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Ocular Manifestations of Rheumatic Diseases: A Hospital-Based Study

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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 ocularpresentations of these systemic inflammatory diseases is vital to arrive expeditiously at the correct diagnosis and treatmentplan withthegoalofpreservingvisual function.

Methods: A cross sectional study was done on patients over a period from June 2019 to March 2021. A total of 100patientswithrheumaticdiseasewereinvestigatedfor any ocularmanifestationsafterobtaininginformedwritten consent.ACR (American College of Rheumatology) criteriawas used for the diagnosis of Rheumatic Diseases. Ocular investigation fordry eye included Schirmer's test and Tear film breaks up time test (TBUT). Positivity for Immunologicalfactorsandtheir associationtoocularmanifestations statisticallyanalysed.

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 andANA positivity is 16 out of 20 (80%). Six (50%) of the twelve patients with Keratoconjunctivitis sicca had highRheumatoidfactor titre values by slide agglutinationor Anti Citrullinated peptide Antibody positive

Conclusion: Therefore,followingamultidisciplinary approachbyophthalmologists,rheumatologists,physicians, andpaediatrician wouldhelpfor an earlyinterventiontopreservevisionwherepossible.

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

I. INTRODUCTION

Rheumatic diseases constitute different types ofillnesscharacterizedbytheinflammationofthecon nectivetissue,usually anautoimmunedisease.Itaffects people of both sexes, all ethnic groups, and ages.Since most of the symptoms of the rheumatic diseasesconcernprimarilythemusculoskeletalsystem [(1)],butocular involvement in the rheumatic diseases may resultfromtheinflammatoryprocessbecauseofimmune-mediatedocularinflammationwhichcausesseveredebilitationandvisualloss [(2)].Patientswithrheumatologicaldiseasehavepoorfollow upwitharheumatologist. Almost all the anatomical parts of theeye could be a target for an immunological reactiondependinguponthe underlyingetiologicaldisease [(3)].Manyocularcomplicationsareindicatorsofactivesystemic disease process and some of them are markersofsevereandpotentiallylife-threateningsystemicinvolvement [(2)].Therefore,byunderstandingthevariouspresentations of these systemic inflammatory diseasesabout the eye is important to be able toarriveexpeditiouslyatthecorrectdiagnosisandtreatmentplanwiththegoalofpreservingvisualfunction.

II. MATERIALS AND METHODS

Acrosssectionalstudywasdoneonpatients visiting RheumatologyO.P.D.The study was done irrespective of age, sex, duration ofseverityofthedisease,thepresenceorabsenceofocularsymptomsandexaminedforanyocularmanifestations.Thestudywascarriedoveraperiodfrom June 2019toMarch 2021.Atotalof100 patients with rheumatic disease were investigatedforanyocularmanifestationsafterinformedwrittenconsent. Clearance from the institute ethical committeewasobtained.ACR[(4)](AmericanCollegeof

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Rheumatology) criteriawere usedfor the diagnosis oftheRheumatic disease.

InclusionCriteria: AllDiagnosedpatientsofRheumaticdiseases presenting to OPD

ExclusionCriteria: Patientswithuncontrolleddiabetes, hypertension, patients with active tuberculosisoranyotherinfectiveaetiologyandwithanyknown predisposing factor that account for the detected ocularmanifestation

A completehistoryregarding the rheumaticand ocular symptoms were obtained from each patientandadetailedsystemicandocularexamination wasdone. Information regarding age and sex was recorded.Through joint and systemic examination were done.

The following investigations were done for thepatients wherever required.Acompletehaematologicalprofile,asteroid work upto rule out other conditions (like uncontrolled DM, hypertension,activetuberculosis)thatcouldbeaggravatedbytheinstitutionofsteroidsasatreatmentfortheocularcondition,assayofimmunological parameters like Rheumatoid factor byslide agglutination, Anti Citrullinated peptide Antibody Assay and Anti-nuclear antibody by FANA(fluorescentanti-nuclearantibodytest)wasdone [5,6]

Ocular examinations included documentation of best-corrected visual acuity, orbital & external eye diseaseexamination, 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 includedthetearfilmadequacyusingSchirmer'stest,its integrity was analysed using Tear film break up timetest (TBUT).

Therefore, firstly the general objective of this study wastoidentifydifferenttypesofocularinvolvementincasesofRheumaticdiseasesinatertiarycarehospital. Secondly, to study age and sex distribution ofthe patients and to establish a source of comparison fortheprevalenceoftheocularfindingsintheseRheumaticdiseasesinthesesettings.Alldatawereanalysedusingstatisticalsoftwarepackage SPSS.Variablesofinterestweresummarized usingdescriptivestatistics.Forcategoricalvariables,frequenciesandpercentageswere used.

III. RESULTS

Of 100 patients enrolled in the study, 31 had Rheumatoid arthritis, 28 had Ankylosing Spondylitis, 11 hadSystemic Lupus Erythematosus (SLE), 10 had Psoriatic arthritis, 10 had Juvenile Rheumatoid Arthritis, 8 hadReactive arthritis and 2 had Systemic sclerosis. Ocular involvement was seen in 65 patients (65%). The demographicpattern of sex and age distribution is shown in Table 2 and Table 3 respectively for different rheumatic diseasesexamined.Thedifferenttypesofocularmanifestationsseeninrheumaticdiseasesisshowninin Table1,thecommonest being Uveitis, 35 cases {(34.3%) 30 as in Table 1 & 5 JIA} followed by KCS, 20 cases (19.6%). ThemeanIOPwas normal.Individualeyepresentationsof differentrheumaticdiseasesare elaboratedinthetablesbelow

Table1: OcularManifestationsinRheumaticDiseases

OcularFindings	**RA**=31cases	**AS**=30cases	**SLE**=11cases	**PA**=10cases	**ReA**=8cases	**SS**=2cases
Uveitis	6	14(11cases ant. uveitis)		6(4cases ant. uveitis)	4(ant. uveitis)	
KCS	12		7			1
Scleritis	5					
Episcleritis	3					
SclerosingKeratitis	2					
SLE-Retinopathy			3			
PUK	2					

RA = Rheumatoid Arthritis**, AS** =Ankylosing Spondylitis**, SLE** = Systemic Lupus Erythematosus**, PA** = PsoriaticArthritis**,ReA** = Reactive Arthritis**, SS** = Systemic Sclerosis, KCS= Keratoconjunctivitis sicca,PUK= Peripheral ulcerativekeratitis.

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Table2:Gender Profile of each Rheumatic Disease

DiseaseEntity	Number ofPatients	Number ofPatients(Male)	Number ofPatients(Female)
RheumatoidArthritis(RA)	31	3	28
AnkylosingSpondylitis(AS)	28	28	_
SystemicLupusErythematosus(SLE)	11	1	10
PsoriaticArthritis(PA)	10	7	3
Juvenile Inflammatory Arthritis (JIA)	10	6	4
ReactiveArthritis (RS/Re)	8	8	_
Systemic sclerosis(SD)	2	_	2
Total	100		

Table3:Agewise distribution of Rheumatic disease

AgeGroup	NumberofPatients						
InYears	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	-	2(100%)
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 withocular manifestations and ANA positivity is 16 out of 20 (80%) as in Table 5. Number of patients without ocularmanifestations and ANA positivity is 4. There was a greater incidence of ANA positivity in patients having ocularmanifestationsoftheRheumatic disease process,thanthosewithoutthem,asinTable5.

Table4:Anti-NuclearAntibody(ANA)PositivityamongRheumaticDiseasepatients

RheumaticDisease	Numberofpatients	Incidenceof ANA positivity[Ref5.]
RheumatoidArthritis	31	22.5% (7cases)
SystemicLupusErythematosus,SLE	11	90.9%(10cases)
Systemic sclerosis	2	50%(1case)
PauciarticularType1JIA	5	80%(4 cases)
PauciarticularType2JIA	2	_
PolyarticularJIA	3	_

Table 5: Anti-Nuclear Antibody (ANA) PositivitywithOcularManifestations

OcularDisorder	Number ofPatients	Proportion ofANAPositivity
Uveitis	35	22.9% (8cases)
KCS	20	25% (5cases)
Retinopathy	3	66.7% (2cases)
SLE-associatedoptic neuritis	1	100%(1case)
No abnormality detected	34	11.8% (4cases)

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Table 6: Correlation between the titre values of RFandincidence of KCS

RFTitreValue (by slideagglutinationtest)	**Patientswith KCS**	**PatientswithoutKCS**
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 thestudy,Table 4.

Juvenile Inflammatory Arthritis (JIA):InPauciarticulartype1JIApatients,therewere5cases (meanage7.6yrs)outofwhich4hadANApositivity as in Table 4. The ocular presentations weremixed i.e., 4 had chronic uveitis, 3 had complicatedcataractand2withbandkeratopathy.InPauciarticulartype2JIApatient,1hadacuteuveitisoutof2cases (meanage9.5yrs).Therewasnoocularinvolvement in 3 of the cases with Polyarticular JIApatients (meanage11.3yrs).AmongJIApatients,uveitis wasseenin5cases.

RheumatoidArthritis(RA)patientshadmixedocularfindings.ThecommonestocularabnormalityseenisKeratoconjunctivitissicca38.7%(12/31)followed by Uveitis 6 cases (19.4%), Scleritis 5 cases(16.1%)and3cases(9.7%)asEpiscleritis.Fivepatientshadcornealinvolvementi.e.,SclerosingKeratitis 2cases(6.4%),PUK2cases(6.4%)andKeratitis 1 case (3.2%). One of the PUK patient withKCSfeaturehadcornealthinningwithsignsofimpendingperforationwheretissueadhesivecyanoacrylate glue was used. While the other patientwithPUKwithoutKCSremainedstablewithconjunctivalresectionand bandagecontactlens use.

Analysis of parameters for KCS**:**All thetwelvepatients of KCS had moderate grade dry eye as per vanBijsterveldscoringsystem [(7)](afterocularsurfacestaining with 1% Rose Bengal dye). These also testedpositive that is moderate dry eye to Schirmer's test andTBUTfordryeyeearlier inthe examination.

Six (50%) of the 12 patients with KCS has high RFtitrevaluebyslideagglutinationmethod(≥1:128).Conversely of the seven patients with RF titre values ≥1:128,six(85.7%) hadKCS

Fourteen (50%) of twenty-eight patients examinedinAnkylosingspondylitishaduveitis,thecommonestbeing anterior uveitis in our study of 39.3% (11 casesout of 28). All the Ankylosing spondylitispatientsweremales.PatientswithPsoriatic arthritisreportedconjunctivitis as 10% (1case), acute anterior Uveitis as40% (4 cases) and intermediate uveitis as 20% (2cases).Thecommonestocularmanifestationdetectedintenpsoriatic arthritis patients in the study is acute anterioruveitis (40%). It involved 7 males and 3 females in ourstudy

TheincidenceofconjunctivitisseeninReactivearthritis is 12.5% (1 case) and acute anterior uveitis as50% (4 cases). Whereas 2 patients had Scleroderma ofwhich one just had lid tightness while otherhad lidtightness and KCS. Eyelid stiffness was associated withdifficulty inlideversion andawoodyfeeluponpalpation.

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For lupus retinopathy afflicted patients with othersystemicinvolvement,acourseofintravenousmethylprednisolone(1 gdailyfor3 days)withoralcorticosteroids(prednisolone1 mg/kg/day)laterwasgiveninitially.Furtheritwassupplementedwithazathioprine.Therewassignificantimprovementofvision in two cases (2/3) with moderate lupus retinopathy.

IV. DISCUSSION

Themagnitudeofeyeproblemsassociatingrheumaticdiseasesisnotwellestimatedinsomepopulationanddataconcerningitspatternishighly defi [(2)].Inourstudy,ocularmanifestationswerefound in 65 of the 102 (63.7%) patients examined. Theoverall prevalence of uveitis in our study is 34.3% (35cases)whichisthecommonestocularabnormalitydetected and is comparable to Birnbaum et al [(8)] study of31%.ThetotalnumberofcaseswithAnti-NuclearAntibody(ANA)positivityinRheumaticdiseaseis21.6%(22/102)asinTable4,thosewithocularmanifestations and ANA positivity is 80% (16/20) as inTable 5. Therefore,it is seen thatthereis agreaterincidence of ANA positivity in patients having ocularmanifestations of the Rheumatic disease process, thanthose without them, as in Table 5. Other Studies haveshown similar link of higher ANA positivity in ocularmanifestations of rheumatic diseases [(5)].Also, from theTable 4 above, it is seen that there is a higher incidenceofANApositivityinSLE,SclerodermaandPauciarticular Type 1 of JRA patients, Marina et al [(5)]and Solomon DH [(6)] also explained similar findings thatisbecauseoftheimmunologicalnatureofthediseas

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Further,amongtheJuvenileRheumatoidArthritis (JRA) patients in our study,10% hadacute and 40%had chronic uveitis, Kanski JJ [9] mentioned prevalencefrom 4% to 38%. It was seen that children(<16years)who are at greatest risk of developing uveitis are thosewitholigoarticular-onsetJRA [10].Ourstudyshowedsimilar findings as above. The period of highest risk forocularinvolvementiswithin4yearsofonsetofarthritis,althoughtheriskisneverentirelyabsent.Studieshave shownantinuclearantibodiestobestronglyassociated withchronicuveitis.Therefore,both involvement of Pauciarticular JRA with positiveantinuclearantibody (ANA)test,haveshownstrongassociation of ocular complications as per Wallace CAetal [11]andEL-Shereefetal [12]asalsoseeninourstudy, Table 4& 5.

ChancesofdevelopingocularmanifestationsinJRA are relatively more common in girls [12] but in ourstudy relative prevalence were little more in boys i.e.,60% (6/10)to girls 40% (4/10). This could be due tounder reporting or neglected hospital trips for the girlson account ofsuburban hospital location orpoor careforthegirlsascomparedtoboys,asIndiabeingadeveloping country.Thetypicalcomplicationspublishedpreviouslyin JRA,includedcataract(19-81%),bandkeratopathy(7-70%)andposteriorsynechiae (8-75%) [12], our study showedcomplicatedcataract 3 cases (30%) and band keratopathy 2 cases(20%)whichisliketheabovestudydone [12].Thecataractwouldhavedevelopedsecondary tochronicuveitisascomplicatedcataract.

WhileinRheumatoidArthritispatientsinourstudy,KCSisseenasthemostcommonocularpresentations of 38.7% (12/31), which is comparable toother population-based studies of 28%, Vignesh AP etal [13]andonestudyshowedKCSas67.7%inRApatients [14].Studieshaveshownthatocularcomplications are more probable among RA patientswith elevated titres of RF (Rheumatoid Factor) as inTable6orAnti–citrullinatedproteinantibodies(ACPAs) [15].

In Ankylosing spondylitis, the commonest findingbeinganterioruveitisof36.7% (11/30)whichiscomparabletoZeboulonetalwhohadmentionedanterior uveitis as 20–30% [16]. The occurrence of AS inourstudywasseenatyoungerage,withallthepatients beingmales,iscomparabletothestudyofElewaut et alwho also showed ASprevalence in thethirddecadeoflifewithmales2.5-timesmorecommonlyaffectedthanwomen [16].Thecommonestocular manifestation detected in ten Psoriatic arthritispatientsinthe study wasuveitisas 60%(anterioruveitis was 40%) and Chang JH et al reported uveitis as50% [17].Ourstudyreportedconjunctivitisas10%(1case)asotherpatientsmighthavereportedafterimprovedconjunctivalinflammation,whileotherstudies presented conjunctivitis differently i.e., Lambertetalas19.6%andZeboulonet alas32.7% [17].

InReactivearthritis,theincidenceofConjunctivitiswas 12.5% (1 case)andanterior uveitisas 50% (4 cases) while study by Kiss et al [18] reportedanterior uveitis as 92%. The syndrome is more commonamongst 20 to 40 years old males [19]. Our study alsorepresented males in the same age group i.e., between21-30 yrs.

Sclerodermaisararedisease,mostofthedataregardingocularinvolvementconsistofsinglecasereportsorsmallcasestudies,therebylimitingthegeneralization of the findings to a larger population ofpatients [20].WehadtwopatientsofSclerodermaofwhich one just had tightness of lid and other had lidtightnesswithKCS(50%),Table 1.Eyelidstiffnesswasassociatedwithdifficultyinlidversionandawoody feel upon palpation. Gomes et al [20]had nearsimilar findings i.e., 51.1% had eyelid skin changes and48.9% as KCS. They also founda prevalence of lidinvolvement to be ranging from 29% to 65% in patientsandrepresentedyoungerpatients,justasoursin Table3.

In our study, ocular manifestations in SLE [21] wereKCS7cases(63.6%)asthecommonest,lupusretinopathyas3cases(27.3%)andSLE-associatedopticneuritis1case(9.1%).Studieshaveshownincidence of KCS as 25-35% [22] andLupus retinopathyincidence of 7–26% [23] to 29% [24]. ANA positivity ratewas higher as in Table 4 and 5 for patients with ocularmanifestations.

SLE patients with retinal involvement as in onestudy which had 77% ANA positivity [25]. Although thefrequencyofthefindingsvariesasseenabove,itdepends on thepatientpopulation being studiedandsystemic disease activity [21]. The serologic hallmark ofSLE is the presence of ANAs which is highly sensitiveand useful screening tool, but anti-dsDNA antibody isSLEspecificand correlates withdiseaseactivity [26].

One case with SLE-associated optic neuritis wastreated as per the guidelines of the ONTT [27],whichshowedsomevisualimprovementasintheresultsabove, as also experienced in the study of Lin et al [28].RetinopathyinSLEissuggestiveofhighdiseaseacti

vity while the disease, and hence, is amarkerofpoorprognosisforsurvival,thatisSLEpatients with retinopathy have overall worse prognosisanddecreasedsurvival,comparedtoSLEpatientswithout retinopathy [29]. Therefore, ocular complaints ofSLE warrant urgent referral to an ophthalmologist formoredetailedassessmentandtimelyinstitutionofsystemic therapy which may minimize morbidity fromthisdiseaseandearlyrheumatologistintervention would reducemortality.

V. CONCLUSION

Thisstudyindicatesthatocularinvolvementis common in rheumatic diseases and there is needforclosefollowup.Therefore,byfollowingamultidisciplinaryapproachbetweenrheumatologist,ophthalmologist,physiciansandpaediatricianforthediscoveryandearlymanagementoftheseocularmanifestations withthegoalofpreservingvisualfunction. The limitation of this study includes a limitedsample of patients visiting one institution which couldhaveintroducedhealth-seekingbias.Hencefurtherstudiesare required.

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