



ORIGINAL RESEARCH PAPER

Rheumatology

OCULAR MANIFESTATIONS OF RHEUMATIC DISEASES: A HOSPITAL-BASED STUDY

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

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ABSTRACT

Background: Ocular manifestations 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 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 June 2019 to March 2021. A total of 100 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 and Tear film breaks up time test (TBUT). Positivity for Immunological factors and their association to ocular manifestations statistically analysed.

Results: The overall incidence of ocular manifestations of the rheumatic disease process in the study was 65%. Uveitis incidence was 35%, being the commonest ocular abnormality detected followed by KCS of 20%. The total number of cases with ANA positivity in Rheumatic disease is 20, those with ocular manifestations and ANA positivity is 16 out of 20 (80%). Six (50%) of the twelve patients with Keratoconjunctivitis sicca had high Rheumatoid factor titre values by slide agglutination or Anti Citrullinated peptide Antibody positive

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

INTRODUCTION

Rheumatic diseases constitute 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 about the eye is important 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 visiting Rheumatology O.P.D. 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 June 2019 to March 2021. A total of 100 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 were used for the diagnosis of the Rheumatic disease.

Inclusion Criteria:

All Diagnosed patients of Rheumatic diseases presenting to OPD

Exclusion Criteria:

Patients with uncontrolled diabetes, hypertension, patients with active tuberculosis or any other infective aetiology and

with any known predisposing factor that account for the detected ocular manifestation.

A complete history regarding 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. Through joint and systemic examination were done.

The following investigations were done for the patients wherever required. A complete haematological profile, a steroid work up to rule out other conditions (like uncontrolled D M, 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, Anti Citrullinated peptide Antibody Assay and Anti-nuclear antibody by FANA (fluorescent anti-nuclear antibody test) was done (5,6)

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, fundus examination after pupil dilation (with 1% Tropicamide) with indirect ophthalmoscopy. Further, ocular investigations involved to test dry eye included the tear film adequacy using Schirmer's test, its integrity was analysed using Tear film break up time test (TBUT).

Therefore, firstly the general objective of this study was to identify different types of ocular involvement in cases of Rheumatic diseases in a 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 analysed using statistical software package SPSS. Variables of interest were summarized using descriptive statistics. For categorical variables, frequencies and percentages were used.

RESULTS

Of 100 patients enrolled in the study, 31 had Rheumatoid

arthritis, 28 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 Systemic sclerosis. Ocular involvement was seen in 65 patients (65%). 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 JIA followed by KCS, 20 cases (19.6%). The mean IOP was normal. Individual eye presentations of different rheumatic diseases are elaborated in the tables below

Table 1: Ocular Manifestations In Rheumatic Diseases

Ocular Findings	RA= 31 cases	AS=30 cases	SLE=11 cases	PA= 10 cases	ReA= 8 cases	SS=2 cases
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			
PUK	2					

RA = Rheumatoid Arthritis, AS =Ankylosing Spondylitis, SLE = Systemic Lupus Erythematosus, PA = Psoriatic Arthritis, ReA = Reactive Arthritis, SS = Systemic Sclerosis, KCS= Keratoconjunctivitis sicca, PUK = Peripheral ulcerative keratitis.

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	3	28
Ankylosing Spondylitis (AS)	28	28	-
Systemic Lupus Erythematosus (SLE)	11	1	10
Psoriatic Arthritis (PA)	10	7	3
Juvenile Inflammatory Arthritis (JIA)	10	6	4
Reactive Arthritis (RS/Re)	8	8	-
Systemic sclerosis (SD)	2	-	2
Total	100		

Table 3: Age Wise Distribution Of Rheumatic Disease

Age Group	Number of Patients						
In Years	RA	SLE	PA	RS/ReA	AS	JIA <16yrs.	SD
01-10	-	-	-	-	-	7	-
11-20	-	4	-	-	6	3	-
21-30	2	5	3	8	17	-	-
31-40	18	2	7	-	7	-	-
41-50	8	-	-	-	-	-	-
51-60	2	-	-	-	-	-	-
> 61	1	-	-	-	-	-	-

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)
Systemic sclerosis	2	50% (1 case)
Pauciarticular Type 1 JIA	5	80% (4 cases)
Pauciarticular Type 2 JIA	2	-
Polyarticular JIA	3	-

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)

Table 6: Correlation Between The Titre 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

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

Juvenile Inflammatory Arthritis (JIA): In Pauciarticular type 1 JIA 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 JIA 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 JIA patients (mean age 11.3yrs). Among JIA 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 ($\geq 1:128$). Conversely of the seven patients with RF titre values $\geq 1:128$, six (85.7%) had KCS

Fourteen (50%) of twenty-eight patients examined in Ankylosing spondylitis had uveitis, the commonest being

anterior uveitis in our study of 39.3% (11 cases out of 28). All the Ankylosing spondylitis patients were males. Patients with Psoriatic arthritis reported conjunctivitis as 10% (1 case), acute anterior Uveitis as 40% (4 cases) and intermediate uveitis as 20% (2 cases). 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.

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.

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 (<16 years) 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 like 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 titres of RF (Rheumatoid Factor) as in Table 6 or Anti-citrullinated protein antibodies (ACPs) (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 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% (1 case) 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 while 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 arrant

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 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.

REFERENCES

1. Brygida Kwiatkowska and Maria Ma li ska. Eye Infection Complications in Rheumatic Diseases, Chp. 10. Institute of Rheumatology. Poland. INTECH;2013:213-230.
2. Manal Yehia Tayel, Nevine Mohannad, Amira Hassan El Gerby et al. Prevalence and pattern of ocular involvement in patients attending Alexandria University, Rheumatology clinic.A Pilot study. International Journal of Advanced Research 2015;3(6):153-158.
3. Nussenblatt MD, Robert B., Whitcup MD, Scott M. Uveitis: Fundamentals and Clinical Practice. 3rd ed. Philadelphia (PA). Mosby;2004:58-68.
4. Aletaha D, Neogi T, Silman AJ, et al: 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/ European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62(9):2569-81.
5. Marina Magrey, Abby Abelson: Laboratory Evaluation of Rheumatic Diseases; August 2010.
6. Daniel H. Solomon. Evidence-Based Guidelines for the Use of Immunologic Tests: Antinuclear Antibody Testing, Arthritis & Rheumatism (Arthritis Care & Research) © 2002, American College of Rheumatology. August 15, 2002; Vol. 47, No. 4:434-444.
7. Van Bijsterveld OP. Diagnostic tests in the Sicca Syndrome. *Arch Ophthalmol*. 1969;82:10-14.
8. Birnbaum AD, Deborah M. Little, Howard H. Tessler, and Debra A. Goldstein: Etiologies of Chronic Anterior Uveitis at a Tertiary Referral Center over 35 Years. *Ocul Immunol Inflamm*. 2011;19(1):19-25.
9. Kanski JJ. Juvenile arthritis and uveitis. *Surv Ophthalmol*. 1990;34:253-267.
10. James Cassidy, Jane Kivlin, Carol Lindsley et al: Ophthalmologic Examinations in Children with Juvenile Rheumatoid Arthritis: *Pediatrics*. May 2006; Volume 117, Number 5:1843-45.
11. Wallace CA, Sherry DD. Juvenile rheumatoid arthritis. In CD Rudolph et al., eds., *Rudolph's Pediatrics*, 21st ed. New York: McGraw-Hill. 2003; chap. 12.4:836-840.
12. EL-Shereef RR, Iofty G, Mohamed AS et al. Ocular Manifestation of Juvenile Idiopathic Arthritis and its Relation to Disease Activity. *J Arthritis*. 2014;3:137.
13. Ammapati Paul Pandian Vignesh and Renuka Srinivasan. Ocular manifestations of rheumatoid arthritis and their correlation with anti-cyclic citrullinated peptide antibodies, *Clin Ophthalmol*. 2015;9:393-397.
14. Fatemeh Rezapour, Sima Sedighi, Negar Boroomand et al: Kerato Conjunctivitis Sicca among Rheumatoid Arthritis Patients: A Cross-Sectional Study. *J. Appl. Environ. Biol. Sci*. 2016;6(1):102-105.
15. Sujit Itty BA, Jose S. Pulido et al: Anti-Cyclic Citrullinated Peptide, Rheumatoid Factor, and Ocular Symptoms Typical of Rheumatoid Arthritis; *Trans Am Ophthalmol Soc*. 2008; Vol 106:75-83.
16. El Maghraoui A, Extra-articular manifestations of ankylosing spondylitis: Prevalence, characteristics and therapeutic implications, *Eur J Intern Med*. 2011;1-7.
17. Shiu-chung Au, Shimrat Yaniv, Alice B. Gottlieb: Psoriatic Eye Manifestations. *FALL 2011 Psoriasis forum*; Vol. 17, No. 3:169-179.
18. Kiss S., Letko E., Qamruddin S et al. 2003. Long-term progression. Prognosis, and treatment of patients with recurrent ocular manifestation of Reiter's syndrome. *Ophthalmology*. 110(9):1764-1769.
19. Lee DA, Barker SM, SU D et al. The clinical diagnosis of Reiter's syndrome. *Ophthalmology* 1986;93:350.
20. Beatriz de A. F. Gomes Marcony R. Santhiago, Priscilla Magalhaães et al. Ocular findings in patients with systemic sclerosis. *CLINICS* 2011;66(3):379-385.
21. MD Sherif Z Yacoub Wasef: Gender differences in systemic lupus erythematosus; ELSEVIER Publication. *Gender Medicine*, August 2004;1(1):12-17.
22. Peponis V, Kytтары VC, Tyradellis C et al (2006) Ocular manifestations of systemic lupus erythematosus: a clinical review. *Lupus* 15:3-12.
23. Read RW. Clinical mini-review: systemic lupus erythematosus and the eye. *Ocul Immunol Inflamm*. 2004;12(2):87-99.
24. Bajwa A, Foster CS. Ocular Manifestations of Systemic Lupus Erythematosus. *J Clin Cell Immunol*. 2014;5:191.
25. Neal V. Palejwala, Harpreet S. Walia, and Steven Yeh: Ocular Manifestations of Systemic Lupus Erythematosus. A Review of the Literature, *Autoimmune Diseases*. Hindawi Publishing Corporation; Volume 2012; 1-9. 26. Ranju Kharel (Sitaula), Dev Narayan Shah, and Divya Singh: Role of lupus retinopathy in systemic lupus erythematosus. *J Ophthalmic Inflamm Infect*. 2016;6:15.
27. Cleary PA, Beck RW, Anderson MM Jr, et al. Design, methods, and conduct of the Optic Neuritis Treatment Trial. *Control Clin Trials*. 1993;14(2):123-42.
28. Y. C. Lin, A. G. Wang, and M. Y. Yen, "Systemic lupus erythematosus-associated optic neuritis: clinical experience and literature review," *Acta Ophthalmologica* 2009; Vol. 87(2):204-210.
29. Sobrin L, CS Foster (1994) Systemic lupus erythematosus choroidopathy *BMJ*, IV.