Secondary Sjogren's Syndrome in 83 Patients With Rheumatoid Arthritis

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Abstract- Sjogren syndrome (SS) can occur alone, primary Sjogren syndrome, or in association with other rheumatic diseases, secondary Sjogren syndrome (sSS), such as Rheumatoid arthritis (RA). The occurrence of Sjogren syndrome with RA makes it course worse and increases high morbidity and mortality of RA. In this exploratory study we aim to determine the prevalence of sSS (diagnosed based on the revised version of American–European consensus Group Classification Criteria: AUCG-criteria), sicca symptoms (dry eye, dry mouth), positive autoantibody tests (Anti RO or Anti-LA antibodies), UWSFR (Unstimulated Whole Salivary Flow Rate), Schirmer and Lissamine test. In this cross-sectional study, eighty three consecutive RA patients (according to American College of Rheumatology criteria 1987) who were visited at rheumatology clinic of Razi General Hospital located in the north of Iran entered into our study. Our exclusion criteria was a positive history of past head and neck radiation treatment, Hepatitis C infection, acquired immunodeficiency disease (AIDS), pre-existing lymphoma, sarcoidosis, graft versus host disease, use of anticholinergic drugs (including neuroleptics, antidepressants, antihypertensive and parasympatholytics). They examined with UWSFR by a rheumatologist and with Schirmer test and Lissamine test by an ophthalmologist. Participants were 90.4% female with the mean age 48.3±13 years. Duration of RA was in 36.1% less than 5 years, in 22.9% 5-10 years, in 12.1% 11-15 years and in 28.9% more than 15 years. Our results demonstrated that the prevalence of sSS was 5.9% (CI:0.6%-10.5%). Number of 27.7% of RA patients positively responded to at least one question about sicca symptoms. Among objective tests, only Positive UWSFR and Lissamine test were significantly more common in RA patients with sSS in comparison to ones without sSS (P<0.001, P=0.01 respectively). In RA patients, we found a linear trend between sicca symptoms and aging (P=0.02). In patients with sicca symptoms, among tests that used for assessing decrease in saliva or tear production, only USWFR significantly more common (P=0.01). In conclusion: In RA population in North of Iran prevalence of sSS was less than 10%. In them, a significant linear trend existed between aging and sicca symptoms. Among objective tests of AUCG-criteria (except for lip biopsy that was not performed in the current study) only UWSFR and Lissamine test were significantly more common in patients with sSS in comparison ones without it.

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Introduction

Sjogren syndrome (SS) is a chronic inflammatory autoimmune disease that mainly involves exocrine glands. This disease is more common in middle-aged women, and can occur alone (primary Sjogren syndrome) or in association with other rheumatic diseases (secondary Sjogren syndrome: sSS) such as RA, systemic lupus erythematosus (SLE), Systemic sclerosis, polymyositis, mixed cryoglobulinemia and polyarteritis nodosa (1).

Rheumatoid arthritis (RA), the most common connective tissue disease associated with Sjogren syndrome (2), may result in some extra-articular manifestations called sicca symptoms that are including keratoconjunctivitis sicca or dry eyes and xerostomia or dry mouth (3).

Despite sicca symptoms (the common presentation

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of sSS) that are keys for diagnosis of sSS, other symptoms are quite uncommon (4) and usually mild (1). Nevertheless, even sicca symptoms can be ignored by patients and/or rheumatologist. Because it is usually mild in comparison to RA symptoms (1). RA usually has high morbidity and mortality and in patients with RA occurrence of sSS makes its course worse (5,6).

In 1993 the association between RA and sSS first described. Prevalence of sSS is heterogenous, 3.8%-39.8%. It can be due to genetic background, geographic factors, diagnostic criteria (especially performing lip biopsy), RA duration, patient characteristics or study design. In Iran, based on our knowledge, there is not any information about Sjogren syndrome in patients with RA, Information such as its prevalence, Characteristics and so on.

Materials and Methods

In this cross-sectional study, eighty three consecutive patients with RA (according to American College of Rheumatology 1987) who were visited at rheumatology clinic of Razi general Hospital located in the center of Guilan Province of Iran were entered into our study. sSS was diagnosed based on the revised version of American–European consensus Group Classification Criteria (AUCG-criteria) (7). Patients were excluded if there was a positive history of past head and neck radiation treatment, Hepatitis C infection, acquired immunodeficiency disease (AIDS), pre-existing lymphoma, sarcoidosis, graft versus host disease, use of anticholinergic drugs (including neuroleptics, antidepressants, antihypertensive and parasympatholytics). Lip biopsy was not performed. A Rheumatologist performed unstimulated whole salivary flow rate (UWSFR), and an ophthalmologist did Schirmer's and lissamine tests.

Among tests for dry eye assessment, Schirmer's test has the best balance between sensitivity and specificity for the diagnosis of Sjogren syndrome. It was performed without anesthesia in accordance with the related guidelines (8). The application of lissamine green that is a vital dye, like fluorescein, can alter the tear production. For this reason, this test was done after performing Schirmer test. Lissamine stains corneal and conjunctiva epithelial defects. Lissamine green dye was instilled in each eye from sterile dropper bottles (containing 1 ml of 1% dye). Unlike Rose bengal, lissamine green is not irritating to the eye. So, it can be applied without using a topical anesthetic. The staining pattern of it was observed by using a neutral density filter over the slit lamp light source (9).

Unstimulated whole saliva flow rate (UWSFR) was done in the morning according to published guidelines. After swallowing, saliva was collected over 15 minutes by passive spitting into pre-weighed containers. Flow rates were expressed as ml/minute (1 gr equals to 1 ml). The production of saliva less than 1.5 ml/15 minutes was considered as abnormal status (8).

The data were analyzed using SPSS version 11 and Gpower software (version 3.1.9.2). Statistical analyses were included Chi-square, and Fisher exact test and Chi-square for trend. $P<0.05$ was considered as statistically significant.

Written informed consent was obtained from all patients. This study was approved by ethics committee of Guilan University of Medical Sciences.

Results

Of 83 participants in this exploratory study, 90.4% (75 from 83) were female. The mean age of them was 48.3±13 years. Duration of RA was in 36.1% less than 5 years, in 22.9% 5-10 years, in 12.1% 11-15 years and in 28.9% more than 15 years. Number of 27.7% positively responded to at least one question about sicca symptoms; other characteristics were presented in table 1.

Table1. Characteristics of the patients with RA

Type of findings		All patients N (%)
Subjective	Dry mouth	17 (20.4%)
	Dry eye	15 (18.1%)
Objective	positive Anti RO or LA	22 (26.5%)
	positive UWSFR	16 (19.3%)
	positive Lissamine Test	20 (24.1%)
	positive Schirmer Test	23 (27.7%)

There was a significant association between duration of RA and presence of sicca symptoms ($P=0.005$). A linear trend existed between sicca symptoms and aging ($P=0.02$). In RA patients with sicca symptoms (in

comparison to RA patients without sicca symptoms), Positive UWSFR was significantly more common (*P*=0.01), but there was not such a significant finding for positive Schirmer test or positive Lissamine test.

sSS was diagnosed in 5 (5.9%,CI:0.6%-10.5%) patients. Their mean age was 50.8±10.1 years. All of them were female, suffered from RA for more than 2 years, the mean of time since diagnosis of RA was 7.2±4.49 years, 80% had dry eye, and %80 had dry mouth. Although the prevalence of positive autoantibodies in patients with sSS more than it in patients without sSS, but it was not statistically significant. Other comparisons displayed in table 2.

Table 2. Comparisons in RA patients with and without sSS

Positive test	In patients		*P*.value[1]	Power of statistical test (%)
	With sSS	Without sSS		
Anti RO or LA	2 (40%)	20(25.6%)	NS	56 [2]
UWSFR	5 (100%)	11(14.1%)	< 0.001	> 80
Lissamine Test	4 (80%)	16(20.5%)	0.01	> 80
Schirmer test	3 (60%)	20(25.6%)	NS	72 [2]

1-Fisher exact test, 2-For achievement to sufficient high statistical power (> 80%) we need to sample size almost equal to 400 for Anti RO or LA and 100 for Schirmer test (calculated by Gpower software: version 3.1.9.2).

Discussion

As we will display in Table 3, the prevalence of sSS considerably varies in different studies (3.8%-39.8%). It may be due to genetic background ,geographic factors, diagnostic criteria (especially performing lip biopsy), presence and/or discrepancies in exclusion criteria, RA duration, patient characteristics and study design. The highest prevalence of sSS in RA has been seen in Greece (32.8%–39.8%) (10,11). Dorroso *et al.*, (10) in a study for comparing clinical and paraclinical expression of RA in two countries, United Kingdom (UK) and Greece, found that prevalence of sSS in Greece was significantly more than the UK, 39.8%, 15.9% respectively (*P*<0.001). This study didn't have exclusion criteria. Three years later in Greece, Ioannidis, *et al.*, (11) published a study with no exclusion criteria which assessed the strength of association among HLA shared epitopes (SE) and some variables in RA. These variables were susceptibility to RA, its severity, and extra articular manifestations. Prevalence of sSS in this study was 32.8%.

In Turkey Calguneri *et al.*, (14) retrospectively evaluated hospital records of 526 patients with RA to assess the association between extra-articular manifestations and RA severity and its mortality. They found that prevalence of sicca symptom was 11.4% that is lower than our finding (26.5%). This discrepancy may be due to nature of retrospective studies that may give a lower estimate of the prevalence of a symptom in comparison to prospective studies. The aims of Uligh *et al.*, study (15) in Norway were an estimation of prevalence of sicca symptoms and its relation to RA activity. For achieving the first aim, all participants completed a detailed questionnaire about sicca symptoms. The questions in this questionnaire were identical with three questions on eyes and mouth in European classification criteria for SS. Although they found that prevalence of having at least one sicca symptoms was 60.7% which is more than it in our study (26.5%) but their reported sSS prevalence was similar to that in the current study. The more common sicca symptoms may be related to the different questionnaire used for screening of dry eye or dry mouth and absence of exclusion criteria in their study. Cimmino *et al.*, (21) studied 587 Italian RA patients from 9 rheumatologic clinics. Their aim was determination of prevalence of extra-articular manifestations in them. The participants were 77.3% female with mean age 60±12.4 and mean of RA duration (in a month) 115.4±103.3. Prevalence of sicca symptoms in them was 17.5%. In comparison to our study, there was older with longer RA duration but less female.

In the current study, there was no significant difference in prevalence of positive autoantibodies between RA patients with and without sSS. This finding is compatible with finding of Baldini *et al.*, They demonstrated that AECG-criteria could be fulfilled in the absence of positive autoantibodies (Anti RO or Anti LA antibodies); one of the debates about AECG-criteria

(22).

In present study, prevalence of positive autoantibodies were 26.5% that was similar to that in Schneeberg *et al*., study (23) (27.5%) and Furukawa *et al*., study (24%) (24).

As regards our results, the Schirmer test was not more common in RA patients with sSS in comparison to ones without sSS. For assessment of the accuracy of this finding, we calculated the power of its statistical test by means of Gpower software (version 3.1.9.2). The statistical power was 72%. The plot of sample size versus power was drawn. It demonstrated for confident of the accuracy of our result about Schirmer test; we need to more sample size (almost 100).The other probable explanations may be the low sensitivity of Schirmer test for diagnosis of SS (25) which is even less in sSS (8).

Table 3. Prevalence of sSS in different countries

Authors	Country	Diagnostic criteria for sSS	Sample size N (%Female)	Age (mean ± sd)	Prevalence of sSS (%)
Haga *et al.*,[12]	Denmark	At least one subjective sicca symptoms in addition to a positive Schirmer I test and positive USWC	307(68.4)	62.5 (19–87)[1]	3.8
Gliboe *et al.*,[2]	Norway	Preliminary criteria for the classification of sSS 1993 (13)	81(89)	44 (21-69) [1]	4 [5]
Calguneri *et al.*, [14]	Turkey	(…) 4	526(86)	48±12.3	5.3
Hajiabbsi *et al.*,[4]	Iran	Revised version of American–European Consensus Group Classification Criteria (AUCG - criteria) (7)	83(90.4)	48.3 ± 13	5.9 [5]
Uligh *et al.*,[15]	Norway	Preliminary criteria for the classification of sSS 1993(13)	636 (80.2)	(…) [3]	7
Young *et al.*,[16]	UK	(…) 4	941(65.5)	(…) [3]	7
Fujita *et al* [17]	Japan	Japanese Criteria	72(93)	64±11.6	10 [5]
Drosos *et al.*,[10]	UK	Keratoconjunctivitis sicca and positive salivary gland biopsy	107(…)[3]	(…) [3]	15.9
Cameron *et al.*, [18]	Spain	Preliminary criteria for the classification of sSS 1993 (13)	788(71.3)	61±13	17 [5]
Turroson *et al.*,[6]	Sweden	Two of three criteria: Sicca symptoms, serological evidence (RF or ANA) and anti-La(SS-B) or hypergammaglobulinemia	609(73.6)	60 [2]	17.1
Antero *et al.*,[19]	Curitiba	Revised version of American–European Consensus Group Classification Criteria (AUCG - criteria) (7)	82(87.8)	51.8±10	24.3 [5]
Massador *et al.*, [20]	Chile	Sjogren ‘ s syndrome was assessed by a specific questionnaire and a Schirmer ‘ s test performed in all patients.	112(87)	50±14	29
Ioannidis *et al.*,[11]	Greece	Preliminary criteria for the classification of sSS 1993 (13)	174(85)	(…) [3]	32.8 [5]
Drosos *et al.*,[10]	Greece	Keratoconjunctivitis sicca and positive salivary gland biopsy	108(…)[3]	(…) [3]	39.8

1. Mean (range), 2 – Median, 3- (…) means there was no data in article. 4- Current study.5- Studies with exclusion criteria

Limitations

There was no gold standard for diagnosis of sSS. In the current study we used from AECG-criteria for this purpose that is a classification criterion and using it as a diagnostic tool is the only way for standardization of sSS diagnosis in clinical studies (7). In addition, there are some different reports about the diagnostic accuracy of it, the range of reported sensitivity is 61.6%-87% and for specificity is 93%-97.2% (25-27). In Iran, based on our knowledge there was no study on the sensitivity of tests used for detecting 2 objective items in AECG-criteria (ocular signs and abnormal tests of salivary gland function) (8,25) and validation of this criteria. We suggest validation of AECG-criteria in Iran as next step for increasing our knowledge about sSS in RA. Other limitations of our study are the relatively small sample size and not having done a lip biopsy.

In RA population in North of Iran prevalence of sSS was less than 10%. In them a significant linear trend existed between aging and sicca symptoms. Among objective

tests of AUCG-criteria (except for lip biopsy that was not performed in the current study) only UWSFR and Lissamine test were significantly more common in patients with sSS in comparison ones without it.

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