Dry eye in rheumatoid arthritis patients: Correlation with disease activity

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Abstract

Introduction and Objectives: Dry eye is a very common disorder of tear film resulting from either decreased tear production or increased tear evaporation. Rheumatoid arthritis is a well-known risk factor for dry eye occurrence. This study was undertaken to assess dry eye prevalence in rheumatoid arthritis patients and assess its correlation with disease activity.

Materials and Methods: The study period was one year. Seventy patients diagnosed to have rheumatoid arthritis were enrolled in this study. They were given an OSDI questionnaire, examined for signs of dry eye and subjected to four tests (Schirmer test, TBUT, rose bengal test, Impression cytology), based on which they were labelled as being positive or negative for dry eye. The arthritis disease activity was determined using DAS score.

Results: Dry eye prevalence in rheumatoid arthritis was found to be 48.5%. OSDI scores were found to correlate well with diagnostic tests done for dry eye only when they were high indicating poor correlation between signs and symptoms in early stages. Prevalence increased with increase in age of patients. There was no correlation between the occurrence of dry eye and duration of rheumatoid arthritis, rheumatoid factor or arthritis disease activity.

Conclusion: Prevalence of dry eye is high in rheumatoid arthritis patients. OSDI questionnaire is a useful screening tool for dry eye. Impression cytology is an easy and useful test to assess surface changes in dry eye patients.

Keywords: Disease activity, Dry eye, Impression cytology, OSDI, Rheumatoid arthritis.

Introduction

Dry eye is a disorder of tear film resulting from either decreased tear production or increased tear evaporation. The National Eye Institute industry workshops have defined dry eye as, "Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort".[1,2] The prevalence of dry eye disease in the general population is estimated to be between 5% to more than 50% at various ages and with various risk factors seen by surveys over the last 20 years have.[3]

The incidence of dry eye is increased recent years due to the increase in predisposing factors such as contact lens use, excessive computer usage. There is shift of focus from other proven risk factors of dry eye such as diabetes, rheumatoid arthritis, use of xerogenic drugs etc to these predisposing factors.

Dry eye is still a serious issue for people who have it, though not a common cause of vision loss. The symptoms become progressively troublesome and exert an increasing burden on the patients as the disease progresses or increases in severity. Dry eye patients are reported to have significant loss of productivity each year, often losing approximately 5 work days and working an average of 208 days with dry eye symptoms as shown by studies.[4]

Rheumatoid arthritis (RA) which is a chronic, immuno inflammatory, systemic disease that affects mainly synovial joints with possibility of extra articular manifestations. Dry eye occurs as a frequent complication of rheumatoid arthritis. Prevalence of rheumatoid arthritis 0.8% in general population (range 0.3-2.1%). Women are affected 3 times more often than men.[5]

There is often a delay in diagnosing dry eye in these patients. Patients often delay seeking care for the dry eyes until the tissue damage is at a more advanced stage. Early medical intervention to arrest the RA-associated damage to the lacrimal glands may preserve healthy moisture levels to the ocular surface and protect the eyes from long-term damage. An accurate knowledge of the prevalence of dry eye in rheumatoid arthritis will increase the case detection rate of dry eye in these patients, thus improving their quality of life.

The purpose of our study was to assess the prevalence of dry eye among rheumatoid arthritis patients in a hospital set up, correlate with disease activity and to determine the best test for screening of these individuals which can be applied even in a busy out patient setting.

Materials and Methods

The study was conducted on 70 adult rheumatoid arthritis patients diagnosed in the department of clinical immunology and rheumatology of the hospital. All these patients fulfilled the ACR criteria for rheumatoid arthritis.[5] It was a one year cross sectional study with the study period ranging from January 2007 to January 2008. Patients aged more than 65 years, patients suffering from diabetes, thyroid disease, those who had undergone cataract or refractive eye surgeries and contact lens users, were excluded from the study as these form independent risk factors for development of dry eye.[6-11] The total study sample was 136 eyes of 70 patients. Four patients had undergone cataract surgery in one of the eyes. That eye was excluded and the other eye was considered for the study. A person was considered as having dry eye if one of the eyes fulfilled the criterion for dry eye diagnosis as detailed below.

Written informed consent was taken before enrolling the patients in the study. An OSDI (Ocular surface disease index) questionnaire was administered to all participants to assess the symptoms of dry eye and correlate them with the signs. This is a standard questionnaire for dry eye evaluation and has been proved to be a reliable and valid tool for assessment of symptoms.[12]

Best corrected visual acuity was measured in all the patients and duration and type of refractive error was noted on the basis of spectacle correction. A complete slit lamp examination was conducted on the patients to identify objective signs, specifically looking for conjunctival congestion, increased conjunctival folds, xerosis, corneal dryness (assessed by the loss of corneal sheen and distorted reflex on torch light examination) and features of other ocular complications of rheumatoid arthritis.

Following this, four diagnostic tests were done, based on which the diagnosis of dry eye was made. Participants were labeled as having dry eye if at least two out of these four diagnostic tests were positive. This criterion of two tests to diagnose dry eye was adopted in order to increase the detection rate of dry eye and hence arrive at an accurate prevalence. The tests were done in the following order:

1. Schirmer test: This was done using Whatman no. 41strips, performed without anesthesia. The strips were placed at the junction of middle and lateral one third of lower lid and patient was asked to keep eyes closed for five minutes. The wetting of the strips was tested in millimeters at the end of five minutes. Schirmer's score (SS), a value of less than 10 mm was taken as positive.[2]

2. Tear film break up time (TBUT): This was performed using commercially available sterile fluorescein strips. Fluorescein was instilled into the eyes and after ensuring even distribution, the time of appearance of first dark spot was noted. A break up time of less than 10 seconds was taken as positive.[2]

3. Rose Bengal staining was done using sterile rose bengal strips. A modified Van Bijsterveld grading was employed. Grade of greater than four was taken as being positive for dry eye.[2]

4. Conjunctival impression cytology (CIC): For impression cytology, after taking an imprint using cellulose acetate strips, it was transferred to a glass slide using glass rod and then was stained using PAS and haematoxilin and eosin stain. The changes of ocular surface were graded according to Nelson grading system.[13] Those with grade 2 or grade 3 changes were labeled as having dry eye. Two samples were taken from each eye, one for each type of stain.

5. The disease activity score (DAS score): Rheumatoid arthritis disease activity was measured by the 28-joint disease activity score (DAS 28). It is a composite score derived from 4 measures which include the number of tender joints (out of a total 28 defined joints), the number of swollen joints (out of a total 28 defined joints), ESR (in mm/hr) and patient's assessment of global health measured on a visual analogue scale (VAS) of 100 mm. This score is calculated by a complex mathematical formula for which a preprogrammed DAS 28 calculator was used. The DAS 28 result was correlated with presence or the absence of dry eyes and also with scores of the ocular tests for dry eyes mentioned above.

The data was analyzed using chi squared test. A 'P' value of < 0.05 was considered to be statistically significant. The tests for dry eye and DAS score for rheumatoid arthritis activity were analyzed using the Pearson correlation coefficient.

Results

The age group of patients was between 21 to 65 years, with the mean age being 47.92 years with a standard error of 1.36years. Of the total number of patients, 57 were females and 13 were males with a female to male ratio of 4.38:1. The duration of rheumatoid arthritis ranged from one month to 19 years, with the mean duration being 4.51 years with a standard error of 0.48 years. The RF titres ranged from 20 to 1280, with a mean titre of 321 with a standard error of 57.4. The minimum DAS score was 3.62, maximum was 8.86. The mean DAS score was 6.47. The Schirmer test scores ranged from one to 30. The minimum tear film break up time was three seconds. Rose Bengal stain grading was from zero to nine.

Only an OSDI scoring of 67-100 which corresponds to severe dry eye, was found to correlate significantly with objective tests of dry eye (p=0.006). The ocular signs suggestive of dry eye were found only in few patients. Conjunctival congestion and corneal dryness were the most common signs observed (Table 1). 65.6% of the patients with conjunctival congestion showed evidence of dry eye. The association between dry eye and conjunctival congestion was found to be statistically highly significant (p=0.001).

Among the entire group, 34 patients (56 eyes) were diagnosed to have dry eye based on the tests. The prevalence of dry eye was found to be 48.5%. The total patient sample was divided into 5 sub groups based on their age. The prevalence of dry eye was found to increase significantly with the increase in age of the patients (p= 0.028) and was found to be significantly higher in persons aged more than 40 years. There was a higher prevalence of dry eye in women compared to men. 40 out of 70 patients (57.4%) had some form of refractive error with history of use of spectacles. Among these, 24 patients (60%) had evidence of dry eye.

Table 1: Signs of dry eye

Signs	Dry Eye		Total
	Present	**Absent**	
Conjunctival congestion	21	11	32
Corneal dryness	15	0	15

$\chi 2$- 10.327 p=0.001

Table 2: Relationship between duration of rheumatoid arthritis and dry eye

Duration of RA (years)	Dry eye present (No. of patients)	Dry eye absent (No. of patients)	Total
0-4	20 (46.5%)	23 (53.4%)	43
5-9	10 (55.56%)	8 (44.4%)	18
10-14	2 (33.3%)	4 (66.6%)	6
15-19	2 (66.6%)	1(33.3%)	3
Total	34	36	70

$\chi2= 0.485, p=0.784$

Table 3: Pearsons correlation between DAS and ocular tests

	Schirmer score	Rose Bengal score	Tear film break up time	Conjunctival impression cytology
Pearsons correlation	-0.0245	0.1126	0.0141	-0.0262

Table 4: Comparison between different dry eye diagnostic tests;

Procedure	Sensitivity	Specificity	+ve predictive value	-ve predictive value
Schirmer test	91.1	93.7	91.1	93.7
TBUT	46.4	100	100	72.7
RB test	85.7	96.2	94.1	90.6
CIC	78.5	92.5	88	86

*TBUT: Tear film break up time; † RB test: Rose Bengal staining;
‡CIC: Conjunctival impression cytology

Table 5: Distribution of patients according to Schirmer test results

Schirmers (mm)	0-5	6-10	>10	Total
No. of patients	20	11	39	70
% of patients	28.6	15.7	55.7	100

The prevalence of dry eye in different groups of duration of rheumatoid arthritis has been depicted in Table 2. No statistically significant correlation between prevalence of dry eye and duration of rheumatoid arthritis was found.

We did not find any statistically significant correlation between the presence of RF and occurrence of dry eye though the prevalence of dry eye was found to be slightly higher (50%) in the RF positive group compared to the RF negative group (47.8%).

The RA activity score could be recorded for 53 patients. Wherever dry eye was absent, the mean RA activity score was found to be 6.50± 1.32. Wherever dry eye was present, the mean score was 6.32± 1.18. There was no significant difference between the two means. (p=0.6009). Further, we tried to find the correlation between dry eye test scores and RA disease activity score. There was no significant positive correlation between the two (Table 3).

Among all the tests, Schirmer test was found to be the most useful test to be done in RA cases as it showed a high sensitivity, specificity and predictive values (positive and negative) (Table 4). A significantly larger number of patients with Schirmer values of ≤5mm were found to have grade 2 or grade 3 changes on impression cytology.

Discussion

Dry eye is the commonest ocular complication of rheumatoid arthritis. Due to its frequent under diagnosis, dry eye can lead to potentially vision threatening complications. Determining the prevalence of dry eye in rheumatoid arthritis was the primary objective of our study. In Indian population prevalence of dry eye ranging from 27 to 29%, compared to western population, which showed a higher prevalence ranging from 45 to 74%.[14-19] However, our study noted a prevalence of 48.5% among the tested rheumatoid arthritis patients which correspond to the observations of Zlatano et al.[15] This is a higher prevalence comparable to that of western studies. Punjabi OS et al[17] reported a prevalence of 27.3% in his comparative study of dry eye in rheumatoid arthritis patients with age matched controls. One reason for this could be that, they considered the Schirmer test result to be positive if it was less than or equal to 5 mm of wetting. When we performed a similar sub grouping in our study, we obtained a prevalence of 28.6% (Table 5), which is comparable to the results obtained by them.

Previous studies have shown a strong correlation between advancing age and dry eye. In another similar study, 80% of the patients testing positive for dry eye were aged 40 years or older.[17] In our study, the percentage of patients testing positive for dry eye among the 40-65 year age group was 79.41%.

OSDI questionnaire has been used by other investigators as a dry eye diagnostic tool. Ozcura et al found a significant inverse correlation between OSDI and TBUT scores.[20] Simpson TL et al[21] have found that this scoring system is highly sensitive in differentiating symptomatic and asymptomatic subjects of dry eye. Srinivasan et al[22] concluded that OSDI could be effectively used to separate post menopausal women who demonstrate clinical signs of ocular dryness. We found that the OSDI scores of 67-100 only correlated significantly with signs of dry eye. One reason for this could be that, the presence of systemic morbidity associated with rheumatoid arthritis might have made them pay more attention to systemic symptoms and ignore or underplay the ocular complaints.

Previous studies have found that longer the duration of rheumatoid arthritis, higher the prevalence of dry eye. Polanska et al found a statistical connection between the presence of dry eye and duration of rheumatoid arthritis longer than ten years.[19] However, we were not able to demonstrate a significant statistical correlation between the duration of rheumatoid arthritis and presence or severity of dry eye (p= 0.784). The reason for this could possibly be the small sample size of our study. Matsuo et al,[23] in their study of ocular complications of rheumatoid arthritis, found that patients with keratoconjunctivitis sicca had a significantly higher titres of RF. We performed a similar analysis but were not able to demonstrate any significant difference in the dry eye prevalence between patients with lower and higher titres of RF.

We could not demonstrate any significant correlation between rheumatoid arthritis activity and occurrence of dry. Our results were similar to those obtained by other investigators.[18]

Though great advances have been made in the field of treatment of dry eye, for diagnosis, most ophthalmologists still depend on tests discovered decades ago. Presently, there is still no test that can be called as a gold standard for diagnosis of dry eye. The poor correlation between the signs and symptoms of dry eye, at least in early stages, has lead to the necessity for performing diagnostic procedures on patients at risk for developing dry eye, in order to diagnose the condition at an early stage. If not detected early, the condition can progress to complications such as, sterile stromal ulcers, blepharitis, conjunctivitis, band keratopathy, keratinisation, corneal vascularisation.

In our study, Schirmer and Rose bengal tests were found to show high sensitivity and specificity for dry eye detection. Despite shortcomings, Schirmer test, combined with OSDI scoring or impression cytology for detecting surface changes can be used as a leading and accurate diagnostic tool for early diagnosis of dry eye in rheumatoid arthritis patients in a busy out patient set up.

There is a high prevalence of dry eye in rheumatoid arthritis patients. The OSDI scoring is helpful only in severe degree of symptoms. The prevalence of dry eye does not depend duration of rheumatoid arthritis. There is no association between RF, RA disease activity and dry eye. Hence all patients of rheumatoid arthritis have to be tested for presence of dry eye irrespective of their systemic disease status.

Conflict of Interest: None.

References

1. Lemp MA. Report of the National Eye Institute/ Industry workshop on clinical trials in dry eyes. *CLAO J* 1995;21:221-2.
2. Rheinstrom SD. Dry eye. In: Yanoff M, Duker JS, editors. *Ophthalmol* 1st ed. Mosby; 1999. p. 14.1-6.
3. Lemp MA. Advances in understanding and managing dry eye disease. *Am J Ophthalmol* 2008;146:350-6.
4. Mertzanis P, Abetz L, Rajagopalan K, Espindle D, Chalmers R, Snyder C et al. The Relative Burden of Dry Eye in Patients' Lives: Comparisons to a U.S. Normative Sample. *Invest Ophthalmol Vis Sci* 2005;46:46-50.
5. Lipsky PE. Rheumatoid arthritis. In: Kasper DL, editors. Harrisons: Principles of internal medicine. 16th ed. Mc Graw Hill Medical publishing division; 2005.p. 1968-2.
6. Schein OD, Hochberg MC, Munoz B, Tielsch JM, Bandeen-Roche K, Provost T et al. Dry eye and dry mouth in elderly: A population based assessment. *Arch Internal Med* 1999;159(12):1359-63.
7. Moss SE, Klein R, Klein BEK. Incidence of dry eye in an older population. *Arch Ophthalmol* 2004;122(3): 369-73.
8. Manaviat MR, Rashidi M, Afkhami-Ardekani M, Shoja MR. Prevalence of dry eye syndrome and diabetic retinopathy in type 2 diabetic patients. *BMC Ophthalmol* 2008;8:10.
9. Ecktein AK, Finkenrath A, Heiligenhaus A, Renzing-Kohler K, Esser J, Kruger C et al. Dry eye syndrome in thyroid associated ophthalmopathy: lacrimal expression of TSH receptor suggests involvement of TSHR- specific autoantibodies. *Acta Ophthalmologica Scandinavica* 2004;82(3):291-7.
10. Nichols JJ, Sinnott LT. Tear film, Contact lens, and patient related factors associated with contact lens related dry eye. *Invest Ophthalmol Vis Sci* 2006;47:1319-28.
11. Hovanesian JA, Shah SS, Maloney RK. Symptoms of dry eye and recurrent erosion syndrome after refractive surgery. *J Cataract Refractive Surg* 2001;27(4):577-84.
12. Schiffman RM, Christianson MD, Jacobson G, Hirsch JD, Reis BL. Reliability and validity of ocular surface disease index. *Arch Ophthalmol* 2000;118(5):615.
13. Nelson JD, Havener VR, Cameron JD. Cellulose acetate impressions of the ocular surface. *Arch Ophthalmol* 1983;101:1869-72.
14. Reddy SC, Gupta SD, Deodhar SD. Ocular manifestations of rheumatoid arthritis. *Ind J Ophthalmol* 1997;25(3):20-6.
15. Zlatanovic G, Stanojevic AP. Keratoconjunctivitis sicca in patients with rheumatoid arthritis. *Facta Universitatis* 1997;4(1):48-50.
16. Uhlig T, Kvein TK, Jensen JL, Axell T. Sicca symptoms, saliva & tear production & disease variables in 636 patients with rheumatoid arthritis. *Ann Rheum Dis* 1999;58(7):415-22.
17. Punjabi OS, Adyanthaya RS, Mhatre AD, Jehangir RP. Rheumatoid arthritis is a risk factor for dry eye in the Indian population. *Ophthalmic Epidemiol* 2006;13(6):379-84.
18. Fujita M. Correlation between dry eye and rheumatoid arthritis activity. *Am J Ophthalmol* 2005;140(5):808-13.
19. Polanska V, Hlinomazova Z, Fojtik Z, Nemec P. Dry eye syndrome in rheumatoid arthritis patients. *Czeck Slov Oftalmol* 2007;63(6):422-30.
20. Ozcura F, Aydin S, Helvaci MR. Ocular surface disease index for the diagnosis of dry eye syndrome. *Ocul Immunol Inflamm* 2007;15(5):389-93.

21. Simpson TL, Situ P, Jones LW, Fonn D. Dry eye symptoms assessed by 4 questionnaires. *Optom Vis Sci* 2008;85(8):692-9.
22. Srinivasan S, Joyce E, Senchyna M, Simpson T, Jones L. Clinical signs & symptoms in post menopausal females with symptoms of dry eye. *Ophthalmic Physiol Opt* 2008;28(4):365-72.
23. Matsuo T, Kono R, Matsuo N, Ezawa K, Natsumeda M, Soda K et al. Incidence of ocular complications of rheumatoid arthritis and the relation of keratoconjunctivitis sicca with its activity. *Scand J Rheumatol* 1997;26(2):113-6.