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Incidence of dry eye in rheumatoid arthritis and associated macular toxicity due to drug

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***Abstract*---**Background: "Dry eye" is used to describe a variety of conditions with diverse origins that affect the tear film and/or the ocular surface. [1]. Although it is well established that dry eye is frequently associated with Rheumatoid Arthritis (RA), the correlation between the severity of dry eye and the activity of RA is unclear. Patients suffering from RA commonly develop dry eye secondary to lymphocytic and plasma cell infiltrate of the lacrimal gland that lead to destruction of acini in the lacrimal glands Aim: To evaluate the incidence of dry eye in rheumatoid arthritis (RA) patients, and to investigate the effect of the routine Hydroxychloroquine drug therapy on the retina. Methods: In 75 RA patients, the severity of dry eye was assessed by the Schirmer I test, tear break-up time, rose Bengal staining, fluorescein staining and OSDI scoring. The RA activity was evaluated by the duration of the disease, Disease Activity Score (DAS)-28 score, Rheumatoid Factor, hs CRP and ESR levels. Results: The

incidence of dry eye increased with the duration of rheumatoid arthritis. A strong correlation between RA factor levels and severity of dry eye was seen. OSDI was a reliable measure of dry eye symptoms. Higher scores indicated severe dry eye, correlated well with the diagnostic tests for dry eye. Conclusion: Dry eye is a common complication in RA patients. We found that there was a correlation between RA and dry eye severity. A significant correlation between DAS and clinical tests of dry eye was noted.

***Keywords*---**rheumatoid arthritis, dry eye syndromes, DAS, Schirmer test, TBUT, OSDI, hydroxychloroquine, retinopathy.

Introduction

The term "dry eye" is used to describe a variety of conditions with diverse origins that affect the tear film and/or the ocular surface.[1] Dry eye can result either from tear deficiency due to lacrimal gland dysfunction or from increased evaporation of tears due to meibomian gland disease. [2] Furthermore, although it is well established that dry eye is frequently associated with RA, the correlation between the severity of dry eye and the activity of RA is unclear. RA involves inflammation of the lining of the joints and/or other internal organs. Because RA is a chronic disease that typically affects various joints and can flare up at different times, the activity of RA should be assessed for proper treatments. One of the methods for the quantification of RA activity is the Disease Activity Score -28 (DAS-28) which has long been used clinically and is a good index for assessing the patient's condition. In this study, we examined the incidence of dry eye in RA patients , and we investigated the correlation between the severity of dry eye and the activity of RA (as determined by DAS-28).

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease that is characterized by significant inflammation of the synovial membrane of joints. The cardinal joint manifestations of this disease include pain, swelling, and tenderness followed by cartilage destruction, bone erosion, and eventually joint deformities [3]. Rheumatoid arthritis is the most common systemic autoimmune disease, affecting approximately 1% of the population. Women are three times more likely to be affected than men, with 80% of patients developing the disease between the ages of 35 and 50 [4]. RA is a systemic disease; therefore, many patients exhibit extra-articular manifestations [5]. Although a variety of cells play a role in RA disease, macrophages may be of particular significance in the disease process. Proinflammatory cytokines secreted by macrophages, such as tumor necrosis factor-alpha (TNF-*a*), interleukin 1 (IL-1), and interleukin 6 (IL-6), are believed to have a critically important role in the induction and propagation of chronic inflammation [6]. Patients with RA who have high titers of rheumatoid factor are most likely to have extra-articular manifestations of the disease, including rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications [7].

Rheumatoid arthritis patients commonly develop dry eye secondary to lymphocytic and plasma cell infiltrate of the lacrimal gland that lead to destruction of acini in the lacrimal glands. Characteristic complaints include itching, burning, foreign body sensation, and photophobia. The severity of the symptoms correlates with the age and duration of RA, but does not correlate with the severity of arthritis.

Objectives of the study

To study the incidence of dry eye in patients with Rheumatoid Arthritis and to study the association between RA factor and dry eye occurrence. To find out associated macular toxicity from routine drug therapy with hydroxychloroquine.

Materials and Methods

A Prior approval was obtained from the institutional review board and ethics committee Ref no: MDC/JNMCIEC/395. The study adhered to the tenets of the Declaration of Helsinki. A cross-sectional study was performed in the Department of Ophthalmology, KLES Dr Prabhakar Kore Hospital & Centre, Belagavi, involving 75 Patients , 58 women and 17 men, selected from a single Rheumatology Clinic chosen according to appointment order and willingness to participate in the study. These patients were referred from the Department of Rheumatology, KLE Hospital during the period May 2017 to April 2018 and were examined for dry eye in the Department of Ophthalmology irrespective of the presence or absence of ophthalmic symptoms after obtaining well-informed written consent.

Inclusion Criteria

The patients with clinical or radiological diagnosis of Rheumatoid Arthritis based on the American Rheumatism Association 1987 (ARA) revised criteria [8] with a disease duration of 5 years or less were included in the study. These patients were on medication i.e oral hydroxychloroquine since past 3 years and on a cumulative dose of less than 6.5mg/kg/ day.

Exclusion Criteria

We excluded patients with ophthalmologic complications such as scleritis, episcleritis, scleromalacia, and those with significant dermatological problems that may be associated with dry eye, such as rosacea. The patients with blepharitis, prior eye surgery and chronic contact lens use which predisposes the patients for dry eye were excluded from the study. Descriptive data of all the participants was taken, like name, age, gender, detailed history. Best corrected visual acuity was taken and detailed slit lamp examination of both the eyes was done to rule out any anterior segment pathology. History of dryness of mouth was taken. Disease activity and severity was asessed by duration of symptoms , DAS-28 which was based on the number of tender and swollen joints, ESR value, and an evaluation of the patient's overall health,and it was categorized as remission (DAS28 _2.6), low disease activity (2.6; DAS28_3.2), moderate disease activity (3.2; DAS28 _5.1),[10] and high disease activity (DAS28 >5.1).10 Serology included

Rheumatoid factor, Acute phase reactant : high sensitivity CRP and ESR . Dry eye was diagnosed on the basis of the presence of both compromised tear dynamics and ocular surface abnormalities [11,12] according to the reported criteria for dry eye.[13] Tear dynamics were assessed by the Schirmer 1 test and tear break-up time (BUT). A standardized Schirmer Whatman No 41 paper strip was placed in the lateral canthus away from the cornea of each eye and left in place for 5 minutes, with the subject keeping the eyes opened. Readings were recorded in millimeters of wetting of schirmer paper strip at the end of 5 minutes. The wetting of schirmer paper strip of less than 5 mm/5 min was considered positive for an aqueous deficiency. Throughout the study, we examined the more severely affected eye of each patient, as determined by the Schirmer test. If one of these tests was positive (Schirmer test - 5 mm; BUT - 5 seconds), the tear dynamics were considered abnormal. Ocular surface abnormalities were identified by positive vital staining with rose bengal strip or fluorescein strip. The degree of rose Bengal staining in the temporal and nasal conjunctiva and the cornea, which were divided into three parallel sections, was recorded and quantified on a scale of 0 to 3. Thus, the maximum score that could be obtained from the staining of one eye was 9. Fluorescein staining, which was evaluated only in the cornea, was similarly rated on a scale of 0 to 3. If either type of staining was positive, the ocular surface was considered to be abnormal. Patients in whom both tear dynamics and ocular surface were abnormal were considered to have definite dry eye, whereas patients in whom only one of the tests was positive were considered to have probable dry eye.

Macula was evaluated by dilated fundoscopy, Colour vision , Central threshold visual field testing. The Pearson's association test for nominal variables was used for statistical evaluation of the association between the rheumatoid arthritis presence and the dry eye syndrome. A p-value <0.05 was considered statistically significant. Statistical analyses were carried out by using the SPSS for Windows software program, version 15.0 (Statistical Package for the Social Sciences, Inc., Chicago, IL).

Results

Of the 75 patients with RA the mean age of the patients was 43.3+/-10.8 years.58 (77.33%) were female patients and 17 (22.67) were male, indicating female preponderance. The mean duration of disease was 3.47 +/- 1.5 years. Of the patients having RA, 50.13% patients had dry eye. The mean DAS-28 was 3.98+/-1.The occurrence of dry eye increased with the duration of rheumatoid arthritis. A strong correlation between RA factor levels and severity of dry eye was seen in our study. In rheumatoid arthritis 17.14% of the patients had a history of dry mouth along with dry eye. These patient need to be evaluated further for definitive diagnosis of Sjogren’s syndrome.

OSDI was a reliable measure of dry eye symptoms .Higher scores indicated severe dry eye , correlated well with the diagnostic tests for dry eye. Blurred vision and gritty eyes were the most common symptom experienced , which was present most of the times. These patients found reading and watching television difficult half of the times. Associated ocular discomfort was noted when patients were exposed to windy conditions and in areas with air conditioners. Schirmer test was

the best test for detecting dry eye in rheumatoid arthritis patients with followed by TBUT and rose bengal staining.

Worthy of mention is that DAS showed a statistically significant correlation with OSDI score and all clinical tests of dry eye. We found OSDI score significantly correlated with Schirmer I-test values (*P*=0.036). Daily dosage is thought to be the most important factor in the development of hydroxychloroquine retinopathy. No significant macular toxicity was detected in the study patients.

Characteristics	Patients with RA (n=75) [n(%)]
Sex : Female	58 (77.33)
Male	17 (22.67)
Age years (mean +/- SD)	43.4 +/- 10.8
RA Characteristics : disease duration (mean +/- SD)	3.47 +/- 5.5
DAS-28 (mean +/- SD)	3.89 +/- 1
Laboratory findings : ESR[median(IQR)](mm/h)	32 (15-54)
hsCRP(mg/l) (mean+/-SD)	0.88+/-0.32
Positive RF	67(89.33)

Table1: Demographic, clinical, and laboratory characteristics of patients with rheumatoid arthritis

SEVERITY OF DRY EYE	N%
MILD	48(64)
MODERATE	12(16)
SEVERE	15(20)
OSDI SCORE (MEAN +/- SD)	19.56 +/- 14.75

Table 2: Dry eye severity

	Correlation co-efficient	Schirmers test	TBUT	OSDI
DAS	p- value	0.043	0.03	0.02

Table 3: Correlation between Disease activity score and tests of dry eye.

Macular Function	N%
Macular changes	6 (8%)
Defective colour vision	2(2%)
Central threshold visual field testing	4(5%)

Table 4: Macular function test for HCQ toxicity

Discussion

Rheumatoid arthritis, a systemic autoimmune disorder leading to inflammatory, symmetric polyarthritis often progressing to joint destruction, deformity, and loss of function, has a worldwide distribution with an estimated prevalence of 1–2%. Since the purpose of this study was to study dry eye in RA patients, we examined patients who visited the Department of Rheumatology for the treatment of RA and

were refered to the Department of Ophthalmology for ocular examination. Age of patients in this study was between 25 to 60 years with mean age of 43.4 ± 10.8 years. In similar study done by Piper et al[14] mean age was 58.89 ± 11.73 years. In this study 58 out of 75 patients (77.33%) were females which is similar to other studies.

Vignesh AP et al[15] study on 196 patients reported 150 patients (77%) were females and Piper et al [14] study on 75 patients reported 59 patients (78.7%) were females. This female preponderance is due to the fact females are affected more commonly than males in rheumatoid arthritis. In this study the mean duration of the disease was 3.47 ± 5.5 years. Polanska V et al [16] study reported duration of rheumatoid arthritis was 12.3 ± 11.0 years. Vignesh AP et al [15] study reported mean duration of RA in patients with ocular manifestations was 5.4± 2.7 years and in patients without ocular manifestations as 2.1 ± 1.6 years. This difference in mean duration of RA with other studies was because of inclusion of RA patients with illness less than or equal to 5 years from the date of diagnosis. In this study 67 out of 75 (89.33%) patients were positive for rheumatoid factor. Reddy et al [17] study reported out of 100 patients, 45 (45%) were positive and 55 (55%) were negative for rheumatoid factor and presence of rheumatoid factor does not correlate with the prevalence of ocular manifestations. Polanska et al [16] study also reported no statistical significance between rheumatoid factor presence and dry eye syndrome. Mean severity of rheumatoid arthritis which was based on DAS28ESR 10 was 3.89+/-1 in dry eye patients (60 patients).The mean ESR and hsCRP value of the patients was 32mm/hr (1554) and 0.88+/- 0.32 mg/l respectively.60 (50.13%) out 75 patients with RA were diagnosed to have dry eye disease among which 38 had mild dry eye ,12 had moderate dry eye and 10 patients had severe dry eye disease .The Schirmer strip wetting cut off of 5mm at the end of 5 minutes was considered and the appearance of the first dry spot on the fluorescene stained cornea tear-film less than 10 seconds was considered abnormal. The mean OSDI score was 19.56+/- 14.75 . We found OSDI score significantly correlated with Schirmer I-test values and TBUT values(P=0.036).The cause of an increased prevalence of dry eye in patients with RA could be that these patients have an increased expression of inflammatory cytokines within the conjunctival epithelium compared to controls.[18-20] Also, TNF-alpha and IL-6 gene expression in keratocytes from patients with rheumatoid corneal ulcerations tended to be up-regulated.[21]

One of the positive elements in our study design was that we took into consideration of the activity of the disease, and hence we were able to correlate RA severity with the presence of dry eye. Studies have shown that dry eye should always be taken into consideration, regardless of the RA activity and disease symptoms, because RA patients often lack the signs and symptoms of dry eye.[22] Worthy of mention is that DAS showed a statistically significant correlation with OSDI score and all clinical tests of dry eye ie,correlation between DAS and Schirmer test, TBUT and OSDI score was 0.043, 0.03and 0.02 respectively. Since the RA patients were not classified into those with and without Sjogren's syndrome, we were unable to see a difference between these two groups.

The exact cause of dry eye in patients with RA is unknown. Various theories have been proposed. There is recent evidence to suggest meibomian gland dysfunction

[24] and androgen deficiency [25] in patients with RA having Sjogren's syndrome. Eyes with meibomian gland dropout have been found to have a significantly higher evaporation rate,[26] leading to the development of dry eye. Chronic dryness may result in excessive nervous stimulation aimed at triggering the mechanisms of regulation and repair, which activate cytotoxic phenomena and result in the release of inflammatory cytokines from T-cells.[27] Once dry eye disease has developed, inflammation becomes the key mechanism of ocular surface injury as both the cause and consequence of cell damage.[28] In this study the patients were on a daily dosage of less than or equal to 6.5 mg/kg/day of Hydroxychloroquine and no associated retinopathy was found in these patients.

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