Ocular manifestations of rheumatoid arthritis and their correlation with anti - cycliccitrullinated peptide antibodies

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Abstract: Background: Rheumatoid arthritis is a chronic systemic inflammatory autoimmune disease that affects approximately 1% of the population worldwide. It is associated with extra-articular manifestations including potentially sight-threatening inflammatory eye disease. **Objective:** To outline the ocular manifestations in RA and to assess their correlation with anti-CCP antibody and RF. **Methods:** 50 consecutive patients with RA were included in the present study. All patients met 2010 ACR/ EULAR Classification criteria for early arthritis. The examination of eyes were done to estimate eye manifestations and to interpretation of the related findings. The findings were statistically analyses. **Results:** 19(38%) patients out of the 50 patients included in the present study had ocular manifestations due to current rheumatoid arthritis. In 33 eyes had ocular involvement (14 patients were bilateral manifestation and only 5 patients were unilateral manifestation). Ocular manifestations were significantly increased in females (94.7%) with more prevalence in older patients. The mean duration of rheumatoid arthritis was 6.7±2.3 years in patients with ocular manifestations and was 4.7 ± 3.7years in without ocular manifestations (***P***= 0.040). The most common manifestation was dry eye (13 patients, 26%). There were six (12%) patients had filamentary keratitis, five (10%) patients had episcleritis and two (4%) patients had scleritis. Corneal deposits were present in 6% of the patients. Peripheral ulcerative keratitis, glaucoma and retinal vasculitis was present in 4% of the studied group each (two patients). However, visual acuity was decreased in 22% of the RA patients The most frequent ocular manifestations found in RA patients positive for anti-CCP antibodies and RF (*P*= 0.006 and 0.019 respectively). **Conclusions:** Ocular involvement is common in RA, the most common ocular manifestation is dry eye. Patients at risk for development of ocular manifestations include longer disease duration, female sex, disease activity and anti-CCP and RF positivity. In addition, using HCQ and steroids drugs contributes to eye pathology in RA. Collaborative efforts between the ophthalmologists and rheumatologists are essential to early detect and effectively manage any ocular complications that may arise in RA patients.

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1. Introduction

Rheumatoid arthritis (RA) is a common, chronic, inflammatory, antibody mediated autoimmune disease with prevalence ranges from 0.5% to 1%[1]. The synovial membrane is the primary target of the inflammatory process in the RA leading to cartilage and bone destruction[2]. Whereas, the corresponding systemic inflammation may result in disorders of multiple organ systems evolving extra-articular manifestations[3]. Thesystemic manifestations of RA may be detected by the release of the pro-inflammatory molecules such as interleukin-1, interleukin-6 and tumor necrosis factor-alpha from the synovium[4, 5]. Interleukin 6 is a pleiotropic cytokine that has a pivotal role in the pathophysiology of rheumatoid arthritis[6].

The incidence of ocular manifestations among RA patients ranges from in 25% to 39%[7]. Ocular diseases mostly include keratoconjunctivitis sicca, episcleritis, scleritis, peripheral ulcerative keratitis, and retinal vasculitis[8]. These Ocular manifestations vary and may affect various components of the eye. Their severity is related to RA chronicity and resistance to therapy[9].

The use of chloroquine (CQ) and hydroxychloroquine (HCQ) are associated with significant ocular toxic effects including corneal deposits and pigmentary retinopathy. CQ has a higher

risk of retinal toxicity than HCQ[10]. CQ and HCQ can cause corneal deposits, which can be associated with halos around lights and are benign and reversible[11]. A corneal deposit was found in approximately 95% of patients on treatment with CQ and 10% of patients taking HCQ[12]. This deposit was a significant predictor of mild retinopathy[13]. In addition to, ocular involvement (posterior subcapsular cataracts) can occur as a result of systemic treatment and long-term use of oral steroids[14]. Chronic topical or systemic steroids can also lead to glaucoma [15].

RF and Anti-CCP Antibodies are the most RA-specific laboratory findings and are used for diagnosis or detect stage of suspected RA. These are associated with high disease activity and detectable in up to 80% of patients[16, 17]. Anti-cyclic citrullinated peptide antibodies (anti-CCP) are a more sensitive and specific marker of systemic involvement in RA than RF antibody. Anti-CCP antibody is emerging as the preferred diagnostic marker for RA especially in early cases. It also predicts the future occurrence of the RA in undifferentiated arthritis. The sensitivity and specificity of anti-CCP reactivity for RA patients diagnosed based on American College of Rheumatology (ACR) criteria were detected as 73.5% and 100%, respectively which shows it to be a highly sensitive and specific marker for the disease[18].

The double positive of anti-CCP antibodies and RF had more severe ocular involvement compared to those who were negative for these antibodies[19]. However there was a strong association between the presence of anti-CCP antibodies (but not RF) and the presence of ocular manifestations of RA[7].

Therefore, the current study aim to outline the presence of ocular manifestations and their relation to the presence of anti-CCP antibodies, RF and /or other factor that had clinical entity.

2. Subjects and Methods

Patients

The current study consisted of 50 patients (37 females and 13 males) with RA in the period from January 2016 to July 2016. Diagnosis of RA was made by 2010 ACR/ EULAR Classification criteria for early arthritis[20]. Patients were recruited from the Rheumatology and Rehabilitation Outpatient Clinic of Al-Azhar University Hospital in Damietta. Patients were selected according to strict and common used criteria (table1). The selected patients who met the inclusion criteria examined by ophthalmologist to undergo routine ophthalmologic screening and subdivided into two 2 groups: patients with ocular manifestations and without ocular manifestations.

Statistical analysis

Statistical analysis was performed using SPSS (version 20.0, Chicago, IL). Continuous data were expressed as mean ±standard deviation (SD). While categorical data were expressed in number and percentage. The differences between the groups were determined using independent sample Student's t test for continuous data or chi-square test for categorical data. Statistical significance was set at $p<0.05$.

3. Results

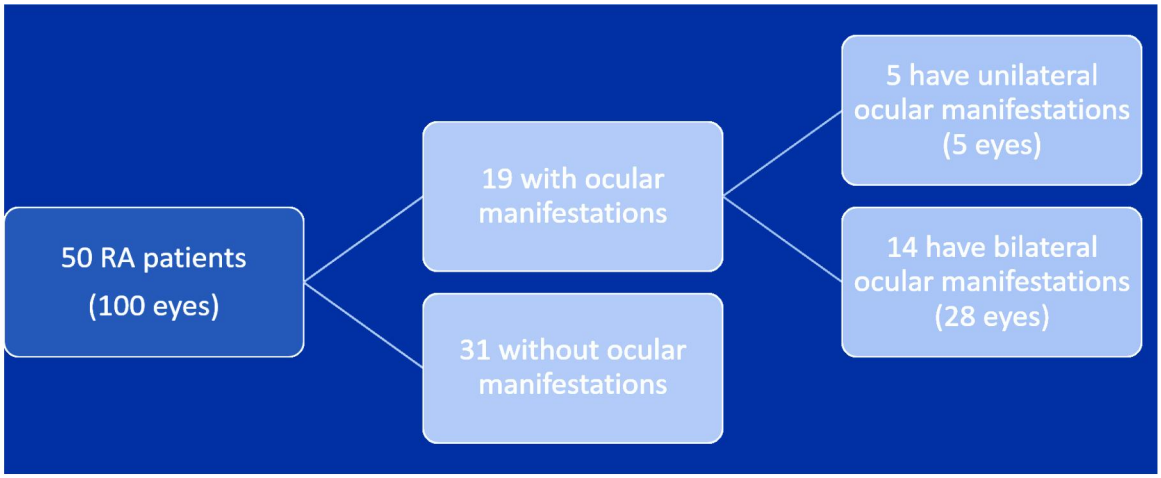
The average age of the RA patients was 36.9 ±8.7 years (ranged from 22 to 59 years). As regards the sex distribution, the RA patients were 37 females and 13 males represent 74% and 26% respectively. Ocular manifestations were found in 19(38%) patients. The frequency of ocular involvement is bilateral manifestation in 14 patients and unilateral in 5 patients, **Fig1**. From the RA patients participated in this study, the most common eye manifestation reported was dry eye being observed in 13 (26%) patients. Corneal involvement includes also filamentary keratitis (12%), PUK (4%) and corneal deposits (6%). Episcleritis was found in 10% of the patients while scleritis was found in 4% of the patients. 6% had cataract and 4% had glaucoma, 4% had retinal vasculitits and 10% had bull's eye retinopathy. Visual acuity was decreased in 22% of the RA patients. **Fig.2.**

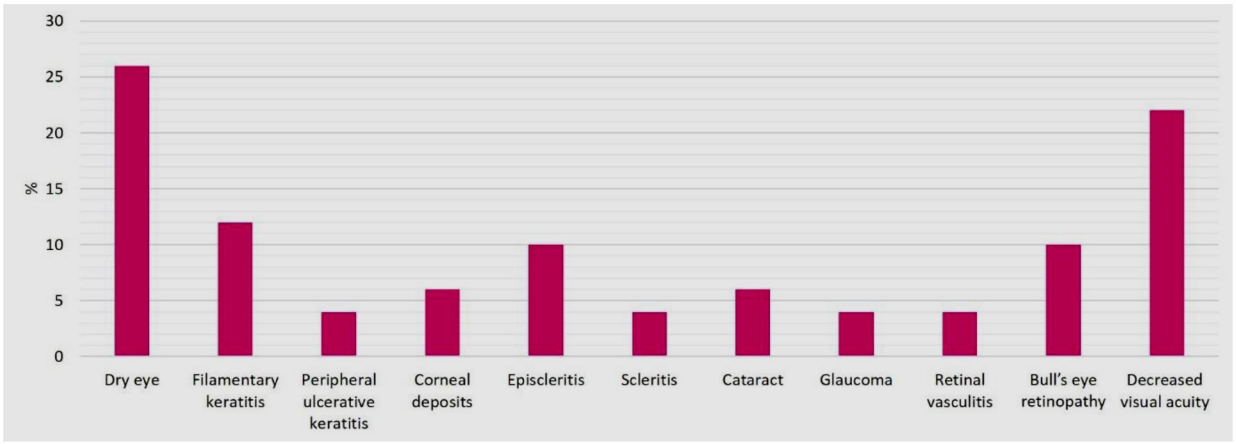
As regard to age and sex, ocular manifestations were significantly increased in females (94.7%) than males (5.3%) with more prevalence in older patients (**table 2).** The mean duration of rheumatoid arthritis was 6.7±2.3 years in patients with ocular manifestations and was 4.7 ± 3.7years in without ocular manifestations (***P***= 0.040). In addition, the DAS28-CRP and DAS28-ESR were significantly higher in patients with ocular manifestations than in patients without ocular manifestations (P=0.022 and P =0.032 respectively). The HAQ-DI score of the RA patients who had ocular manifestations was 2.0 ±0.8 compared to 1.3 ±0.8 in other RA patients (P =0.008). **Fig.3.**

In a comparison between mean±SD of ESR and CRP in the two patients groups, the serum level of ESR 1st hour and serum level of CRP were significantly higher in RA patients with ocular manifestations than patients without ocular manifestations (P=0.022 and P=0.039 respectively), **table3**.

The complication related to use of drugs for RA was seen in **table 4**. RA patients were commonly treated with methotrexate, leflunomide, hydroxy - chloroquine, steroids, and biological therapy. Only patients who take HCQ and steroids had more frequently ocular manifestations than patients not treated with these drugs. On the other hand, no significant association had been found between the

MTX, leflunomide and biological therapy and the presence ocular manifestations.





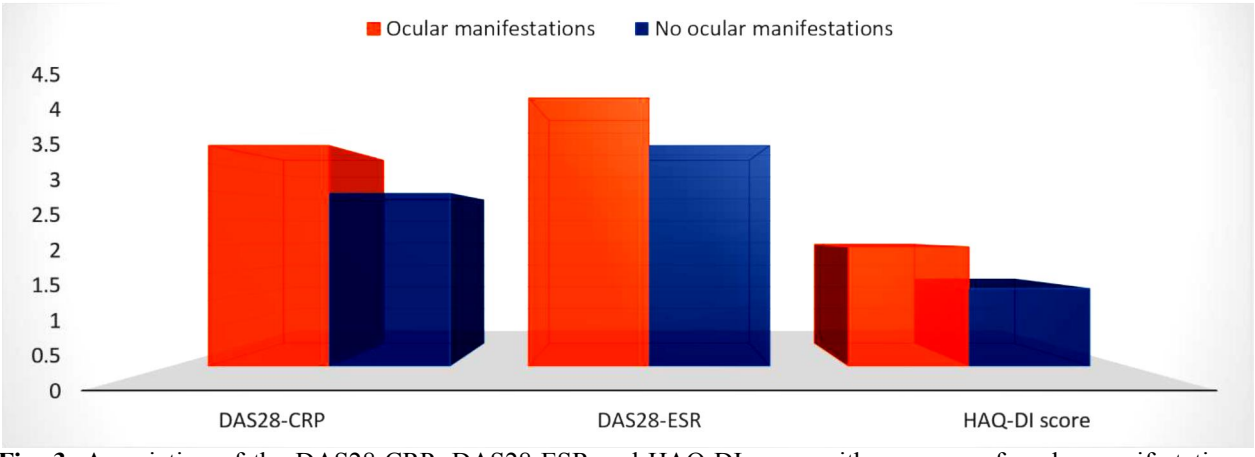


Fig. 3. Association of the DAS28-CRP, DAS28-ESR and HAQ-DI score with presence of ocular manifestations among RA patients

Fig. 4. Bull`s eye retinopathy in the right eye of 30 years old male patient with RA**.**

Table 1: Patient Screening Criteria and workup

Exclusion Criteria:

1. Age less than 18 years or older than 60 years
2. Subjects with any local eye disease due to causes other than the RA
3. Presence of any systemic disease that may affect the eye e.g. hypertension, diabetes
4. Presence of other systemic autoimmune diseases

All patients were subjected to the following:

1. Medical History Taking (Personal *History, History of the Present Medications, and Past History).*
2. General and Musculoskeletal System Examination (Full *Systemic Examination, and Musculoskeletal Examination).*
3. Evaluation of Rheumatoid Arthritis Activity and Severity (Visual Analog Scale – Pain, Disease Activity Score 28 –CRP, and Health Assessment Questionnaire–Disability Index).
4. Ocular Examination (Detailed Anterior Segment Examination, Dry eye and fundus examination).
5. Laboratory Investigations include (CRP, Anti-CCP Ab, and RF)

Table 2. The association of ocular manifestations with the age, sex and the RA related clinical features

	Ocular manifestations Mean ±SD		No ocular manifestations Mean ±SD		Student's t test t	p
Age (years)	40.1 ±10.4		35.0 ±6.9		2.069	0.044
Sex (n, %)						
Females	18	94.7	19	61.3		
Males	1	5.3	12	38.7	6.849*	0.009
Duration of RA (years)	6.7 ±2.3		4.7 ±3.7		2.114	0.040
Duration of morning stiffness (minutes)	41.5 ±19.3		36.8 ±21.7		0.760	0.451
TJC	16.5 ±6.0		15.6 ±4.9		0.549	0.585
SJC	13.9 ±5.1		13.1 ±4.0		0.632	0.530
VAS-pain	3.1 ±2.0		2.9 ±1.5		0.233	0.817
DAS28-CRP	3.7 ±1.0		2.9 ±1.0		2.369	0.022
DAS28-ESR	4.5 ±1.0		3.7 ±1.3		2.206	0.032
HAQ-DI score	2.0 ±0.8		1.3 ±0.8		2.751	0.008
ESR 1st hour (mm)	46.8 ±27.7		32.0 ±16.5		2.376	0.022
CRP (mg/dl)	32.2 ±15.1		22.9 ±14.9		2.117	0.039

Table 3. Ocular manifestations involvement in the presence of anti-CCP and RF

	Ocular manifestations N	%	**No ocular manifestations** N	%	**Chi square test** X^2	P
Anti-CCP						
-ve	11	57.9	17	54.8	0.045	0.833
+ve	8	42.1	14	45.2		
RF						
-ve	2	10.5	13	41.9	05.534	0.019
+ve	17	89.5	18	58.1		

Table 4. Ocular manifestations involvement with the medications used

	Ocular manifestations N %	No ocular manifestations N %	Chi square test X^2 P
Methotrexate No Yes	11 57.9 8 42.1	17 54.8 14 45.2	0.045 0.833
Leflunomide No Yes	9 47.4 10 52.6	15 48.4 16 51.6	0.005 0.944
Hydroxy-chloroquine No Yes	3 15.8 16 84.2	14 45.2 17 54.8	4.529 0.033
Steroids No Yes	9 47.4 10 52.6	24 77.4 7 22.6	4.741 0.029
Biological therapy No Yes	16 84.2 3 15.8	21 67.7 10 32.3	1.661 0.198

4. Discussion

Rheumatoid arthritis (RA) is the most common autoimmune disease and has the underlying inflammatory process often result in disorders of multiple organ systems leading to the occurrence of the extra-articular manifestations. Recently, most studies pay attention to ocular manifestations and risk assessment. The incidence of ocular manifestations among RA patients ranges from in 25% to 39%. Ocular involvement is often significant, causing varying degrees of ocular morbidity[7]. The present study revealed that 38% of the patients had eye ocular involvement related to the current RA. This is agreement with ***Zlatanović et al. (2010)***[21] who reported ocular manifestations in 27.2% of the patients[21]. In addition, the incidence of ocular manifestations was reported to be 39% of RA patients [7, 22].

The most common eye manifestation reported in our study was dry eye (26%) of the patients. This is constitutes with ***Punjabi et al (2006)***[23]reported that 27.3% of RA patients had dry eye. ***Amir et al. (2013)***[24]dry eye was the most prevalent ocular manifestations and reported in 29.8% of the RA patients. Also, the prevalence of dry eye was 28% and was the most common manifestation of RA[7]. Moreover, according to the study of ***Tonget al. (2014)***[25], RA is the most common autoimmune disorder associated with dry eye. This may be explained by autoimmune reactions cause the destruction of lacrimal gland, which intern reduced secretion and lead to dry eye. As regards corneal involvement, filamentary keratitis was diagnosed in 12%, PUK in 4% and corneal deposits in 6% of the RA patients in the present study. This is agreement with the diagnosis of filamentary keratitis in 14.4%, and corneal ulcers in 3.8% of the RA patients[24]. ***Watanabe et al. (2017)***[26]demonstrated PUK in RA patients 1.4% while in the study of ***Lee et al. (2012)***[27]estimated the prevalence of PUK in 3.7% of patients. In the study of ***Zlatanović et al. (2010)***[21], episcleritis and scleritis were diagnosed in 5% and 2% respectively of the RA patients. ***Lamba et al. (2016)***[8] reported episcleritis to range from 0.17% to 3.7% among RA patients. This is accordance with our results episcleritis was found in 10% and scleritis in 4% of the RA patients.

The current study revealed that RA patients with ocular manifestations are significantly older, more females prevalence, and longer disease duration than others without ocular manifestations. This is constitutes with, the ocular manifestations were more common with prolonged duration of the disease[7], and women had higher rates of ocular involvement than men[21]. The female prevalence can be explained by the fact that ocular immune process is mediated by Th1 cells, which is stronger in females compared to males[28]. In addition, higher levels of prolactin and growth hormones that found in females enhance autoimmunity [29].

In the present study, we outline the clinical impact of the anti-CCP antibodies and RF positivity. It was clear that patients with +ve anti-CCP and/or +ve RF in their sera had significantly more frequent ocularmanifestations than patients with –ve anti-CCP and RF. This is in agreement with ***Vignesh and Srinivasan (2015),*** there was a strong association between the presence of anti-CCP antibodies and the presence of ocular manifestations of RA. The combined presence of anti-CCP antibodies and RA factor had more severe ocular involvement compared to those who were negative for these antibodies [30].

Gathering these findings together indicate that anti-CCP and RF are risk factors for development of ocular complications.

On the other hand, ocular manifestations can be occurred as side effects of treatment drugs such as steroids, chloroquine and hydroxychloroquine. Our results estimated that RA patients taking HCQ or steroids had more ocular manifestations than patients not taking these drugs. The most concerning side effect is retinal toxicity. We found 3 of the RA patients out of 33 who were taking HCQ had Bull'e eye retinopathy, representing 15% of the patients taking HCQ had this side effect. This is accordance with previous studies, **Latasiewicz et al. (2017)** reported the association of retinal toxicity with the prolonged duration of HCQ use in RA patients[31]. Moreover, ***Sebastiani et al. (2017)*** had examined 10 RA patients receiving treatment with HCQ and no ophthalmic symptoms found all patients had evidence of retinal involvement albeit asymptomatic[32].

Conclusion

Ocular involvement is common in RA, the most common ocular manifestation is dry eye. Patients at risk for development of ocular manifestations include longer disease duration, female sex, disease activity and anti-CCP and RF positivity. Drugs such as HCQ and steroids contribute to eye pathology in RA. Collaborative efforts between the ophthalmologists and rheumatologists are essential to early detect and effectively manage any ocular complications.

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