Prevalence of Dry Eye Disease in Rheumatoid Arthritis Patients

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Received: October 2019; Accepted: November 2019; Published: December 1, 2019.
Citation: Hiba AbdelmageedYounis, Zinah Yahya Jawad Al-Quzweeni. Prevalence of Dry Eye Disease in Rheumatoid Arthritis Patients. World Family Medicine. 2019; 17(12): 21-26. DOI: 10.5742MEWFM.2019.93709

Abstract

Background: Dry eye, is a common extra-ocular manifestation of Rheumatoid Arthritis (RA), It causes discomfort and complications. Little is known about its epidemiology among RA patients.

Patients and Method: A descriptive cross-sectional study was conducted at the Rheumatology Unit in Baghdad Teaching Hospital, a tertiary referral center in Iraq. A total of 103 adult Iraqi patients with rheumatoid arthritis were enrolled in this study. Data collection was done using standard questionnaire, investigation of RF, ACPA and erythrocyte sedimentation rate (ESR), Schirmer test, and ocular examination by ophthalmologist.

Results: Dry eyes were found among (27.2%) of RA cases. The age of the study group ranged between 23-60 years with a mean of 41.5 years. Females were more frequent than males with a female to male ratio of 7.6 to 1. Dry eye was more prevalent among those with positive ACPA (anti-citrullinated peptide antibody) 25(34.7%), with positive RF 28(37.3%), and those treated with biologic DMARDs 15 (42.9%). These relations were statistically significant, and those who had a positive family history were 8(57.1%), compared with those without family history 20(22.5%). This study revealed a significant correlation between ocular dryness with RF, ACPA, high disease activity and treatment with biological drugs.

Conclusion: Prevalence of dry eye was 27.2%. There was a significant association between ocular dryness with RF, ACPA, high disease activity, family history of RA and treatment with biological drugs.

Key words: Rheumatoid arthritis, dry eye, ocular manifestation.

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease which affects different ethnic groups around the world. Females are more likely to be affected than males with a ratio (2.5:1)[1]. Primarily it affects synovial joints but 40% of cases had extra-articular structures involvement [2]. The incidence of ocular findings in the Iraqi population is 32%.[3]

The estimated prevalence for RA was between (0.5% - 1.0%) in European and North American populations but in China and Japan society was (0.2%–0.3%), and native American populations was 5% [4]. The prevalence of RA is approximately 1% in the Iraqi population [5].

All these differences in regional RA prevalence may suggest environmental and genetic factors contribute to RA [6].

Initial presentation of classic rheumatoid arthritis is synovitis of small joints of the hands and feet, and with the disease progression large joints may be involved, associated with morning stiffness more than one hour, fatigue, weight loss, and low-grade fever. [7]

Dry eye (Keratoconjunctivitis sicca (KCS)), is a disorder of the tear film either due to tear deficiency or excessive tear evaporation which subsequently leads to intraepalbebral ocular surface damage [8]. The dry eye syndrome (keratoconjunctivitis sicca) can be divided into two major group; aqueous layer deficiency (Sjögren's syndrome, non-Sjögren's syndrome) and evaporative type (meibomian gland diseases, exposure, contact lens-associated and environmental) [9].

Symptoms of eye dryness include ocular burning, foreign body sensation, stinging sensation and photophobia [9].
The causes of dry eyes can be divided into primary and secondary. [9] Dry eye diseases can be secondary to environmental, hormonal, physiological, contact lens wear and pathological causes [9]. Systemic diseases that cause ocular dryness include diabetes mellitus, thyroid disease, rheumatoid arthritis, Sjögren's syndrome etc.; in addition, patients with previous eye surgeries or regular use of eye medications/systemic medications such as antihistamines, antidepressants, beta-blockers and oral contraceptives can predispose to dry eyes [9].

In terms of diagnostic criteria, Ohashi reported that: (1) Symptoms of dry eyes, (2) Schirmer tests (< 5 mm after 5 min.) and clearance test (< 8x) (3) Fluorescein stain and Rose Bengal staining (>3+) are qualified as clinical dry eyes. [10]

Treatment is targeted towards the correction of underling pathology as well as replacement of deficient tear include artificial tears and the patient with functional impairment of the hand can use an opticare device (eye drop dispenser) that may result in less wastage of tears and increase independence and compliance of the patients; gel and ointment can be used in mild to moderate dry eyes [9]. In severe dry eyes, surgical approaches such as punctal occlusion can be used to save the tear [9]. Other treatments such as topical steroids, topical immuno-modulating drugs, topical antibiotics, bandage contact lens, autologous serum and amniotic membrane may be useful in very severe cases [9].

The most common extra-articular manifestation of rheumatoid arthritis is secondary Sjögren's syndrome which is characterized by dry eyes (KCS) with positive minor salivary glands biopsy or abnormal salivary flow study (dry mouth) and occurring in approximately 35% of patients with rheumatoid arthritis [1].

Little has been reported about dry eye prevalence among RA patients in Iraq. This study aimed to evaluate the prevalence of dry eye and its associated risk factors, in a sample of adult Iraqi patients with rheumatoid arthritis.

Patients and method

A descriptive cross-sectional study was conducted at the Rheumatology Unit in Baghdad Teaching Hospital, a tertiary referral center in Iraq. A total of 103 adult Iraqi patients with rheumatoid arthritis were enrolled in this study; all of them fulfilling both the 1987 revised ACR criteria [39] and the 2010 ACR / EULAR criteria [11].

Patients above 60 year old and any patients with history of infection, retinal detachment, surgery or trauma to the eye, hypertension, diabetes mellitus or overlap with other autoimmune disease were all excluded from the study.

Ethical issues, approval and official permission: a signed consent from each of the participants was obtained after explaining the purpose of the study and ensuring privacy of the data. The approval and official permission were obtained from the Ministry of Higher Education and Scientific Research, Baghdad University, College of Medicine to conduct the present study.

Data collection:
Demographic data: name, age, gender and body mass index (BMI) were obtained from the patients. Clinical data included: symptoms of RA (presence of joint pain and/or swelling with morning stiffness), duration of disease, presence of eye symptoms (pain, redness, photophobia, discharge, blurring of vision, dryness), medical history, family history of rheumatoid arthritis, previous and current treatment, CDAI [12], and functional class of the patient [13].

Patients were investigated for RF, ACPA and erythrocyte sedimentation rate (ESR). Schirmer test was done to all patients and then all were examined by the same consultant ophthalmologist.

Statistical Analysis:
Data were translated into a computerized database structure. The database was examined for errors using range and logical data cleaning methods, and

inconsistencies were remedied. Expert statistical advice was sought. Statistical analyses were done using SPSS version 21 computer software (Statistical Package for Social Sciences).

The Pearson Chi-square ($\chi 2$) test was used to assess the statistical significance of association between 2 nominal or ordinal level variables. We assumed the level of statistical significance at $P < 0.05$. All analyzed tests were bilateral. Reference category: In any estimate of risk the calculated index measures the risk for one category in comparison to a reference category, which always has a risk of one (neutral).

Frequency distributions for selected variables were done first. To measure the strength of association between 2 categorical variables, such as the presence of certain risk factors and for disease status the odds ratio (OR) was used.

Results

The age of study group ranged between 23-60 years with a mean of 41.5 years. Females were more frequent than males with a female to male ratio of 7.6 to 1.

A positive serum for RF was obtained in 72.8% of subjects. Similarly a positive ACPA was obtained in 69.9% of subjects. About a third of patients were treated with biologic DMARDs (34%) and slightly more than a half (52.5%) had steroid treatment.

As shown in Table 1, dry eye prevalence was high among cases with RA (27.2%).

Dry eye was more prevalent among those with positive ACPA (anti-citrullinated peptide antibody) 25(34.7%),with positive RF 28(37.3%), and those treated with biologic DMARDs15(42.9%); these relations were statistically significant, as shown in Table 3.

Dry eye was more prevalent among those who had positive family history 8(57.1%), than those without family history 20(22.5%). This relation was statistically significant, as shown in Table 2.

As shown in Tables 2 and 3, a positive family history of RA significantly increased the risk of having dry eye by 4.6 times. Clinical disease activity index was positively associated with the probability of having dry eye. The risk of having dry eye was increased by 6.12 times among RA cases with high disease activity compared to those with low activity. The calculated risk estimate, however failed to reach the level of statistical significance (probably due to small sample size). A positive serum RF and ACPA significantly increased the risk of having dry eye by 34.2 and 4.96 times respectively. Treatment with biologic DMARDs also significantly increased the risk of having dry eye by 3.17 times. Treatment with steroid on the other hand was negatively, but not significantly associated with the risk of having dry eye. A long duration of treatment (2 or more years) reduced the risk by 0.39 compared to those never treated with steroids. Age, gender, duration of the disease, functional class showed no obvious or statistically significant association with dry eye.

Table 1: Point prevalence rate of dry eye in the study sample

Ocular manifestations	N	%
Dry eye (Ocular surface disease)	28	27.2
Negative for dry eye	75	72.82
Total	103	100

Table 2: The risk of having dry eye by selected general factors

	Negative		Positive			95% CI of OR	Inverse OR	
	N	%	N	%	OR			P
Age group (years)								
<35	16	66.7	8	33.3	Reference			
35-49	39	76.5	12	23.5	0.62	(1.8 to 0.2)	1.6	0.373[NS]
50+	20	71.4	8	28.6	0.8	(2.6 to 0.2)	1.3	0.711[NS]
Gender								
Female	66	72.5	25	27.5	Reference			
Male	9	75	3	25	0.88	(3.5 to 0.2)	1.1	0.856[NS]
Duration of the disease (years)-categories								
First (lowest) quartile (<= 3.0)	23	67.6	11	32.4	Reference			
Average (inter-quartile range) 3.1 - 15.0	36	73.5	13	26.5	0.76	(2 to 0.3)	1.3	0.566[NS]
Fourth (Highest) quartile (15.1+)	16	80	4	20	0.52	(1.9 to 0.1)	1.9	0.332[NS]
Family history of Rheumatoid arthritis								
Negative	69	77.5	20	22.5	Reference			
Positive	6	42.9	8	57.1	4.6	(1.4 to 14.8)	**	0.011

CI, confidence interval; N, number; NS, not significant; OR, odd ratio; RF, rheumatoid factor

Table 3: The relation between dry eye and different disease characteristics

	Negative		Positive			95% CI of OR	Inverse OR	
	N	%	N	%	OR			P
CDAI (Clinical disease activity index)-categories								
Low activity	13	92.9	1	7.1	Reference			
Moderate activity	28	71.8	11	28.2	5.11	(0.6 to 43.9)	**	0.137[NS]
High activity	34	68	16	32	6.12	(0.7 to 50.9)	**	0.094[NS]
Functional class 3								
Class-I	49	74.2	17	25.8	Reference			
Class-II	14	70	6	30	1.24	(0.4 to 3.7)	**	0.708[NS]
Class-III and IV	12	70.6	5	29.4	1.2	(0.4 to 3.9)	**	0.761[NS]
Steroid use								
Never used	33	67.3	16	32.7	Reference			
< 2 years of use	21	72.4	8	27.6	0.79	(2.2 to 0.3)	1.3	0.64[NS]
2+ years	21	84	4	16	0.39	(1.3 to 0.1)	2.5	0.135[NS]
RF								
Negative	28	100	0	0	Reference			
Positive	47	62.7	28	37.3	34.2	(4.4 to 264.6)	**	<0.001
ACPA								
Negative	28	90.3	3	9.7	Reference			
Positive	47	65.3	25	34.7	4.96	(1.4 to 18)	**	0.015
Treatment with biologic DMARDs								
Not used	55	80.9	13	19.1	Reference			
Used	20	57.1	15	42.9	3.17	(1.3 to 7.8)	**	0.012

ACPA, anti-citrullinated peptide antibody;
CDAI, Clinical disease activity index;
CI, confidence interval;
DMARDs, disease modifying anti-rheumatoid drugs;
N, number;
NS, not significant;
OR, odd ratio;
RF, rheumatoid factor

Discussion

This study shows that the prevalence of ocular manifestation in rheumatoid patients was 57.2% which is less than that obtained by Kumar et al which was 66% [14] and much higher than that obtained from Reddy et al which was 39% [15]. This might be explained by the large number of patients in the current study or may be attributed to a different ethnic group.

The prevalence of KCS in this study is 27.2% which is lower than Yumori J W (44%) [16], (54%) and by Aboud S A et al [17] and it was higher than the result obtained from Zlatanović et al which was 17.65% [18].

The keratoconjunctivitis in RA is classically described as an aqueous tear deficiency. Those patients with this disorder need supplementation of artificial tears for lifetime. Hori, Maeda and Sakamoto showed that patients with an altered ocular environment or chronic topical medication use demonstrate a disruption of the natural flora with a marked increase in antibiotic resistant organisms [19]. Sometimes disease-modifying anti-rheumatic drugs (DMARDs) systemic immunosuppressive agents may be necessary to improve tear production and to resolve severe keratoconjunctivitis sicca like Cyclosporin A, or a monoclonal antibody to TNF-alpha such as infliximab [20, 21].

This may be attributed to a large number of patients, the longer follow up period and genetic factor but it agrees with the study done by Itty et al which was 26% [22] and the study done by Bettero et al which was 29.8% [23].

This study shows that positive serum RF and ACPA significantly increased the risk of having dry eye which agrees with the result obtained from Itty et al. [22].

The study showed that positive family history of RA significantly increased the risk of having dry eye OR 4.6 times; this goes with Moss SE and Klein BEK [24].

This study experienced that the dry eye prevalence was significantly more common among patients receiving treatment with biologic DMRADs. To the best of our knowledge the only available data to support this correlation is the study done by Meijer et al who explained that TNF-targeting treatment (one of the biological DMARDs) could not be proven to be of benefit in reducing the complaints of patient with Sjögren's syndrome including dry eye [25].

Dry eye was more prevalent with increasing age, female gender, increased duration of the disease and functional class. This agreed with that obtained from the study by Reddy et al [15], Bettero et al [23] and Zlatanović et al [18], and Moss SE and Klein BEK [23]. There is no available data to support correlation between disease duration and functional class with ocular eye manifestation in rheumatoid arthritis.

Conclusion

Prevalence of dry eye was 27.2%. There was significant association between ocular dryness with RF, ACPA, high disease activity, family history of RA and treatment with biological drugs. Early and frequent eye checking for patients with RA is recommended to diagnose ocular manifestations and aggressively treat it as well as to prevent serious complications, especially in those with high disease activity, positive RF, positive ACPA, positive family history of RA and those treated with biological DMARDs.

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