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Kerato Conjunctivitis Sicca among Rheumatoid Arthritis Patients: A Cross-Sectional Study

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ABSTRACT

Rheumatoid arthritis is an inflammatory systemic disease associated with some Extra-Articular Manifestations. Keratoconjunctivitis sicca, episcleritis, scleritis, corneal changes, and retinal vasculitis are the most common ocular complications among Extra-Articular Manifestations of RA. The molecular mechanisms and the correlation between the severity and the activity of RA among RA patients suffering from KCS is still unknown. Thus, we aimed to determine the correlation between the severity of KCS and the activity of RA in an Iranian population. In the present study, 96 RA patients referring to the rheumatology clinic of Sayyad Hospital in Gorgan, Iran were included. The presence of RA was confirmed according to ACR/EULAR criteria. Blood specimens were drawn. RA activity was measured using DAS-28. Anti CCP serum levels were determined using ELISA standard assay. A set of precise eye examinations were done in order to determine different ocular complications including Schirmer's activity test. Statistical software SPSS22.0 was used for the analysis and P-values ≤ 0.05 were considered as statistically significant. Among 96 examined RA patients, 69 individuals presented Ocular complications including 65 KCS cases. We observed that DES increases with age and significantly peaks in persons aged 40-59 years (P-value=0.004). We also reported that by increasing the duration of RA the chance of developing KCS complications increases significantly (P-value=0.035). Statistical analyses showed no significant difference between the means of other variables with the severity of KCS. The results imply that the severity of RA does not determine the occurrence of KCS. Women and men are affected equally and at any stage of the disease. Therefore, RA patients should be screened for KCS at any stage and regardless of sex while considering the age of the patient.

KEYWORDS: Keratoconjunctivitis Sicca, Ocular Manifestations, Rheumatoid Arthritis, Dry Eye Syndrome, Extra-Articular Manifestations Iran

Abbreviations:

Rheumatoid arthritis	**RA**
Extra-Articular Manifestations	**EAM**
Rheumatoid Factor	**RF**
Anti–citrullinated protein antibody	**ACPA**
Keratoconjunctivitis sicca	**KCS**
Dry Eye Syndrome	**DES**
Sjögren Syndrome	**SS**
Chloroquine	**CQ**
Hydroxichloroquine	**HCQ**
Nonsteroidal anti-inflammatory drug	**NSAID**
The European League Against Rheumatism	**EULAR**
Intraocular Pressure	**IOP**

INTRODUCTION

Rheumatoid arthritis (RA) is an inflammatory systemic disease associated with some Extra-Articular Manifestations (EAM) [1, 2]. Systemic features in RA are mostly related to vasculitis and a consequence of

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persistent inflammation[3]. EAMs which occur among almost 40% of RA patients affect various tissues and organ systems[4]. EAM is associated with a high risk for morbidity among RA patients[5]. These manifestations including rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications are more probable among RA patients with elevated titers of RF (Rheumatoid Factor) or Anti–citrullinated protein antibodies (ACPAs) [1, 4, 5]. ACPAs occur independently of rheumatoid factors. Antibodies against CCP are predominantly of IgG class and have a specificity of 95% for RA which can be found in the serum of 70%-80% of patients very early during the development of the disease[6]. Keratoconjunctivitis sicca (KCS), episcleritis, scleritis, corneal changes, and retinal vasculitis are the most common ocular complications observed among RA patients. Several population-based studies have revealed that KCS is naturally the most frequent ocular complication in RA patients [7-11]. Although RA is the most common systemic situation associated with scleritis, the reported incidence rate is not comparable to KCS[12].KCS which is also known as Dry Eye Syndrome (DES), is a multifactorial disease of the tears and the ocular surface that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface[13]. KCS is subdivided into associated with Sjögren syndrome (SS KCS) and unassociated with SS (non-SS KCS). SS is a complication occurring among the majority of RA patients [7, 9]. Administering systemic treatments such as Corticosteroids, Chloroquine (CQ), Hydroxichloroquine (HCQ), Nonsteroidal anti-inflammatory drugs (NSAIDs) and methotrexate which are widely prescribe among RA patients could result in more EAMs including ocular manifestations[3]. In order to monitor the efficacy of treatment, the activity of RA should be measured[14]. Disease Activity Score (DAS) is one of the methods indicating current RA disease activity[15]. Although ocular complications especially KCS are frequently observed among RA patients, the underlying molecular mechanisms and the correlation between the severity and the activity of RA among this group of RA patients is still remained to be studied. Furthermore, to make the best decision on a proper drug regimen, trusted epidemiologic data should be available. Therefore, we aimed to determine the correlation between the severity of KCS and the activity of RA in an Iranian population in Northeast of Iran in the present study.

MATERIALS AND METHODS

We examined 96(14 men and 82 women) RA patients referring to the rheumatology clinic of Sayyad Hospital in Gorgan, Northeast of Iran during August 2014 till March 2015. The presence of RA was confirmed according to ACR/EULAR criteria among all patients [16]. Blood specimens were taken of all patients and isolated serum samples were stored at -20°C until experimental procedure. The means±SD patient age was 47.63±12.72 years (range 16 to 76 years). Informed consent was obtained from all participants in this research study. Physical examination regarding the swollen, painful and/or deformed joints was accomplished followed by a brief history of the disesease. RA activity was measured using DAS-28 as a defined disease activity measurement tool validated by EULAR[17]. In order to diagnose RA patients with higher sensitivity, serum samples of all patients were assessed using anti CCP ELISA assay (Euroimmun, Germany) according to the manufacturers protocols. Moreover, RF IgM and ESR levels in serum samples of all patients were measured by standard test methods. To determine different ocular complications associated with RA and/or systemic treatments, a set of precise eye examinations including detection of visual acuity, close observation of the anterior and fundus of the eye using Slit Lamp (Takagi, Japan), determination of intraocular pressure (IOP), and Schirmer's test[18] to evaluate the severity and grade of DES were done by an expert ophthalmologist.

All of the experiments were repeated at least in duplicates and data were demonstrated as means±SD (standard deviation). Statistical software SPSS22.0 was used for data analysis. The parametric independent T-test, and nonparametric Kruskal-Wallis and Mann-Whitney U tests were used to compare means of samples. P-values less than 0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

Among 96 examined RA patients, 69(71.8%) individuals presented Ocular complications including 65(67.7%) patients suffering from KCS, 2(2.1%) from scleritis, 1(1%) from episcleritis and 1(1%) from Secondary glaucoma. Schirmer's test was done on RA patients with KCS to evaluate the severity and grade of eye dryness. We demonstrated that 62(95.5%) RA patients had Slight KCS complications while the number of patients suffering from Moderate and Severe KCS were 1(1.5%) and 2(3%) respectively. The mean ESR level among patients participated in this study was 33.11±26.16.

RA patients were divided into different age groups. The mean age of RA patients with DES was 50.2±11.91 while the mean age among RA patients without DES was reported as 42.25±12.86 (Table 1). We observed that DES

increases with age and significantly peaks in persons aged 40-59 years (P-value=0.004). Logistic regression analyses represent that the risk of developing KCS among RA patients increases almost 2% each year (CI=1.009-1.028, OR=1.019, P-value<0.0001)

Table1. Distribution of DES among different Age groups

Age Groups(yrs)	RA patients with DES N (%)	RA patients without DES N (%)	P-value (t-test)
≤20	0(0)	1(100)	
20-39	10(47.6)	11(52.4)	
40-59	42(71.2)	17(28.8)	
≥60	13(86.7)	2(13.3)	
means±SD	50.2±11.91	42.25±12.86	**0.004***

*The differences between two groups were significant.

The clinical manifestations of chronic and systemic diseases are influenced by the disease duration[2]. Here, RA patients with KCS complications had been suffering for approximately 8.26±7.8 years of RA while the duration of disease among patients without KCS was reported to be 4.74±5.2 years. This reflects that by increasing the duration of RA the chance of developing KCS complications increases as well among RA patients significantly (P-value=0.035).

Anti CCP was reported to be positive among 65.6% of RA patients with ocular manifestations. Although there were some minor differences while comparing the means of different sex groups, Anti CCP serum levels and RA activity but despite our expectations, statistical analyses showed no significant difference between these means with the severity of KCS among RA patients (Table 2).

Table2. Distribution of DES by disease activity, sex and Anti CCP serum levels

KCS Status	Disease activity (DAS28)				Sex		Anti CCP Level		
	Remission N (%)	Low Disease Activity N (%)	Moderate Disease Activity N (%)	High Disease Activity N (%)	Male N (%)	Female N (%)	Normal (N/%)	Low Positive (N/%)	High Positive (N/%)
Without DES	8(66.6)	8(42.1)	13(29.55)	2(22.23)	5(35.7)	26(31.7)	6(24)	7(46.7)	15(68.75)
With DES	16(33.4)	11(57.9)	31(70.45)	7(77.77)	9(64.3)	56(68.3)	19(76)	8(53.3)	33(31.25
P-value	**0.701****				**0.767****		**0.415****		

**No significant difference was observed between two groups.

Rheumatoid arthritis (RA) is an inflammatory systemic disease of unknown cause that primarily affects the peripheral joints in a symmetric pattern [1, 2]. Genetic factors and immune system abnormalities contribute to disease development and progression. Although, RA is associated with different Extra-Articular Manifestations (EAMs) including rheumatoid nodules, rheumatoid vasculitis, and pleuropulmonary, neurologic, digestive, cardiovascular, cutaneous, hematologic, and ocular complications[3, 5, 19]. The most prevalent ocular complications observed among RA patients are Keratoconjunctivitis sicca (KCS), episcleritis, scleritis, corneal changes, and retinal vasculitis [9-11, 14].

The most common ocular manifestation among RA patients was Keratoconjunctivitis sicca (67.7%), which was greater than previous studies [7, 11, 18]. KCS is described as an aqueous tear deficiency while patients with this disorder need supplementation of artificial tears for lifetime [3, 5, 10]. We observed that the severity of KCS increases with age significantly. It could be discussed that the Histopathologic destruction of tear glands increases with age directly[20]. The ocular manifestations of RA as a chronic and systemic disease are influenced by the disease duration. Disease duration which is a consequence of aging in chronic diseases is a factor determining the severity of KCS significantly which was in accordance with different previous studies [7, 11].

Although the ratio of sex distribution among RA patients included in the present study (F/M:5.85/1) was higher than previous ones [7, 9, 11, 14] but the severity of KCS was not greater in any of each sex group. This represents that the possibility of emerging KCS as an EAM is equal regardless of sex.

We also showed that there are no significant relationships between the severities of KCS, disease activity and Anti CCP serum level. These results are against other previous studies [7, 9, 11, 14], reflecting that the possibility of emerging KCS as an ocular complication is regardless of disease activity and RA patients are prone to develop KCS at any stage of the disease. These results confirmed the results derived from Anti CCP Elisa assays.

Conclusion

In conclusion, KCS is the most visited ocular manifestation involved with RA in the present study in Gorgan, Northeast of Iran. Although the duration of disease and aging are major determinants of KCS status, the severity of RA does not determine the occurrence of these ocular complications and the distribution of KCS is not sex specific. Thus, women and men are affected equally and at any stage of the disease. Therefore, RA patients should be screened for KCS at any stage and regardless of sex while considering the age of the patient.

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