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Correlation Between Subjective and Objective Severity of Oral and Ocular Dryness in Primary Sjögren Syndrome

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ABSTRACT. ***Objective.*** Sjögren syndrome (SS) is a common autoimmune disease primarily affecting the eyes and mouth. With no single gold standard test for its diagnosis, accurate identification of patients with SS continues to be challenging. We aimed to assess the correlation of ocular and oral symptoms of dryness with objective measures in order to evaluate reliability in the screening of primary SS (pSS) in clinical practice.

Methods. We conducted a cross-sectional analysis of pre-screened pSS and sicca control patients assessed in the Multidisciplinary Sjögren's Clinic at the University Health Network in Toronto. The signs, symptoms, and objective measure of oral and ocular dryness and damage of each patient were prospectively recorded using a standardized protocol.

Results. Subjective measures of severity for xerophthalmia and xerostomia correlated in general with objective severity. Oral symptoms tend to have a stronger correlation with objective findings than ocular symptoms. Many patients with few or insignificant eye symptoms had profound ocular dryness and damage. Similarly, some patients with few or no symptoms of oral dryness had profound objective salivary hypofunction. The absence of symptoms does not rule out profound eye and mouth dryness or damage.

Conclusion. Although objective measures of xerostomia may not be practical for general population screening, it is crucial that practicing specialists perform objective testing of all patients suspected of pSS, instead of relying on symptoms. Without objective testing, the physician cannot ensure the diagnosis of pSS and that the existence of significant damage is not overlooked and left untreated.

Key Indexing Terms: cohort analysis, correlation study, dry eye, mouth dryness, Sjögren syndrome, symptom evaluation

Sjögren syndrome (SS) is one of the most common autoimmune conditions.[1] It is characterized by a lymphocytic invasion and destruction of exocrine glands, primarily affecting the lacrimal and salivary glands.[1,2] The condition can lead to punctate erosions of the corneal surface[3] and dental damage. Extraglandular manifestations of this syndrome also can occur, affecting, for example, the musculoskeletal, neurological, and respiratory systems.[2] The disease can affect quality of life, physical function, and health costs.[4,5,6,7] A lack of patient understanding of the symptoms caused by their disease has been cited as one of the major psychological concerns of patients with SS.[4] Prompt diagnosis is crucial, both to help provide patients with insight into their condition and to initiate treatment to mitigate the accumulation of dental caries and decay, punctate epithelial erosions, or even corneal melts.[8]

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There has been an evolution in classification criteria for this condition, aiming at identification of patients for study and clinical trials. In 2002, the most universally accepted criteria to date were published by the American European Consensus Group (AECG).[9] For the next 10 years, 2 of the 6 criteria used to classify patients consisted of subjective questions used to identify symptoms. Despite an increasing shift toward objective items, the 2012 internationally devised provisional American College of Rheumatology (ACR) classification criteria and the more recent 2016 ACR/European League Against Rheumatism (EULAR) classification criteria depend at least partly upon the same questions used in 2002 to screen people.[10,11,12] This is done before applying the more objective criteria to determine classification for study.

It is unclear if relying on patient-reported symptoms is an effective tool to screen for the disease. Despite its relatively high prevalence, SS tends to be an underdiagnosed condition.[8,13] General dry eye (xerophthalmia) symptoms have not been shown to correlate with clinical tests for tear flow, ocular surface dryness, or Meibomian gland dysfunction.[14] Concerningly, the diagnosis of dry eye by physicians tends to be more influenced by patient symptoms than objective measures.[3] In fact, several studies have found poor correlation between the objective measures of dry eye and ocular symptoms in patients with SS.[15,16,17,18]

Complaints of dry mouth (xerostomia) are not reliably associated with decreased stimulated whole salivary flow (SWSF) in a

general population.[19] The study of 688 patients with pSS showed a moderate correlation between symptoms of oral dryness and unstimulated whole salivary flow (UWSF).[18] A study of 49 patients with pSS demonstrated that questionnaires focused on oral dryness correlated only weakly with SWSF and UWSF.[20] A 6-item questionnaire, with 3 questions on ocular symptoms and 3 questions on oral symptoms, was validated as a screening tool in a 154-patient cohort with rheumatic diseases, identifying 19 patients with SS with 70% specificity.[21] These questions were used in the European preliminary criteria for the classification of SS in 1993 and were subsequently incorporated as criteria in the AECG classification for SS published in 2002.[9] These questions are also used as screening tools before applying the 2016 ACR/EULAR classification criteria.[9,10]

The purpose of this study was to document the association between patient symptom severity and the scores for well-validated clinical tests used to diagnose and characterize SS. We investigated the correlation between these symptoms and the Schirmer test score, the van Bijsterveld staining score for ocular surface dryness, SWSF, UWSF, and minor salivary gland (MSG) biopsy focus scores.

METHODS

Patients who were assessed for pSS in the Multidisciplinary Sjögren's Clinic at the University Health Network in Toronto from 1996 to 2016 were used in this analysis. This is a cross-sectional database of a 1-time comprehensive evaluation of patients performed using a consistent protocol. Patients are pre-screened before referral to this clinic and must have at least 1 documented abnormality: anti-Ro antibody, abnormal salivary flow, or abnormal Schirmer test. This is not a general population study; it is an analysis of patients who have already been selected because they had some manifestation suggestive of SS. Approval for this database study (19-5454) was obtained from the University Health Network Research Ethics Board. Individual consent was not deemed necessary for this retrospective analysis because all data are anonymized and reported in the conglomerate.

Item 1 of the 6-item AECG Classification Criteria is a series of 3 questions pertaining to dry eye. Every patient in this study was asked these questions. We then used a 10-cm visual analog scale (VAS) to ask patients to mark the severity of their dry eye symptoms overall.

The AECG second classification criterion is a series of 3 questions: 2 about dry mouth (which we used for this study), and 1 about parotid gland swelling (which we did not use for this analysis). All patients then marked a VAS for severity of dry mouth symptoms.The VAS is one of the most widely used measures of patient symptom severity. It has often been used for study of patients with SS.[22–29]

Objective measures of dry eye included the van Bijsterveld staining score for ocular surface dryness using Rose Bengal or Lissamine Green dye (≥ 4/9 is considered abnormal) and Schirmer-1 test (≤ 5 mm/5 min is considered significant, where the eye secreting the least amount of tear was recorded). Salivary flow tests were performed with patients off all sialogogues and medication with known atropine side effects for 48 hours. Artificial tears were held for at least 2 hours before the visit. UWSF was performed with patients left alone in a room to drool into a container for 5 minutes. SWSF was performed with patients collecting saliva for 1 minute while chewing on a wad of wax. The volume of SWSF per minute was recorded (< 1 mL is considered abnormal), and volume of UWSF per minute was also recorded (≤ 0.1 mL/min is abnormal). All patients had an MSG biopsy. Focus score was determined by the same observer for all patients using a graduated slide with a calibrated eyepiece grid. A focus is a clump of ≥ 50 lymphocytes. One focus per 4 mm^2 of glandular tissue is considered abnormal. Presence of SSA (anti-Ro) and SSB (anti-La) antibodies was determined by multiplex bead technology (Luminex).

Although data collection spanned 20 years, only patients who met the 2016 ACR/EULAR classification criteria for pSS were compared with sicca control patients, who have measures of dry eye or dry mouth but do not meet the classification criteria for pSS. Additional comparisons were made between patients with pSS who were very symptomatic and those who had few symptoms. All data were collected prospectively, on protocol, done at the time of the visit to the multidisciplinary clinic.

The charts of patients who had no eye or mouth symptoms in the pSS cohort were reviewed in further detail. The physician who referred these patients, the physician who established a diagnosis of SS, the symptoms upon presentation, and the key criteria that helped establish a SS diagnosis were recorded.

Statistical analysis. Patients whose data were not recorded for a symptom or objective measure were excluded from the analysis for any comparison involving the missing measure. Both Pearson and Spearman correlation analyses were used to assess for linear and nonlinear relationships and to ensure outliers would not obscure any existing correlations. Both types of analyses have been employed to assess dry eye data in the past.[14,15] For testing differences in the means between populations of patients, 2-sided *t* tests were employed to provide an unbiased comparison of the groups.

RESULTS

The database contained 619 patients. There were 97 patients who had an associated connective tissue disorder and were not included in the analysis. There were 385 patients who met the 2016 ACR/EULAR classification criteria for SS and 137 patients who did not meet the criteria; 1 patient without SS was discarded due to missing data. The 136 patients who did not meet classification criteria for SS and did not have a connective tissue disease were used as the sicca control group.

The sicca control group had a slightly lower proportion of females 115/136 (85%) compared to the pSS cohort 349/385 (91%; Table 1). The average age in the sicca control group (55.2 ± 14.4 yrs, range 24–79) was slightly older than the average age of patients presenting with pSS (52.8 ± 13.5 yrs, range 18–82, $P < 0.05$).

The average reported VAS score of dry eye in the pSS cohort (6.2 ± 2.7) was significantly higher than the sicca control cohort (5.6 ± 2.9, $P < 0.05$). Severity of symptoms did not differentiate the 2 groups. We documented that 101/333 (30%) of the

Table 1. Characteristics of patients with pSS and sicca controls.

	pSS, n = 385	Sicca Controls, n = 136
Female sex	349/385 (91)	115/136 (85)
Age, yrs, mean ± SD (range)	52.8 ± 13.5* (18–82)	55.2 ± 14.4* (24–79)
UWSF ≤ 0.1 mL/min	233/262 (89)	30/38 (68)
SWSF < 1 mL/min	284/380 (75)	51/130 (39)
van Bijsterveld score ≥ 4	311/382 (81)	41/133 (31)
Schirmer test ≤ 5	278/385 (72)	62/134 (46)
Biopsy focus score ≥ 1	303/356 (85)	11/101 (11)
Anti-La–positive	225/381 (59)	7/135 (5.2)
Anti-Ro–positive	326/382 (85)	6/135 (4.4)

Values are expressed as n/N (%) unless otherwise indicated. * $P < 0.05$ between pSS and sicca cohorts. pSS: primary Sjögren syndrome; SWSF: stimulated whole salivary flow; UWSF: unstimulated whole salivary flow.

Table 2. Severity and absence of symptoms in patients with pSS and sicca controls.

	pSS, n = 385	Sicca Controls, n = 136
VAS for dry eye, mean ± SD	6.2 ± 2.7*	5.6 ± 2.9*
Eye VAS < 5, n/N (%)	101/333 (30)	29/79 (37)
No symptoms in 3-question eye screen, n/N (%)	29/385 (7.5)	18/136 (13)
VAS for dry mouth, mean ± SD	6.6 ± 2.5*	5.6 ± 2.9*
Mouth VAS < 5, n/N (%)	78/335 (23)	32/80 (40)
No symptoms in 2-question mouth screen, n/N (%)	12/385 (3.1)	19/136 (14)

* $P < 0.05$ between pSS and sicca cohorts. pSS: primary Sjögren syndrome; VAS: visual analog scale.

patients with pSS and 29/79 (37%) of the sicca control patients reported a VAS of < 5/10. Moreover, 29/385 (7.5%) of patients with pSS answered no to all 3 validated screening questions for dry eye compared to 13% (18/136) in the sicca control group (Table 2).

Within the pSS cohort, the VAS of eye dryness severity weakly correlated with the van Bijsterveld scores for ocular surface dryness (Pearson r = 0.18, $P < 0.001$, and Spearman ρ = 0.19, $P < 0.001$; Supplementary Figure 1, available with the online version of this article) and the Schirmer test scores (r = 0.20, $P < 0.001$, and ρ = 0.21, $P < 0.001$; Supplementary Figure 2).

The 29 patients with pSS who answered no to all 3 screening questions for dry eye were further characterized (Table 3). They were found to report a lower VAS score (average 1.9 ± 1.0) compared to the 356 patients with at least 1 positive answer (6.5 ± 2.5, $P < 0.0001$). A similar proportion of abnormal van Bijsterveld scores (≥ 4/9) was found in the symptomatic

Table 3. Objective ocular and oral dryness in symptomatic and asymptomatic patients with primary Sjögren syndrome.

	Eye Symptoms, n = 356	No Eye Symptoms, n = 29
VAS for eye distress, mean ± SD	6.5 ± 2.5*	1.9 ± 1.0*
van Bijsterveld score ≥ 4	288/353 (82)	23/29 (79)
Schirmer score ≤ 5	259/356 (73)	19/29 (66)
	Mouth Symptoms, n = 373	**No Mouth Symptoms, n = 12**
VAS for mouth distress, mean ± SD	6.8 ± 2.3*	0.8 ± 0.8*
UWSF ≤ 0.1 mL/min	227/257 (88)	5/7 (71)
SWSF < 1 mL/min	282/368 (77)	2/12 (17)
Biopsy focus score ≥ 1	294/345 (85)	9/11 (82)

Values are expressed as n/N (%) unless otherwise indicated. * $P < 0.0001$ between those with and those without eye or mouth symptoms; SD used as error range. SWSF: stimulated whole salivary flow; UWSF: unstimulated whole salivary flow; VAS: visual analog scale.

Table 4. Primary Sjögren syndrome patients with limited symptoms and severe objective signs of eye dryness.

	No Eye Symptoms	Eye dryness VAS < 5
Schirmer score ≤ 5	19/278 (6.8)	64/237 (27)
Schirmer score < 3	13/168 (7.7)	33/141 (23)
van Bijsterveld score ≥ 4	23/311 (7.4)	76/274 (28)
van Bijsterveld score ≥ 7	4/144 (2.8)	24/133 (18)

Values are expressed as n/N (%). VAS: visual analog scale.

288/353 (82%) and the asymptomatic 23/29 (79%) patients. Abnormal Schirmer tests (≤ 5 mm/5 min) were documented in the symptomatic 259/356 (73%) and the asymptomatic 19/29 (66%) groups of patients with similar frequency as well.

Many of the pSS patients with significant eye dryness or damage had few eye symptoms (Table 4). Among the patients with some ocular dryness (Schirmer score ≤ 5), 19/278 (6.8%) answered in the negative to all 3 validated screening questions for ocular symptoms and 64/237 (27%) reported a VAS of < 5 for severity of dry eye. Of patients who had profound eye dryness (Schirmer score < 3), 13/168 (7.7%) reported they did not have any eye symptoms while 33/141 (23%) reported a VAS of < 5. Similarly, of the patients with significant ocular surface dryness (van Bijsterveld score ≥ 4), 23/311 (7.4%) answered no to the 3 validated screening questions and 76/274 (28%) had a VAS for severity of ocular dryness of < 5. Of the patients who had profound ocular surface dryness (van Bijsterveld score ≥ 7), 4/144 (2.8%) reported they did not have any eye symptom and 24/133 (18%) had a VAS of < 5 for dry eye.

Average reported VAS for dry mouth in the pSS cohort (6.6 ± 2.5) was significantly higher than in the sicca controls (5.6 ± 2.9, $P < 0.05$; Table 2). In the patients with pSS, the VAS of severity for dry mouth correlated significantly with UWSF (r = 0.29, $P < 0.0001$ and ρ = 0.47, $p < 0.0001$, Supplementary Figure 3, available with the online version of this article) and SWSF (r = 0.43, $P < 0.0001$ and ρ = 0.48, $P < 0.0001$; Supplementary Figure 4). The VAS for mouth dryness severity also correlated, to a lesser extent, with the MSG focus score (r = 0.25, $P < 0.0001$ and ρ = 0.25, $P < 0.0001$; Supplementary Figure 5).

The 12 patients with pSS who answered no to the 2 screening questions for dry mouth were further characterized (Table 3). They were found to report a lower VAS score (average VAS 0.8 ± 0.8) compared to the 356 patients with at least 1 positive answer (6.8 ± 2.3, $P < 0.0001$). Abnormal UWSF (< 1 mL/min) was more common in the symptomatic patients (227/257 [88%]) than the asymptomatic (5/7 [71%]) patients. Abnormal SWSF (≤ 1.5 mL/15 min) was found substantially more often in the symptomatic (282/368 [77%]) than the asymptomatic (2/12 [17%]) group of patients. A similar proportion of positive biopsy focus score (≥ 1 focus per 4 mm^2) was found in the symptomatic 294/345 (85%) and the asymptomatic 9/11 (82%) patients.

Despite the correlations between oral symptoms and diagnostic tests, patients with abnormal and even extremely abnormal

UWSFs, SWSFs, and biopsy focus scores did not consistently express dramatic mouth symptoms. Among the patients with abnormal UWSF, 44/227 (19%) had a VAS of < 5 for oral dryness. Even with a UWSF ≤ 0.05 mL/15 min, 28/172 (16%) reported a VAS for mouth dryness of < 5/10. Similarly, findings were identified with low SWSF and variable severity of symptoms. There were a few patients with no symptoms of xerostomia at all, despite very reduced saliva production. Similarly, 17/111 patients with profound inflammation on MSG biopsy (focus score ≥ 5) had mild symptoms of dry mouth (VAS < 5/10) and 3/122 (2.5%) had no symptoms at all (Table 5).

We reviewed the records of 16 patients with no eye symptoms to see how they presented. They were referred by family physicians (n = 6), otolaryngologists (n = 4), rheumatologists (n = 4), an obstetrician (n = 1), and a dentist (n = 1). Diagnosis of pSS was first suggested by rheumatology (n = 14), oral pathology (n = 1), and pediatrics (n = 1). Presentations in these patients included mouth symptoms (n = 7), parotid swelling (n = 7), dental problems (n = 1), and the birth of a baby with neonatal lupus (n = 1).

We also reviewed the records of 7 patients with no mouth symptoms. Referrals came from family practice (n = 3), otolaryngology (n = 1), oncology (n = 1), rheumatology (n = 1), and ophthalmology (n = 1). These patients were diagnosed by rheumatologists (n = 5) and ophthalmologists (n = 2). The presenting symptoms in these patients included eye dryness (n = 5), and facial swelling (n = 2).

DISCUSSION

Our cohort consisted exclusively of patients who were referred by a physician and had objective signs or serology indicative of potential pSS. All patients, including those used as controls, had some significant stigmata, which were worrisome features for SS. This rigorous pre-screening ensured that most patients assessed in the clinic did in fact have SS. However, some of these patients, despite having sicca syndromes, eye or mouth damage, or positive serology, did not have sufficient objective signs to be diagnosed with pSS. These patients were used as a control cohort that may not be representative of the larger population of patients with dry eye or mouth symptoms who do not have pSS. Among older adults, 21% of the population have symptoms of dry mouth, 31% have symptoms of dry eye, and over 10% have symptoms of both.[30] However, contrasting our patient population with pSS against our sicca control group may give us some indication of the differences from an unselected general population with dry eye or dry mouth complaints. From what we can see in the comparisons that we have made between our patients with SS and sicca control group, there appear to be significant caveats to depending upon the VAS score and questionnaires for selecting patients who might have pSS.

Table 5. Primary Sjögren syndrome patients with severe objective signs and limited symptoms of oral dryness.

	No Mouth Symptoms	Mouth Dryness VAS < 5
UWSF ≤ 1.5 mL/15 min	5/233 (2.1)	44/227 (19)
UWSF ≤ 0.5 mL/15 min	3/193 (1.6)	28/172 (16)
SWSF < 1 mL/min	2/284 (0.7)	28/244 (11)
SWSF < 0.5 mL/min	1/193 (0.5)	12/157 (7.6)
Biopsy focus score ≥ 1	9/303 (3)	73/312 (24)
Biopsy focus score ≥ 5	3/122 (2.5)	17/111 (15)

Values are expressed as n/N (%). SWSF: stimulated whole salivary flow; UWSF: unstimulated whole salivary flow; VAS: visual analog scale.

Most of the patients in the SS and control cohorts had eye and mouth complaints. While there were more intense eye and mouth symptoms as measured by VAS in the pSS cohort compared to the sicca controls, the difference was very modest. A significant portion of patients reported very minor or no eye symptoms in both groups. Corneal neuropathy, which can be caused by pSS, may impair symptom correlation with eye damage or tear dysfunction as captured by the Schirmer test or van Bijsterveld score.[31,32] This may be a confounding factor limiting the reliability of symptoms for identifying objective findings in the patients with pSS in our cohort. A small number of patients with pSS reported no mouth symptoms and more reported symptoms of minor intensity. There were only slight differences in symptom severity between patients with pSS and sicca controls. In some cases, symptoms were absent.

The closest linear relationship in this cohort was the correlation between SWSF and symptoms of mouth dryness. Other studies have also found a closer correlation between SWSF and symptom severity than between UWSF and symptom severity.[20] Patients tend to be most aware of and distressed by a lack of salivary production when eating. Interestingly, SWSF tests have also been shown to correlate more closely with the biopsy results than UWSF.[33]

In the general population, it is quite likely that the correlation of symptoms with objective signs will be even weaker. Ultimately, the diagnosis of pSS must be made using objective measures. Too often, rheumatologists screen for this condition by asking about dryness, but do not perform simple screening tests when appropriate, other than serology. As we have demonstrated, objective tests play a key role in identifying those patients with pSS who have limited or atypical symptoms. Schirmer test and UWSF can easily be performed in the physician's office and can provide more effective tools for determining whether further investigation is required.

Consequently, we recommend an examination that includes objective measures, such as Schirmer test and UWSF, for all patients who present to a rheumatologist with symptoms, laboratory findings, or history that can be consistent with pSS.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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