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Ocular Manifestations in Rheumatoid Arthritis: A Descriptive Cross-Sectional Study from Iraq

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Abstract

Background: Ocular involvement.is one of the most important extra articular manifestation of rheumatoid arthritis (RA)
Objective: To evaluate the ocular manifestations in patients with RA.
Patients and Methods: A cross sectional study was conducted on (103) patients with RA diagnosed according to either 1987 revised American College of Rheumatology (ACR) criteria or the 2010 ACR /European League Against Rheumatism (EULAR) criteria for diagnosis of RA. Baseline demographic and clinical characteristics of patients were recorded. Ocular manifestations were assessed in all patients.
Results: A total of 103 patients with RA enrolled in this study, the mean age was 41.5 years with a female to male ratio of 7.6: 1. A positive serum for rheumatoid factor was obtained in 72.8% of patients, and a positive anti-cyclic citrullinated peptide antibody (ACPA) was obtained in 69.9% of patients. Dry eyes were the most frequently identifiable ocular manifestation (27.2%), followed by drug induced ocular disease (12.6%), in this category, posterior subcapsular cataract ranked first (8.7%), followed by blepharitis (3.9%). The occurrence of ocular inflammatory diseases was 8.7%, among this category of ocular diseases, conjunctivitis was at the top of the list (5.8%). A significant correlation was found between ocular dryness with RF, ACPA, high disease activity and treatment with biological drugs.
Conclusions: The prevalence of ocular findings in patients with RA was 57.2%. The commonest was ocular dryness followed by posterior subcapsular cataract, other types of cataract, conjunctivitis, blepharitis, uveitis, episcleritis, keratitis and scleromalacia. Ocular dryness had a significant correlation with RF, ACPA, high disease activity and treatment with biological drugs but there was no correlation of these predictors with drug induce ocular disease or inflammatory ocular disease. There was no significant correlation between ocular manifestation with age, gender, functional class and disease duration.
Keywords: Rheumatoid arthritis, Ocular manifestations, Dry eyes, Drug induced ocular manifestations, Ocular inflammatory diseases.

1. Introduction

Rheumatoid arthritis (RA) is one of the most common systemic autoimmune inflammatory disease [1]. Primarily the target structure of disease is the synovial joints but extra-articular structures may be involved. [2] Forty percent of RA have an extra-articular manifestation either from the beginning or during the course of their disease and occurs more frequently with seropositive patients. [3, 4] one of the most important extra articular manifestations of RA is ocular involvement. [1] The incidence of ocular finding in Iraqi population is 32% [4]. The most common extra-articular manifestation of RA is secondary Sjögren's syndrome which is characterized by dry eyes (keratoconjuctivitis sicca 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]. The prevalence of episcleritis in RA is reported to be about 0.17%.[5]. The prevalence of scleritis in RA is reported to be 0.67% to 6.3%. [5, 6]]. Keratitis is a common disorder that affect peripheral cornea. Corneal changes such as sclerosing keratitis, peripheral corneal thinning, acute stromal keratitis and acute corneal melting are manifestations. [7, 8] Long-term use of oral glucocorticoids in treating RA can produce posterior subcapsular cataracts [9]. Chronic use of topical or systemic steroids can also cause glaucoma. [10] This study design to assess ocular manifestations among Iraqi patients with RA.

2. Patient and Method

2.1 Study design and population
A descriptive cross-sectional study was conducted at the Rheumatology Unit in Baghdad Teaching Hospital, a tertiary referral center in Iraq, from August 2014 to May 2015..A total of 103 patients with rheumatoid arthritis were enrolled in this study, all of them either fulfilled the 1987 revised ACR criteria [11] or the 2010 ACR / EULAR criteria for diagnosis of RA. [12] Patients above 60 year old and patients with history of infection,

retinal detachment, surgery or trauma to the eye, hypertension, diabetes mellitus or overlap with other autoimmune disease all were excluded from the study.

2.2 Methods

Baseline demographic and clinical characteristics were colledted from the patients included: Age, gender and body mass index (BMI) duration of RA, presence of eye symptoms (pain, redness, photophobia, discharge, blurring of vision, dryness), medical history, family history of rheumatoid arthritis, previous & current treatment, clinical disease activity index (CDAI) [13] and functional class of the patient. [14] Patients were investigated for RF, ACPA and erythrocyte sedimentation rate (ESR). Schirmer test was done to all patients and then all of them were examined by a same consultant ophthalmologist by fundoscopy and slit lamp examination.

2.3 Statistical analysis

Statistical software (SPSS version 22, IBM, USA) was used for analysis. Kolmogorov-Smirnov test was used to assess the normal distribution of continuous variables. Continuous variables were reported as mean ±SD, and categorical variables as frequencies and percentages. Multiple logistic regression analysis was used to assess the net risk for each of selected explanatory variables on having the ocular manifestation. P value < 0.05 was considered statistically significant.

3. Results

The results were based on the analysis of a random sample of 103 cases with RA.The age of study group ranged between 23-60 years with a mean of 41.5±10 years. A female to male ratio was 7.6:1. A positive serum for RF was obtained in 72.8% of patients. While a positive ACPA was 69.9%. About a third of patients ((34%) were treated with biologic disease modifying antirheumatic drugs (DMARDs) and slightly more than a half (52.5%) had steroid treatment.

As shown in Figure1, a dry eye was the most frequently identified ocular manifestation among cases with RA (27.2%), followed by drug induced ocular disease (12.6%). In this category, posterior subcapsular cataract ranked first (8.7%), followed by Blepharitis (3.9%). Ocular inflammatory diseases were ranked as the third manifestation (8.7%). Among this category of ocular diseases, conjunctivitis was at the top of the list (8.7%). All patients with ocular findings were symptomatic. All the study subjects had a positive history of using at least one of non-biological DMARDs, therefore such an attribute is no longer a variable and will not include in this study.

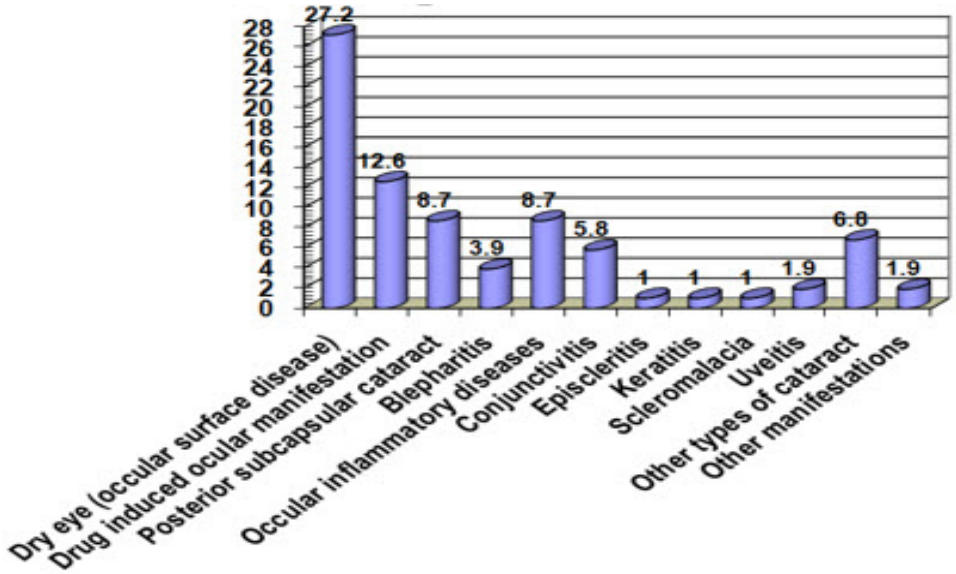

Figure 1: Bar chart showing the point prevalence rate of selected ocular manifestation in the study sample.

To study the net and independent effect of each of a set of explanatory (predictor) variables on the risk of having dry eye as an outcome (response) variable a multiple logistic regression model was used. Age, duration of disease, CDAI and treatment with biologic DMRADs and steroids were included in the logistic model as predictors. Only treatment with biologic DMRADs and high disease activity significantly increased the risk of

having dry eye after adjusting for the remaining explanatory variables included in the model. The model was statistically significant with an overall prediction accuracy of 75.7% for the tested outcome (dry eye),as in table 1.

And on studying the net and independent effect of each of a set of explanatory (predictor) variables on the risk of having drug induced ocular manifestations as an outcome (response) variable using a multiple logistic regression model it revealed that only long duration (2 or more years) of treatment with steroids significantly increased the risk of having drug induced ocular manifestations by 9.66 times after adjusting for the remaining explanatory variables included in the model. The model failed to reach the level of statistical significance (since only one predictor was relevant) with an overall prediction accuracy of 87.4% for the tested outcome (drug induced ocular manifestations) as shown in table 2.

In table 3, none of the variables showed any important prediction for the risk of having ocular inflammatory disease when tested in multivariate models.

Table 1: Multiple logistic regression model with the risk of having dry eye (ocular surface disease) as the dependent (outcome) variable and selected explanatory variable.

Dry eye (Ocular surface disease)	**Adjusted OR**	**P**
Age group (years)		0.77[NS]
35-49 compared to <35	0.63	0.47[NS]
50+ compared to <35	0.78	0.73[NS]
Duration of the disease (years)-categories		0.54[NS]
Average (inter-quartile range) compared to "first (lowest) quartile (<= 3.0)"	0.64	0.42[NS]
Fourth (Highest) quartile (15.1+) compared to "first (lowest) quartile (<= 3.0)"	0.45	0.3[NS]
CDAI (Clinical disease activity index)-categories		0.15[NS]
Moderate activity compared to Low activity	7.13	0.09[NS]
High activity compared to Low activity	9.46	0.05
Treated with Biologic DMRADs compared to untreated	4.50	0.004
Steroid use		0.47[NS]
< 2 years of use compared to "never used"	0.86	0.81[NS]
2+ years compared to "never used"	0.43	0.22[NS]

P (Model) = 0.046
Prediction accuracy of positive outcome= 28.6%
Overall prediction accuracy = 75.7%
OR, Odds ratio; NS, not significant

Table2: Multiple logistic regression model with the risk of having drug induced ocular manifestations as the dependent (outcome) variable and selected explanatory variable.

Drug induced ocular manifestation	Adjusted OR	P
Age group (years)		0.55[NS]
35-49 compared to <35	2.33	0.47[NS]
50+ compared to <35	3.82	0.29[NS]
Duration of the disease (years)-categories		0.39[NS]
Average (inter-quartile range) compared to "first (lowest) quartile (<= 3.0)"	3.56	0.17[NS]
Fourth (Highest) quartile (15.1+) compared to "first (lowest) quartile (<= 3.0)"	2.42	0.41[NS]
CDAI (Clinical disease activity index)-categories		0.42[NS]
Moderate activity compared to Low activity	0.40	0.42[NS]
High activity compared to Low activity	1.11	0.93[NS]
Use of Biologic DMRADs compared to non-users	1.29	0.73[NS]
Steroid use		0.013
< 2 years of use compared to "never used"	1.38	0.75[NS]
2+ years compared to "never used"	9.66	0.006

P (Model) = 0.09[NS]
Prediction accuracy of positive outcome= 23.1%
Overall prediction accuracy = 87.4%
OR, Odds ratio; NS, not significant

Table 3: Multiple logistic regression model with the risk of having ocular inflammatory diseases as the dependent (outcome) variable and selected explanatory variable.

Ocular inflammatory diseases	Adjusted OR	P
Age group (years)		0.9[NS]
35-49 compared to <35	1.476	0.67[NS]
50+ compared to <35	1.139	0.9[NS]
Duration of the disease (years)-categories		0.76[NS]
Average (inter-quartile range) compared to "first (lowest) quartile (<= 3.0)"	1.277	0.76[NS]
Fourth (Highest) quartile (15.1+) compared to "first (lowest) quartile (<= 3.0)"	2.016	0.46[NS]
CDAI (Clinical disease activity index)-categories		0.65[NS]
Moderate activity compared to Low activity	1.082	0.94[NS]
High activity compared to Low activity	.557	0.57[NS]
Treated with Biologic DMRADs compared to untreated	1.540	0.53[NS]
Steroid use		0.35[NS]
< 2 years of use compared to "never used"	1.506	0.59[NS]
2+ years compared to "never used"	.268	0.24[NS]

P (Model) = 0.87[NS]
Prediction accuracy of positive outcome= 0%
Overall prediction accuracy = 89.3%
OR, Odds ratio; NS, not significant

4. Discussion

This study showed 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%. [11] And much higher than that obtained from Reddy et al which was 39% [12]. This may be explained by the large number of patients in current study or attributed to the different ethnic group. The most common ocular manifestation in the present study was eye dryness (KCS), the prevalence of KCS in this study was 27.2% which is more than the result obtained from Zlatanović et al which was 17.65% [13]. This may be related to large number of patients, the longer follow up period and genetic factor but it agreed with Itty et al study which was 26% [14] and the study done by Bettero et al which was 29.8% .[15] In this study, CDAI was positively associated with the probability of having dry eye which disagreed with the study done by Zakeri et al, and this may be explained by different ethnic population and environmental factors. [16] This study showed that positive serum RF and ACPA significantly increased the risk of having dry eye which agreed to the result obtained by Itty et al. [14]. The current study showed that positive family history of RA significantly increased the risk of having dry eye. This study experiences that the dry eye prevalence significantly more common among patients receiving treatment with biologic DMRADs, to best our knowledge the only available data to support this correlation is the study that done by Meijer et al who explained that TNF-targeting treatment (one of biological DMARDs) had not be proven to be of benefit in reducing the complaints of patient with Sjögren's syndrome including dry eye[17]. Age, gender, duration of the disease, and functional class showed no statistically significant association with dry eye which disagreed with Reddy et al [12], Bettero et al [15] and Zlatanović et al [13] studies that reported women were more affected than men, this can be explained by different environmental and genetic factors between these populations. No available data to support correlation between disease duration and functional class with ocular eye manifestation in rheumatoid arthritis.

In current study, the prevalence of conjunctivitis was 5.8% which is closely similar to that obtained by Kumar et al. [11] Episcleritis prevalence in this study was 1% which is lower than to 5.06% that obtained by Zlatanović et al [13], this variation may be related to the smaller number of patients in our study, short duration of the study or may be due to earlier attending of the patients for ophthalmic evaluation.

The prevalence of keratitis in the current study was 1% closely similar to the study done by Kumar et al. [11]. Also Scleromalacia perforans was 1%. Uveitis was 1.9% which is lower than 20 % that was determined by Kumar et al. [11] this may be due to the smaller number of patients in the present study or regular eye follow up and evaluation. In rheumatoid arthritis, uveitis is rare, it can occur as a complication of scleritis in about 42% especially with anterior scleritis. [19] Also it can occur as a complication of anti-TNF agents that used as a treatment of RA [20], this fact was mentioned by Wendling et al which reviewed publications describing the occurrence of uveitis in patients on anti-TNF treatment especially with etanercept [21]. On the other hand Daguano et al published a case report about presence of uveitis earlier in the absence of scleritis in a patient with rheumatoid arthritis. [22]

None of the explored risk factors or predictors had a statistically significant association with the risk of having ocular inflammatory diseases in this current study. Regarding drug induced ocular manifestations in RA in the present study, the most common one is the posterior subcapsular cataract as complication of systemic glucocorticoids 8.7% which is slightly higher than 5.4% that obtained by Hamied et al. [4] the reason may due to different steroid dose and duration. Followed by other types of cataract 6.8% then by blepharitis as a complication of methotrexate which was 3.9%. [9, 5].

The current study revealed that a long duration of treatment with steroid (2 or more years) increased the risk of having the ocular manifestation by 9.66 times compared to those never treated with steroids, Black et al [23] noted that the higher the steroid dose and/or longer duration of treatment more than one year, the greater the prevalence of steroid induced cataract whereas those on doses of less than 10 mg/day of prednisone or equivalent were unlikely to develop lenticular changes [23, 24]. Age, Gender, family history of RA, functional class, RF, ACPA duration of disease, CDAI, and treatment with biologic DMRADs showed no statistically significant association with drug induced ocular diseases in the present study.

Other miscellaneous finding in this study was 1.9% represented in optic disc swelling and asteroid hyalosis. Optic disc swelling which was only one case out of 103 patients with RA, this finding is consistent with Kumar et al study, no other cause was found on investigation and so we presume it was due to inflammatory arthritis that the patient had [11]. Asteroid hyalosis (AH); (is a common degenerative process in which fatty calcium globules collect within the vitreous humour), was noted in one patient in current study, AH has been associated with systemic diseases such as diabetes mellitus [25]. No available data to support the correlation between AH and RA.

In conclusion**,** the prevalence of ocular findings in a sample of Iraqi patients with RA was 57.2%. The ocular findings were ocular dryness 27.2%, posterior subcapsular cataract 8.7%, other types of cataract 6.8%, conjunctivitis 5.8%, Blepharitis 3.9%, uveitis 1.9%, episcleritis, keratitis, scleromalacia 1% for each and others 1.9%. There was significant association between ocular dryness with RF, ACPA, high disease activity, family history of RA and treatment with biological drugs but not with the form of ocular manifestation. There was no significant association between ocular manifestation with age, gender, functional class and disease duration.

There was significant association with use of steroid more than 2 years and the prevalence of posterior subscapular cataract.

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