Prevalence of Dry Eye Syndrome and Sjogren's Syndrome in Patients with Rheumatoid Arthritis

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Background: *Rheumatoid arthritis has manifestations in various organs including ophthalmic involvement. The present study evaluates prevalence of dry eye and secondary Sjogren's syndrome using salivary scintigraphy which has not been used in previous reports.*
Objective: *To evaluate the prevalence of secondary Sjogren's syndrome in patients with rheumatoid arthritis, including clinical characteristics and dry eye, compared with non-Sjogren's syndrome.*
Design: *Descriptive cross sectional study.*
Material and Method: *Sixty-one patients with rheumatoid arthritis were recruited at Siriraj Hospital during March 2009-September 2010 and filled in the questionnaires about dry eye for Ocular Surface Disease Index (OSDI) with a history taking of associated diseases, medications, duration of symptoms of dry eyes and dry mouth. The Schirmer I test without anesthesia, tear break-up time, rose bengal staining score, severity of keratitis and salivary scintigraphy were measured and analyzed.*
Results: *Prevalence of secondary Sjogren's syndrome and dry eye were 22.2% (95% CI 15.4 to 30.9) and 46.7% (95% CI 38.0 to 55.6), respectively. Dry eye interpreted from OSDI, Schirmer I test, tear break-up time and rose bengal staining was16.4%, 46.7%, 82% and 3.3% respectively. Fifty-two percent of patients had a history of dry eye and dry mouth with mean duration 27.4 and 29.8 months, respectively. Superficial punctate keratitis and abnormal salivary scintigraphy were found in 58.2% and 77.8%. Duration of rheumatoid arthritis, erythrocyte sedimentation rate were not correlated with secondary Sjogren's syndrome. Dry eye from OSDI with secondary Sjogren's syndrome (33.3%) compared with non-Sjogren's syndrome (9.5%) was significant difference ($p = 0.008$). Adjusted odds ratio for secondary Sjogren's syndrome in OSDI score > 25 was 13.8 (95% CI 2.6 to 73.8, $p = 0.002$) compared to OSDI score < 25.*
Conclusion: *Awareness and detection of dry eye syndrome and secondary Sjogren's syndrome in rheumatoid arthritis was crucial for evaluation of their severity and proper management.*

Keywords: *Dry eye, Sjogren's syndrome, Rheumatoid arthritis, Ocular Surface Disease Index (OSDI)*

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Rheumatoid arthritis (RA) affects not only various organs but also ocular involvement, especially dry eye syndrome[1]. Discomfort, burning, foreign body sensation and heaviness of eyelids disturb daily life in working and studying. Severe dry eye with dry mouth, as in Sjogren's syndrome (SS), includes difficulty in swallowing of dry food, dental caries, esophagitis and vaginitis[2]. The incidences of dry eye diagnosed by Ocular Surface Disease Index (OSDI) questionnaires and Schirmer I test without anesthesia in patients with RA were 74% and 67%, respectively[3]. Contrary to the prevalence of dry eye in some reports varied from 27.3-70.7%[4-6]. Diagnosis of Sjogren's syndrome is crucial in severe dry eye for proper management in order to prevent keratitis, corneal ulcer, perforation and visual impairment. According to the revised International Classification Criteria for diagnosis of secondary Sjogren's syndrome (SSS) require evaluating salivary gland function by salivary flow measurement, or parotid sialography, or salivary scintigraphy[7,8]. The prevalence of Sjogren's syndrome in patients with RA was 10-17.1% in a few reports using only the salivary flow

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measurement[9,10]. Whereas the prevalence of secondary Sjogren's syndrome using salivary scintigraphy with more details about measurement of absorption and excretion has not been reported. Blood test for antibody to Ro (SS-A) or antibody to La (SS-B) antigen in diagnosis of primary Sjogren's syndrome should be investigated for exclusion as well. Furthermore, the screening test for dry eye in patients with RA requires awareness of dry eye to prevent those complications.

The purpose of the present study was to evaluate the prevalence of dry eye and secondary Sjogren's syndrome, including clinical manifestations and complications, as compared with non-Sjogren's syndrome.

Material and Method

Patients with RA, diagnosed by the American Rheumatism Association 1987 revised criteria, aged over 18 years old with informed consent were enrolled with Institutional Review Board/Ethics Committee approval No. 100/2009 at the rheumatology clinic and eye clinic at Faculty of Medicine Siriraj Hospital, Mahidol University during March 2009 to September 2010[11]. Exclusion criteria included patients with a history of chemical injury, Stevens-Johnson syndrome, allergic conjunctivitis, systemic diseases such as lymphoma, human immunodeficiency viral infection, hepatitis C viral infection, sarcoidosis, bone marrow transplantation with graft-versus-host disease, head and neck radiation and those taking medications that caused dry eye such as cholinergic drugs, antihistamine, diuretic etc. Ophthalmologists recorded symptoms, frequency and duration of RA, feeling of dry eye, dry mouth, burning, foreign body sensation, heaviness of eyelids, difficulty of swallowing, systemic diseases, drug hypersensitivity and medications. The patients filled in Ocular Surface Disease Index (OSDI) questionnaires (12 items) and their scores were calculated[12]. Summation of score for all questions answered, times 25 divided by amount of answers, was assessed in the chart and matched with the corresponding shade to determine as normal, mild, moderate and severe dry eye for the main outcome measure. Eye examination included visual acuities measurement with Snellen chart, collecting the amount of tear wetting filter paper strip length in millimeters (mm) by the Schirmer I test without anesthesia in 5 minutes. If it were less than 5 mm in one or both eyes, it was diagnosed as dry eye. Ophthalmologists assessed the severity of inflammation as superficial punctate keratitis (SPK) which was graded as follows: 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Dry eye diagnosed by fluorescein tear break-up time (TBUT) for tear film stability less than 10 second. Rose bengal staining ocular surface after instillation anesthesia 1-2 drops, score more than 4 was interpreted as dry eye with quantified score 0-9 as described by van Bijsterveld[13].

Most patients were willing to have a blood test performed of 15 milliliters for anti-Ro, anti-La, HIV (ELISA), hepatitis C titer, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) and rheumatoid factor (RF). The normal range for ESR was less than 20 mm/hr in males and less than 30 mm/hr in females.

Salivary scintigraphy was acquired after an intravenous injection of 10 mCi of Tc-99m pertechnetate. The data were collected at a rate of 1 frame per minute for a total time of 60 minutes. At 30 and 45 minutes after injection, the patient received stimulations for salivary excretion by dropping lemon juice on the anterior dorsum of the tongue through an injection syringe. Four regions of interest (ROIs) were chosen over the bilateral parotid and submandibular glands; one ROI was placed on the forehead as a background. Four time-activity-curves were obtained from each salivary gland and considered to represent a summation of salivary functions in terms of accumulation (uptake) and excretion of the saliva. There were four types of time-activity curve. For type I, normal salivary gland function showed the most prominent change in excretion after lemon stimulation. Type II and type III showed mild and moderate impaired function and excretion greater than type I, respectively. Type IV (severe impairment) showed non-function with no response to lemon stimulation. The pattern of type II-IV were classified as abnormal salivary gland involement[14].

The diagnosis of secondary Sjogren's syndrome follows the revised International Classification Criteria for the diagnosis of secondary Sjogren's syndrome[8], consisting of:-

1. ocular symptoms: persistent dry eye everyday for more than 3 months, or foreign body sensation off and on, or using artificial tear over 3 times a day, or

2. oral symptoms: dry mouth everyday over 3 months, or recurrent swollen salivary glands, or drinking fluid required to swallow dry food, accompanied with,

3. ocular signs: Schirmer I test without anesthesia measured wetting paper strip equal or less than 5 mm in 5 minutes, or rose bengal staining ocular surface score equal or more than 4, and

4. abnormal salivary gland involvement: in the present study, salivary scintigraphy showed delayed radioactive uptake or absorption, decreased concentration and/or delayed radioactive excretion.

Data analysis

All statistical analysis was performed using PASW statistics 18.0 (SPSS Inc., Chicago, IL, USA). Data described in number and percentage for categorical variables and mean with standard deviation (SD), median and range for continuous variables. Comparison of the proportions of categorical and continuous variables between groups used Chi-square test or Fisher's exact test and unpaired t-test or Mann-Whitney U test, respectively. Simple and multiple logistic regression were employed to determine the independent predictors of factors associated with Sjogren's syndrome. Measuring factors of association with Sjogren's syndrome used odds ratio with 95% confidence interval (95% CI). All tests of significance were two tailed and p-values < 0.05 were considered statistically significant.

Results

OSDI questionnaire

Sixty-one patients filled in OSDI questionnaires with mean age 53.9 $\pm$ 10.6 years (median: 55; range: 31 to 73). Fifty-eight patients (95.1%) were female. Only 8-12 items were answered, due to non-applicability in those activities. Most replies were: no symptom, can work and feel comfortable (Table 1). Mean OSDI score was 12.3 $\pm$ 12.0 (median: 10; range: 0 to 55). Ten patients (16.4%) had dry eye from interpreted score, graded mild 8 (13.1%) and moderate 2 (3.3%), as in Fig. 1.

Ocular and Oral symptoms

Mean duration of RA was 8.7 $\pm$ 7.4 years (median: 6; range: 0.5 to 35). Thirty-two patients (52.5%) had a history of dry eye with mean duration 27.4 $\pm$ 38.3 months (median 12; range: 1 to 156) (Table 2).

Fourteen patients (58.3%) had frequent photophobia. Mean duration of artificial tear usage was 14.8 $\pm$ 22.4 months (median: 6; range: 1 to 96). Only 52.5% of patients felt dry mouth, with mean duration of dry mouth was 29.8 $\pm$ 85.1 months (median: 12; range: 1 to 480).

Ocular signs

Thirty-one out of 104 eyes (29.8%) of patients had normal uncorrected visual acuities (UCVA 6/6), UCVA 6/9-6/12 in 48 eyes (46.2%), UCVA 6/18-6/36 in 22 eyes (21.2%), UCVA 6/60-3/60 in 2 eyes (1.9% from high myopia) and UCVA 1/60 in 1 eye (1%) from cataract.

Fifty-six out of 120 eyes in 60 patients (46.7%, 95% CI 38.0 to 55.6) were diagnosed as dry eye (< 5 mm in 5 minutes) by Schirmer I test without anesthesia with mean tear wetting paper strip 8.2 $\pm$ 8.7 mm (median: 5; range: 0 to 35).

Seventy-one out of 122 eyes (58.2%) of

Table 1. Eyes symptoms with severity as OSDI questionnaire (n = 61)

	n (%) of the time					
	All	Most	Half	Sometime	None	Not answered
	4	3	2	1	0	
1. Sensitive to light	1 (1.6)	2 (3.3)	4 (6.6)	22 (36.1)	32 (52.5)	0 (0)
2. Feel gritty	0 (0)	1 (1.6)	5 (8.2)	27 (44.3)	28 (45.9)	0 (0)
3. Painful	0 (0)	0 (0)	0 (0)	9 (14.8)	52 (85.2)	0 (0)
4. Blurred vision	2 (3.3)	1 (1.6)	1 (1.6)	30 (49.2)	27 (44.3)	0 (0)
5. Poor vision	2 (3.3)	1 (1.6)	1 (1.6)	23 (37.7)	33 (54.1)	1 (1.6)
6. Limited in reading	1 (1.6)	4 (6.6)	0 (0)	4 (6.6)	51 (83.6)	1 (1.6)
7. Limited in driving at night	0 (0)	0 (0)	0 (0)	1 (1.6)	13 (21.3)	47 (77.1)
8. Limited in working with computer or bank machine	0 (0)	1 (1.6)	0 (0)	0 (0)	26 (42.6)	34 (55.7)
9. Limited in watching television	1 (1.6)	1 (1.6)	1 (1.6)	5 (8.2)	52 (85.2)	1 (1.6)
10. Uncomfortable in windy condition	6 (9.8)	8 (13.1)	2 (3.3)	19 (31.1)	24 (39.3)	2 (3.3)
11. Uncomfortable in low humidity	1 (1.6)	0 (0)	2 (3.3)	6 (9.8)	46 (75.4)	6 (9.8)
12. Uncomfortable in air conditioning	1 (1.6)	1 (1.6)	2 (3.3)	9 (14.8)	48 (78.4)	0 (0)

patients had superficial punctate keratitis (SPK) with mild involvement in 59 eyes (48.4%) and moderate severity in 12 eyes (9.8%).

One hundred out of 122 eyes (82%) of patients had tear film instability from TBUT (< 10 seconds) as dry eye with mean TBUT 6.6 ± 3.7 seconds (median: 5.5; range: 2 to 33). Four out of 120 eyes (3.3%) of 60 patients had rose bengal staining score (> 4) as dry eye.

Dry eye diagnosed by abnormal Schirmer I test with tear film instability and abnormal staining was 3.3% (no data presented).

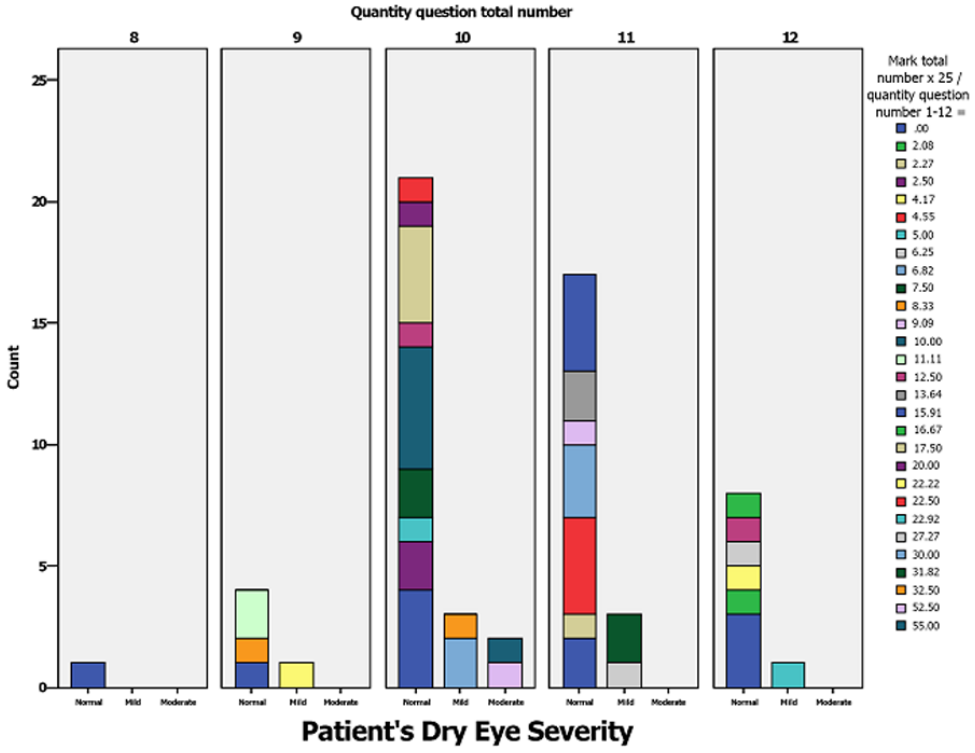

Fig. 1 Number of OSDI answered questions in patients with rheumatoid arthritis and dry eye severity

Table 2. Number of patients with history of dry eye and dry mouth

History	n (%)			
	Sometimes	Frequent	All the times	Total
Dry eye	18 (56.3)	9 (28.1)	5 (15.6)	32 (52.5)
Foreign body sensation	25 (75.8)	6 (18.2)	1 (3)	32 (52.5)
Burning	25 (75.8)	5 (15.2)	3 (9.1)	33 (54.1)
Heaviness of eyelids	10 (58.8)	5 (29.4)	1 (5.9)	16 (26.2)
Photophobia	room light	sun light	closed eye	
	9 (37.5)	14 (58.3)	1 (4.2)	24 (40)
Artificial tear usage	< 3/day	3-5/day	> 5/day	
	10 (52.6)	7 (36.8)	2 (10.5)	19 (31.1)
Dry mouth	19 (59.4)	9 (28.1)	4 (12.5)	32 (52.5)
Swollen salivary glands	5 (83.3)	1 (16.7)	0	6 (9.8)
Drinking fluid for swallowing dry food	NA	NA	NA	13 (21.3)

NA = not applicable

Table 3. The association of eye symptoms, OSDI, history, ocular test in patient with secondary Sjogren's syndrome (SSS) and non-Sjogren's syndrome (nonSS)

	n (%)		Total (54)	p-value
	non SS (42)	SSS (12)		
Mean age (yrs) ± SD	54.7 ± 10.2	52 ± 12.7	54.1 ± 10.7	0.445*
Female	39 (92.9)	12 (100)	51 (94.4)	1.000^{++}
Mean duration of RA (yrs) ± SD	9.2 ± 8.3	7.8 ± 5.5	8.9 ± 7.7	0.810°
Median (Min; Max)	6.5 (1,35)	5.5 (2,19)	6.5 (1, 35)	
OSDI questionnaire				
Photophobia	18 (42.9)	9 (74.9)	27 (50)	0.011^{+}
Eye pain	8 (19.0)	0 (0)	8 (14.8)	0.02^{++}
Dry eye interpretation	4 (9.5)	4 (33.3)	8 (14.8)	0.008^{++}
Mean duration of dry eye (months) ± SD	16.6 ± 22.7	41.3 ± 46.0	23.6 ± 3.2	0.043°
Median (Min; Max)	12 (1; 96)	18 (6; 120)	12 (1, 120)	
Artificial tear usage	9 (21.4)	8 (72.7)	17 (32.1)	0.002^{++}
Drinking fluid for swallowing	6 (14.3)	7 (58.3)	13 (24.1)	0.004^{++}
Schirmer I (mm) ± SD	10.0 ± 8.9	2.3 ± 2.9	8.3 ± 8.6	< 0.001°
Median (Min; Max)	7 (0;35)	1 (0;10.5)	5 (0,35)	
Dry eye (≤ 5 mm)	27 (32.9)	21 (87.5)	48 (45.3)	< 0.001^{+}
Keratitis (eyes)	45 (53.6)	21 (87.5)	66 (61.1)	0.006^{+}
TBUT (sec) ± SD	7 ± 3.7	4.8 ± 2.5	6.5 ± 3.6	0.002°
Median (Min; Max)	6 (3;23)	4.5 (2;12)	5 (2;23)	
Dry eye (< 10 sec)	69 (82.1)	22 (91.7)	91 (84.3)	0.351^{++}
Mean rose bangal score ± SD	0.39 ± 0.9	1.5 ± 2.0	0.64 ± 1.29	< 0.001°
Median (Min;Max)	0 (0;5)	1 (0;7)	0 (0;7)	
Dry eye (score > 4)	1 (1.2)	3 (12.5)	4 (3.7)	0.034^{++}
Abnormal salivary gland function	30 (71.4)	12 (100)	42 (77.8)	0.007^{+}
Abnormal excretion of submandibular gland	28 (66.7)	11 (91.7)	39 (72.2)	0.031^{+}

*Unpaired t-test, $^{++}$Fisher's Exact test, °Mann-Whitney U test, $^{+}$Chi-square test with continuity correction

Salivary scintigraphy

Forty-two out of 54 patients (77.8%) had abnormal salivary gland function such as decreased absorption of parotid glands and submandibular glands in 4 patients (7.4%), abnormal excretion of parotid glands in 22 patients (40.7%) and abnormal excretion of submandibular glands in 39 patients (72.2%, Table 3). Impaired salivary gland function were graded as type II (mild), type III (moderate) and type IV (severe) in 44, 25 and 49 salivary glands, respectively.

Blood test

Twenty-two out of 56 patients (39.3%) had a positive result for anti-Ro (SS-A), but for anti-La (SS-B) 4 patients (7.1%). Positive results of anti-Ro between Sjogren's syndrome (33.3%) and non-Sjogren's syndrome (41.5%) were not significantly different (p = 0.632), the same as positive result of anti-La in Sjogren's syndrome (16.7%) and non-Sjogren's syndrome (4.9%), respectively (p = 0.076).

Positive results of anti-Ro in the dry eye group (38%) and the non-dry eye group (41.7%) diagnosed by the Schirmer I test without anesthesia were not statistically significant difference (p = 0.845), the same as anti-La in the former 10% and in the latter 5%, respectively (p = 0.465). Positive results of anti-Ro and anti-La in the dry eye group diagnosed by TBUT and rose bengal staining score were compared with non-dry eye group and were not different (no data presented).

Forty-seven out of 61 patients (77%) had a mean ESR of 53.4 ± 27.6 mm/hour (median: 49; range: 6 to 115). Only one patient did not performed the Schirmer I test, therefore 46 out of 60 patients had high ESR (Table 4).

Twenty-five out of 53 patients (47.2%) had positive ANA. Forty-three out of 53 patients (81.1%)

had positive rheumatoid factor with mean 197.8 ± 254.8 IU/millilitre (median: 118; range: 8 to 1,280). But one patient did not performed the Schirmer I test, therefore 42 out of 52 patients had positive RF (Table 4).

Diagnosis of secondary Sjogren's syndrome (SSS)

Twelve out of 54 patients with RA met the criteria for secondary Sjogren's syndrome with the prevalence being 22.2% (95% CI 13.2 to 34.9).

There was no difference in age, gender, duration of RA, positive result of anti-Ro, anti-La, ESR, ANA and RF between secondary Sjogren's syndrome and non-Sjogren's syndrome. Regarding OSDI questionnaires, photophobia and stinging in secondary Sjogren's syndrome when compared with non-Sjogren's syndrome, indicated statistically significant difference (p = 0.011 and 0.02, respectively). Dry eye from OSDI score interpretation in secondary Sjogren's syndrome (33.3%) was significantly more than from non-Sjogren's syndrome (9.5%) (p = 0.008, Table3).

Duration of dry eye, artificial tear usage and drinking fluid for swallowing dry food in secondary Sjogren's syndrome with frequently found more than in non-Sjogren's syndrome with significant differences (p = 0.043, 0.002 and 0.004, respectively) (Table 3).

The results were the same as for the ocular test in numbers of dry eye and mean Schirmer I test without anesthesia, superficial punctate keratitis, mean TBUT, numbers of dry eye and mean rose bengal staining score (p < 0.001, < 0.001, 0.006, 0.002, 0.034 and < 0.001, respectively) (Table 3).

Abnormal salivary scintigraphy in secondary Sjogren's syndrome was significantly more than in non-Sjogren's syndrome (p = 0.007), especially abnormal submandibular salivary gland excretion (p = 0.031) (Table 3).

Accuracy of OSDI questionnaires

The accuracy of dry eye from OSDI questionnaires interpretation, compared with dry eye diagnosed by rose bengal staining score, was 83.8% (95% CI 75.7 to 88.9), whereas with the Schirmer I test without anesthesia, superficial punctate keratitis and TBUT were 58.3% (95% CI 49.4 to 66.8), 38.5% (95% CI 30.4 to 47.4) and 27.9% (95% CI 20.7 to 36.4), respectively (no data presented).

Univariate and multivariate analysis in diagnosis of secondary Sjogren's syndrome

Table 4 demonstrates that SPK, TBUT, rose bengal score, abnormal salivary gland function and high ESR in dry eye diagnosed by Schirmer I test without anesthesia, were found significantly more often than for the non-dry eye group (p < 0.001, 0.006, 0.041, 0.009 and 0.048, respectively).

Sixty-nine out of 100 eyes with SPK (69%) were dry eye diagnosed by TBUT but more than 2 out of 22 non-dry eyes (9.1%), p < 0.001. Fifty-seven out of 66 eyes (86.4%) with abnormal salivary gland function were encountered with SPK, more than the non-SPK group (27 out of 42 eyes, 64.3%) with significant difference (p = 0.014). Impairment of excretion of parotid salivary glands with corneal involvement SPK was especially found in 34 eyes (51.5%) more than non-SPK group in 10 eyes (23.8%), p = 0.008 (no data presented).

The odds ratio of diagnosis of secondary Sjogren's syndrome in OSDI score interpretation more

Table 4. Association of history, ocular examination and blood test with Schirmer I test without anesthesia

	Schirmer I test		Total	p-value
	Not dry	Dry		
History of dry eye (cases)	16/29 (55.2)	15/31 (48.4)	31/60 (51.7)	0.789[+]
SPK (eyes)	27/64 (42.2)	44/56 (78.6)	71/120 (59.2)	< 0.001[+]
TBUT < 10 sec (eyes)	46/64 (71.9)	52/56 (92.9)	98/120 (81.7)	0.006[+]
Rose bengal score > 4 (eyes)	0/64 (0)	4/54 (7.4)	4/118 (3.4)	0.041[++]
Abnormal salivary gland function (glands)	40/58 (69)	44/48 (91.7)	84/106 (79.2)	0.009[+]
High ESR (cases)	22/32 (68.8)	24/28 (85.7)	46/60 (76.7)	0.048[+]
Positive ANA (cases)	14/28 (50)	11/25 (44)	25/53 (47.2)	0.985[+]
Positive RF (cases)	24/29 (82.8)	18/23 (78.3)	42/52 (80.8)	0.743[+]

[+]Chi-square test with continuity correction, [++]Fisher's Exact test

than 25 was 6.5 (95% CI 2.0 to 21.3, p = 0.002) (Table 5).

From multivariate analysis for adjusted odds ratio of diagnosis of secondary Sjogren's syndrome in OSDI, a score of more than 25 was 13.8 (95% CI 2.6 to 73.8, p = 0.002).

The adjusted odds ratio of secondary Sjogren's syndrome in the Schirmer I test without anesthesia ≤ 5 mm was 11.1 (95% CI 2.0 to 62.0), p = 0.006.

Discussion

The prevalence of secondary Sjogren's syndrome in the present study was 22.2% with 95% CI 13.2 to 34.9, similar to Matsuo's study (17.1%), but contrary to Fujita's study (10%)[9,10]. These discrepancies might be due to different geography, climate, humidity and severity of rheumatoid arthritis, especially different salivary gland function measurement done by salivary volume. Although salivary scintigraphy took more time and expense to investigate, the absorption and excretion of saliva data gave more details about function than salivary volume.

Regarding OSDI questionnaire diagnosed dry eye only 16.4%, in contrast to feeling of dry eye from history resulting in 58.2%, dry eye in the Schirmer I test without anesthesia (≤ 5 mm) 46.7%, keratitis 58.2%, dry eye diagnosed by TBUT (< 10 sec) 82% and dry eye by rose bengal staining (score > 4) 3.4%, with different accuracy. Vitale's study in primary Sjogren's syndrome reported that no correlation was found among OSDI, Schirmer I test without anesthesia, TBUT and rose bengal staining score[15]. Therefore, the evaluation of dry eye requires many tests to assess for accuracy.

Patients with rheumatoid arthritis in the present study had dry eye by Schirmer I test without anesthesia (46.7%), which is different from previous studies (27.4-70.7%)[3-6,16]. This may be due to various severities of RA disease, different age, especially decreased tear secretion in older persons. In comparison the prevalence of dry eye in patients with rheumatoid arthritis and without dry eye was 12-22%[4,6]. This was contrary to some studies which reported dry eye in volunteers, with different criteria of Schirmer I test without anesthesia at less than 10 mm[17].

The present study reported abnormal salivary gland function (77.8%), mostly excretion, but only 52.5% of patients feel dry mouth. Various severities and amounts of gland involvement affect different results in other studies, mostly collected salivary volume.

Erythrocyte sedimentation rate (ESR) indicated the severity of rheumatoid arthritis, these were correlated with the Schirmer I test without anesthesia, except secondary Sjogren's syndrome and similar to Fujita's study[9]. Many causes resulted in high ESR, including age, inflammation, infection, anemia etc, or different medications.

The limitation in the present study was its small sample size and being unable to use a questionnaire to evaluate the severity of rheumatoid arthritis as with the European League of Association for Rheumatology (EULAR) response criteria for RA or the Disease Activity Score (DAS 28)[18]. However, Wangkaew et al reported no strong correlation in age, duration of RA, disease activity and severity, including anti-Ro and anti-La with dry eye or dry mouth[4].

However, some errors in the questionnaire might not be understood clearly or indicate recall bias in duration of symptoms. Furthermore, incomplete data caused from difficult and inconvenient to follow-up and many systemic disease with medication caused dry eye result in small sample size.

Multivariate analysis of OSDI and the Schirmer I test without anesthesia had more probability to diagnose secondary Sjogren's syndrome than other variables. Therefore, dry eye evaluation with a history of dry mouth should lead one to suspect secondary Sjogren's syndrome in order to assess salivary gland

Table 5. Univariate and multivariate analysis of factors associated with secondary Sjogren's syndrome

	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
OSDI score (> 25)	6.5 (2.0, 21.3)	0.002	13.8 (2.6, 73.8)	0.002
Schirmer I test without anesthesia (≤ 5 mm)	13.4 (3.0, 60.6)	0.001	11.1 (2.0, 62.0)	0.006
TBUT (< 5 sec)	5.1 (1.7,14.9)	0.003	5.2 (1.3, 20.2)	0.018
Rose bengal score (> 4)	8.2 (1.4, 48.0)	0.020	4.2 (0.5, 37.4)	0.199

* Multivariate model was adjusted for all variables in the table. OR = Odds Ratio

function.

Conclusion

Awareness and detection of dry eye syndrome and secondary Sjogren's syndrome in rheumatoid arthritis was important for evaluation of their severity and proper management.

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Potential conflicts of interest

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References

1. Goldberg MA, Pham CT, Lubniewski AJ. Corneal disease in rheumatoid arthritis. In: Krachmer JH, Mannis MJ, Holland EJ, editors. Cornea. St.Louis: Mosby Year Book; 1997: 1359-75.
2. Moutsopoulos HM. Sjogren's syndrome. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al, editors. Harrison principle's of internal medicine. Vol. 2. 17th ed. New York: McGraw Hill; 2008: 2107-9.
3. Polanska V, Hlinomazova Z, Fojtik Z, Nemec P. Dry eye syndrome in rheumatoid arthritis patients. Cesk Slov Oftalmol 2007; 63: 422-30.
4. Wangkaew S, Kasitanon N, Sivasomboon C, Wichainun R, Sukitawut W, Louthrenoo W. Sicca symptoms in Thai patients with rheumatoid arthritis, systemic lupus erythematosus and scleroderma: a comparison with age-matched controls and correlation with disease variables. Asian Pac J Allergy Immunol 2006; 24: 213-21.
5. Piper H, Douglas KM, Treharne GJ, Mitton DL, Haider S, Kitas GD. Prevalence and predictors of ocular manifestations of RA: is there a need for routine screening? Musculoskeletal Care 2007; 5: 102-17.
6. Punjabi OS, Adyanthaya RS, Mhatre AD, Jehangir RP. Rheumatoid arthritis is a risk factor for dry eye in the Indian population. Ophthalmic Epidemiol 2006; 13: 379-84.
7. O'Connor MK. Salivary gland study. In: O'Connor MK, editor. The Mayo clinic manual of nuclear medicine. New York: Churchill Livingstone; 1996: 273-6.
8. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61: 554-8.
9. Fujita M, Igarashi T, Kurai T, Sakane M, Yoshino S, Takahashi H. Correlation between dry eye and rheumatoid arthritis activity. Am J Ophthalmol 2005; 140: 808-13.
10. Matsuo T, Kono R, Matsuo N, Ezawa K, Natsumeda M, Soda K, et al. Incidence of ocular complications in rheumatoid arthritis and the relation of keratoconjunctivitis sicca with its systemic activity. Scand J Rheumatol 1997; 26: 113-6.
11. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24.
12. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and validity of the Ocular Surface Disease Index. Arch Ophthalmol 2000; 118: 615-21.
13. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 1969; 82: 10-4.
14. Tsuni H. Quantitative dose-response analysis of salivary function following radiotherapy using sequential RI-sialography. Int J Radiat Oncol Biol Phys 1985; 11: 1603-12.
15. Vitale S, Goodman LA, Reed GF, Smith JA. Comparison of the NEI-VFQ and OSDI Questionnaires in patients with Sjogren's syndrome-related dry eye. Health Qual Life Outcomes 2004; 2: 44-54.
16. Uhlig T, Kvien TK, Jensen JL, Axell T. Sicca symptoms, saliva and tear production, and disease variables in 636 patients with rheumatoid arthritis. Ann Rheum Dis 1999; 58: 415-22.
17. Lekhanont K, Rojanaporn D, Chuck RS, Vongthongsri A. Prevalence of dry eye in Bangkok, Thailand. Cornea 2006; 25: 1162-7.
18. van Gestel AM, Haagsma CJ, van Riel PL. Validation of rheumatoid arthritis improvement criteria that include simplified joint counts. Arthritis Rheum 1998; 41: 1845-50.

ความชุกกลุ่มอาการตาแห้ง และกลุ่มอาการโซเกรนในผู้ป่วยโรคข้ออักเสบรูมาตอยด์

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***ภูมิหลัง**: โรคข้ออักเสบรูมาตอยด์มีอาการแสดงในหลายระบบรวมทั้งทางตา จึงเป็นที่มาของการศึกษานี้ เพื่อศึกษาความชุกกลุ่มอาการตาแห้ง และกลุ่มอาการโซเกรนทุติยภูมิโดยการตรวจต่อมน้ำลายด้วยการฉีดสารรังสี ซึ่งไม่เคยมีรายงาน*

***วัตถุประสงค์**: เพื่อศึกษาความชุกกลุ่มอาการตาแห้งและกลุ่มอาการโซเกรนทุติยภูมิในผู้ป่วยโรคข้ออักเสบรูมาตอยด์ รวมถึงลักษณะอาการทางคลินิก และความสัมพันธ์กับตาแห้ง*

***รูปแบบการวิจัย**: เชิงพรรณนาและแบบตัดขวาง*

***วัสดุและวิธีการ**: ทำการศึกษาในผู้ป่วยโรคข้ออักเสบรูมาตอยด์จำนวน 61 ราย ที่โรงพยาบาลศิริราช ในช่วงมีนาคม พ.ศ. 2552 ถึง กันยายน พ.ศ. 2553 โดยใช้แบบสอบถาม Ocular Surface Disease Index (OSDI) บันทึกประวัติอาการโรคที่เป็นร่วม ยาที่ใช้ ระยะเวลาที่มีอาการตาแห้งและปากแห้ง ตรวจตาโดยใช้วิธีเชอร์เมอร์ I ที่ไม่ใช้ยาชา วัดระยะเวลาความคงตัวของน้ำตา การย้อมสีโรสเบงกอล ความรุนแรงของกระจกตาอักเสบ การตรวจการทำงานของต่อมน้ำลายหลังฉีดสารรังสี เจาะเลือดตรวจหาภูมิต้านทาน และอัตราการตกตะกอนของเม็ดเลือดแดง*

***ผลการศึกษา**: ความชุกกลุ่มอาการโซเกรนทุติยภูมิพบร้อยละ 22.2 (ค่าความเชื่อมั่นร้อยละ 95 อยู่ในช่วง 13.2 ถึง34.9) พบตาแห้งจากแบบสอบถาม OSDI ร้อยละ 16.4 ผู้ป่วยมีประวัติตาแห้งและปากแห้ง ร้อยละ 52.5 ระยะเวลาเฉลี่ยตาแห้งและปากแห้ง นาน 27.4 และ 29.8 เดือนตามลำดับ จากการตรวจปริมาณน้ำตาด้วยวิธีเชอร์เมอร์ I ที่ไม่หยอดยาชา ระยะเวลาความคงตัวของน้ำตา และผิวตาติดสีโรสเบงกอล พบร้อยละ 46.7 ร้อยละ 82 และร้อยละ 3.4 ตามลำดับ พบกระจกตาอักเสบ ร้อยละ 58.2 ผลตรวจการทำงานของต่อมน้ำลายหลังฉีดสารรังสี พบความผิดปกติ ร้อยละ 77.8 ระยะเวลาที่เป็นโรคข้ออักเสบรูมาตอยด์ และผลบวกการตกตะกอนของเม็ดเลือดแดงไม่สัมพันธ์กับกลุ่มอาการโซเกรนทุติยภูมิ ในกลุ่มที่วินิจฉัยกลุ่มอาการโซเกรนพบตาแห้งจากแบบสอบถามร้อยละ 33.3 มากกว่ากลุ่มที่ไม่มีอาการโซเกรนร้อยละ 9.5 อย่างมีนัยสำคัญทางสถิติ (p = 0.008) ผู้ที่มีคะแนน OSDI มากกว่า 25 มีโอกาสเป็นกลุ่มอาการโซเกรนทุติยภูมิ 13.8 เท่า (ค่าความเชื่อมั่นร้อยละ 95 อยู่ในช่วง 2.57 ถึง 73.77 และ p = 0.002) เมื่อเทียบกับผู้ที่มีคะแนน OSDI น้อยกว่า 25*

***สรุป**: การตรวจพบกลุ่มอาการตาแห้งและกลุ่มอาการโซเกรนทุติยภูมิในผู้ป่วยโรคข้ออักเสบรูมาตอยด์มีความสำคัญการประเมินความรุนแรง มีประโยชน์ต่อการดูแลและให้การรักษาอย่างเหมาะสมต่อไป*