocular abnormality seen is Keratoconjunctivitis sicca 38.7% (12/31) followed by Uveitis 6 cases(19.4%), Scleritis 5 cases (16.1%) and 3 cases (9.7%) as Episcleritis. Five patients had corneal involvement i.e., Sclerosing Keratitis 2 cases (6.4%), PUK 2 cases (6.4%) and Keratitis 1 case (3.2%). One of the PUK patient with KCS feature had corneal thinning with signs of impending perforation where tissue adhesive cyanoacrylate glue was used. While the other patient with PUK without KCS remained stable with conjunctival resection and bandage contact lens use.

Analysis of parameters for KCS**:** All the twelve patients of KCS had moderate grade dry eye as per van Bijsterveld scoring system[7] (after ocular surface staining with 1% Rose Bengal dye). These also tested positive that is moderate dry eye to Schirmer's test and TBUT for dry eye earlier in the examination.

Six(50%)of the 12 patients with KCS has high RF titre value by slide agglutination method (≥ 1:128). Conversely of the seven patients with RF titre values ≥ 1:128, six (85.7%) had KCS.

Table 6: Correlation between the titer values of RF and incidence of KCS

RF Titre Value (by slide agglutination test)	**Patients with KCS**	**Patients without KCS**
1 : 32	2	15
1 : 64	4	2
≥1 : 128	6	1

RF = Rheumatoid factor

Fourteen (46.7%) of the thirty patients examined in Ankylosing spondylitis had uveitis, the commonest being anterior uveitis in our study of 36.7% (11 cases out of 30). All the Ankylosing spondylitis patients were males. Patients with Psoriatic arthritis reported conjunctivitis as 10% (1case), acute anterior Uvetis as 40% (4 cases) and intermediate uveitis as 20% (2cases). The commonest ocular manifestation detected in ten Psoriatic arthritis patients in the study is acute anterior uveitis (40%). It involved 7 males and 3 females in our study.

The incidence of conjunctivitis seen in Reactive arthritis is 12.5% (1 case) and acute anterior uveitis as 50% (4 cases). Whereas, 2 patients had Scleroderma of which one just had lid tightness while other had lid tightness and KCS. Eyelid stiffness was associated with difficulty in lid eversion and a woody feel upon palpation.

Ocular manifestations in SLE patients were seen in 11 cases of which KCS being the commonest, 63.6%(7cases), lupus retinopathy involvement was seen in 27.3%{3cases(2 bilateral moderate lupus retinopathy and 1 unilateral mild lupus retinopathy)} and SLE-associated optic neuritis as 9.1%(1case).While other systemic presentations were malar rash 10 cases, arthritis 6 cases and renal disorder in 2 cases.

For lupus retinopathy afflicted patients with other systemic involvement, a course of intravenous methylprednisolone (1 g daily for 3 days) with oral corticosteroids (prednisolone 1 mg/kg/day) later was given initially. Further it was supplemented with azathioprine. There was significant improvement of vision in two cases(2/3)with moderate lupus retinopathy that is one patient vision improved from 6/24 to 6/9 in right eye and left eye from 6/60 to 6/18.While in other patient vision improved from 6/36 to 6/9 in right eye and left eye from 6/60 to 6/12. Azathioprine was started in these patients under strict haematological monitoring.1 Case with SLE-associated optic neuritis was treated as per the guidelines of the ONTT trial (Optic Neuritis Treatment Trial) where vision in both eyes improved by one Snellen line from 6/60 to 6/36.

Discussion

The magnitude of eye problems associating rheumatic diseases is not well estimated in some population and data concerning its pattern is highly deficient[2]. In our study, ocular manifestations were found in 65 of the 102 (63.7%) patients examined. The overall prevalence of uveitis in our study is 34.3% (35 cases) which is the commonest ocular abnormality detected and is comparable to Birnbaum et al[8] study of 31%. The total number of cases with Anti-Nuclear Antibody (ANA) positivity in Rheumatic disease is 21.6% (22/102) as in Table 4, those with ocular manifestations and ANA positivity is 80%(16/20) as in Table 5. Therefore, it is seen that there is a greater incidence of ANA positivity in patients having ocular manifestations of the Rheumatic disease process, than those without them, as in Table 5. Other Studies have shown similar link of higher ANA positivity in ocular manifestations of rheumatic diseases[5]. Also from the Table 4 above, it is seen that there is a higher incidence of ANA positivity in SLE, Scleroderma and Pauciarticular Type 1 of JRA patients, Marina et al[5] and Solomon DH[6] also explained similar findings that is because of the immunological nature of the disease.

Further, among the Juvenile Rheumatoid Arthritis (JRA) patients in our study, 10% had acute and 40% had chronic uveitis, Kanski JJ[9] mentioned prevalence from 4% to 38%. It was seen that children(<16years) who are at greatest risk of developing uveitis are those with oligoarticular-onset JRA[10]. Our study showed similar findings as above. The period of highest risk for ocular involvement is within 4 years of onset of arthritis, although the risk is never entirely absent. Studies have shown antinuclear antibodies to be strongly associated with chronic uveitis. Therefore, both involvement of pauciarticular JRA with positive antinuclear antibody (ANA) test, have shown strong association of ocular complications as per Wallace CA et al[11] and EL-Shereef et al[12] as also seen in our study, Table 4 & 5.

Chances of developing ocular manifestations in JRA are relatively more common in girls[12] but in our study relative prevalence were little more in boys i.e., 60%(6/10) to girls 40%(4/10). This could be due to under reporting or neglected hospital trips for the girls on account of suburban hospital location or poor care for the girls as compared to boys, as India being a developing country. The typical complications published previously in JRA, included cataract (19-81%), band keratopathy (7-70%) and posterior synechiae (8-75%)[12], our study showed complicated cataract 3 cases (30%) and band keratopathy 2 cases (20%) which is similar to the above study done[12]. The

cataract would have developed secondary to chronic uveitis as complicated cataract.

While in Rheumatoid Arthritis patients in our study, KCS is seen as the most common ocular presentations of 38.7%(12/31), which is comparable to other population-based studies of 28%, Vignesh AP et al[13] and one study showed KCS as 67.7% in RA patients[14]. Studies have shown that ocular complications are more probable among RA patients with elevated titers of RF (Rheumatoid Factor) as in Table 6 or Anti–citrullinated protein antibodies (ACPAs)[15].

In Ankylosing spondylitis, the commonest finding being anterior uveitis of 36.7%(11/30) which is comparable to Zeboulon et al who had mentioned anterior uveitis as 20–30%[16]. The occurrence of AS in our study was seen at younger age, with all of the patients being males, is comparable to the study of Elewaut et al who also showed AS prevalence in the third decade of life with males 2.5-times more commonly affected than women[16]. The commonest ocular manifestation detected in ten Psoriatic arthritis patients in the study was uveitis as 60% (anterior uveitis was 40%) and Chang JH et al reported uveitis as 50%[17]. Our study reported conjunctivitis as 10% (1case) as other patients might have reported after improved conjunctival inflammation, while other studies presented conjunctivitis differently i.e., Lambert et al as 19.6% and Zeboulon et al as 32.7%[17].

In Reactive arthritis, the incidence of Conjunctivitis was 12.5% (1 case) and anterior uveitis as 50% (4 cases) while study by Kiss et al[18] reported anterior uveitis as 92%. The syndrome is more common amongst 20 to 40 years old males[19]. Our study also represented males in the same age group i.e., between 21-30 yrs.

Scleroderma is a rare disease, most of the data regarding ocular involvement consist of single case reports or small case studies, thereby limiting the generalization of the findings to a larger population of patients[20]. We had two patients of Scleroderma of which one just had tightness of lid and other had lid tightness with KCS (50%), Table 1. Eyelid stiffness was associated with difficulty in lid eversion and a woody feel upon palpation. Gomes et al[20] had near similar findings i.e., 51.1% had eyelid skin changes and 48.9% as KCS. They also found a prevalence of lid involvement to be ranging from 29% to 65% in patients and represented younger patients, just as ours in Table 3.

In our study, ocular manifestations in SLE[21] were KCS 7 cases (63.6%) as the commonest, lupus retinopathy as 3 cases (27.3%) and SLE-associated optic neuritis 1 case (9.1%). Studies have shown incidence of KCS as 25-35%[22] and Lupus retinopathy incidence of 7–26%[23] to 29%[24]. ANA positivity rate was higher as in Table 4 and 5 for patients with ocular manifestations.

SLE patients with retinal involvement as in one study which had 77% ANA positivity[25]. Although the frequency of the findings varies as seen above, it depends on the patient population being studied and systemic disease activity[21]. The serologic hallmark of SLE is the presence of ANAs which is highly sensitive and useful screening tool but anti-dsDNA antibody is SLE specific and correlates with disease activity[26].

One case with SLE-associated optic neuritis was treated as per the guidelines of the ONTT[27], which showed some visual improvement as in the results above, as also experienced in the study of Lin et al[28]. Retinopathy in SLE is suggestive of high disease activity during the course of the disease, and hence, is a marker of poor prognosis for survival, that is SLE patients with retinopathy have overall worse prognosis and decreased survival, compared to SLE patients without retinopathy[29]. Therefore, ocular complaints of SLE warrant urgent referral to an ophthalmologist for more detailed assessment and timely institution of systemic therapy which may minimize morbidity from this disease and early rheumatologist intervention would reduce mortality.

Conclusion

This study indicates that ocular involvement is fairly common in rheumatic diseases and there is need for close follow up. Therefore by following a multidisciplinary approach between rheumatologist, ophthalmologist, physicians and paediatrician for the discovery and early management of these ocular manifestations with the goal of preserving visual function. The limitation of this study includes a limited sample of patients visiting one institution which could have introduced health-seeking bias. Hence further studies are required.

Conflict of Interest: None

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