Psychological and Somatic Predictors of Perceived and Measured Ocular Dryness of Patients with Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** To test if age, disease activity, pain, fatigue, and depression are associated with subjective and objective ocular dryness of patients with primary Sjögren's syndrome (pSS).

Methods. Sixty female patients with pSS and 60 age matched healthy controls filled out visual analog scale (VAS) scores of ocular dryness and pain, and questionnaires regarding fatigue (Multidimensional Fatigue Inventory) and depression (Zung). Lacrimal tear production was measured by Schirmer I test. As surrogate indicators of disease activity the erythrocyte sedimentation rate, hemoglobin concentration, and total serum immunoglobulin G were determined.

Results. Perceived ocular sicca symptoms were not related to Schirmer I test scores. The rate of tear production was related to age ($r = -0.47$, $p < 0.001$), disease activity ($r = -0.27$, $p < 0.05$), and pain ($r = 0.42$, $p < 0.001$). Age and pain together explained 42% of the variance of the Schirmer I test results.

Conclusion. Not unexpectedly, age and disease activity were associated with ocular dryness, but contrary to expectation, pain was associated with more instead of less tear production. We did not find evidence that pain, fatigue, or depression are associated with reduced tear production or perceived ocular dryness. (J Rheumatol 2005;32:2351–5)

Key Indexing Terms:
SJÖGREN'S SYNDROME KERATOCONJUNCTIVITIS SICCA
PAIN FATIGUE DEPRESSION

Primary Sjögren's syndrome (pSS) is one of the most prevalent autoimmune disorders, characterized by chronic inflammation, predominantly in the exocrine glands. PSS has a female preponderance and manifests itself most frequently in the fourth and fifth decade of life. The hallmark symptoms are dry eyes (keratoconjunctivitis sicca) and a dry mouth (xerostomia). In most patients, the production of tears (as measured by Schirmer I test) and the unstimulated flow rate of whole saliva are decreased. In population studies, the correlation between perceived and objective measures of dryness is low to moderate[1,2]. This may suggest that subjective and objective ocular dryness reflect different phenomena.

It can be hypothesized that the core symptom of pSS (dryness) is affected by the actual psychological state of a patient. Stress affects the levels of transmitter substances in the autonomic nervous system, such as adrenergic or cholinergic agonists, which in turn affect salivary and lacrimal gland function[3]. A role of the autonomic nervous system is also indicated by improvement of dryness symptoms in patients with pSS after intake of the parasympathetic nervous system agonists pilocarpine[4,5] or cevimeline[6,7]. Many patients with pSS experience debilitating fatigue, joint pain, and depression that greatly impair their quality of life. The stress associated with these symptoms may affect sicca symptoms owing to central inhibitory interactions in the midbrain salivary and lacrimal nuclei[8]. Salivary secretion and subjective oral dryness have been shown to be associated with stress, depression, and anxiety[3,9,10]. However, the possible influence of psychological characteristics on lacrimal function is unknown.

In a study with a small sample size no predictors of per-

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ceived sicca symptoms were found, but the objective salivary dryness of the submandibular glands was predicted by autoimmune and disease measures as well as psychological characteristics[8]. Our study examines ocular dryness. We expect that perceived and measured ocular dryness correlate with age (because both lacrimal and salivary gland functions decrease with age), with disease activity (because the primary SS disease process inflicts damage to its own exocrine glands), and with symptoms (because the stress associated with symptoms affects salivary and lacrimal gland function through autonomic nervous system processes). The aim of our large-sample cross-sectional study was to examine these possible determinants of perceived and objective ocular dryness of patients with pSS and healthy controls.

MATERIALS AND METHODS

Participants. Participants were 60 patients with pSS from the departments of rheumatology and clinical immunology of the University Medical Center Utrecht and the University Hospital Groningen, The Netherlands, who were enrolled in a placebo-controlled study on the effects of administration of dehydroepiandrosterone (DHEA) on fatigue and general well being. The research and ethics committees of both institutions approved the study. The patients were all women, had a focus score of at least one on minor salivary gland biopsy specimen, met at least 4 of the European criteria for the classification of pSS[11], had normal serum creatinine and thyroid stimulating hormone levels, and did not use glucocorticoids in the preceding year. Forty-six (76.7%) patients had positive findings for Ro/SSA or La/SSB autoantibodies; 27 (45%) patients had a positive serological marker on La/SSB only. We used the baseline assessments before the start of treatment with DHEA or placebo.

The mean age of the patient group was 53.3 (± 13.1) years and 54 patients were Caucasian (91.5%). The healthy control group (n = 60) comprised age matched female participants (age 52.5 ± 12.1) from a pool of 91 healthy participants enrolled in the DHEA study. Fifty-seven control participants were Caucasian (95%). Sixty-two percent of the patients used artificial tears: 14 (23.3%) patients 2 times a day, 15 (25%) 3 to 5 times a day, and 8 (13.3%) ≥ 5 times a day. Ten (16.7%) patients used xerogenic medication known to affect the dryness symptoms: 3 patients antidepressants and ß-blockers, 3 patients antidepressants, 3 patients ß-blockers, and one patient antihistamines. Further characteristics of the participants are given in Table 1.

Table 1. Characteristics of 60 female patients with primary SS and 60 age matched healthy controls*.

	Patients with pSS†	Controls
Mean age, yrs (SD)	53.3 (13.1)	52.5 (12.1)
Education, %		
Primary	4 (6.8)	5 (8.3)
Secondary	36 (61)	40 (66.7)
Post-secondary	19 (32.2)	15 (25)
Marital status, %		
Single	7 (11.9)	7 (11.7)
Married	44 (74.6)	43 (71.7)
Widowed/divorced	8 (13.6)	10 (16.7)
Employment status, %		
Employed	25 (42.4)	31 (51.7)
Unemployed	34 (57.6)	29 (48.3)

* None of the differences was significant; p values range from 0.31 for employment status to 0.89 for marital status. † Scores of one patient missing for the variables education, marital status, and employment.

Questionnaires. Fatigue was evaluated with the Multidimensional Fatigue Inventory (MFI)[12], a 20 item self-report questionnaire covering 5 dimensions of fatigue: general fatigue (e.g., "I feel tired"), physical fatigue ("Physically, I feel able to do only a little"), reduced activity ("I feel very active"), reduced motivation ("I am not up to much"), and mental fatigue ("Thinking requires effort"). Scores range from 4 to 20; a higher score corresponds with more symptoms. This scale has been used and validated in a variety of conditions, including pSS[13]. As an assessment of fatigue, the standardized mean of the 5 scales of the MFI was calculated. The internal consistency of this fatigue score ($\alpha = 0.83$) was higher than 0.70, and thus qualified as "high"[14].

Depressive mood was assessed with the Zung self-rating scale of depressive symptoms, a 20 item questionnaire (score per item between 1 and 4) representing affective, psychological, and somatic characteristics[15].

Pain intensity and self-reports of dry eyes were assessed by 100 mm VAS. In terms of power of items to discriminate between patients with pSS and healthy persons, the items "feeling of dry eye" and "feeling of sand in the eye" display the highest accuracy: 82.7% and 73.6%, respectively[16]. We asked, "On average, how troublesome was the feeling of dry eyes in the last 2 days," and, "On average, how troublesome was the feeling of gritty eyes in the last 2 days." Answers were measured on a VAS ranging from 0, not troublesome, to 100 mm, extremely troublesome. For the perceived ocular sicca symptoms the mean of the 2 ocular VAS scales was calculated ($\alpha = 0.91$).

Clinical assessments. A Schirmer I test was performed in patients and healthy controls. Participants were instructed to refrain from use of artificial tears for one day prior to the assessment of ocular dryness. A strip was placed in the lower fornix between the medial and lateral third of the unanesthetized eye. After 5 minutes, the amount of wetting of the strip (range 0–35 mm) was measured from the notch corresponding to the inferior lid margin. A value ≤ 5.5 mm/5 min is considered abnormal and can be taken as a criterion for pSS according to the European classification[11,17]. As a score for tear production the highly reliable ($\alpha = 0.96$) mean of 2 Schirmer I tests (left and right eye) was calculated.

As surrogate markers of disease activity the erythrocyte sedimentation rate (ESR), hemoglobin concentration (Hb), and total serum immunoglobulin G (IgG) were determined. A mean disease activity measure was computed from the standardized scores of ESR, Hb, and IgG ($\alpha = 0.83$).

Statistical analyses. Comparisons between patients with pSS and healthy controls were made using independent sample t tests for continuous variables and chi-square test or Mann-Whitney test for categorical variables. Spearman rank correlations were calculated to examine the bivariate associations, because the scores of the dependent variables (i.e., objective and perceived ocular sicca symptoms) and some of the potential predictors (i.e., disease activity and fatigue) were not normally distributed in the patient population. Associations between Ro/SSA and/or La/SSB, the salivary gland focus score, and ocular dryness were examined using Mann-Whitney or Spearman rank correlation analyses where appropriate. After (log) transformation of the Schirmer I test and disease activity to improve normality, stepwise multiple linear regression analyses were employed to evaluate the independent effects of potential predictors on tear production and perceived ocular sicca symptoms. This stepwise method entered only the predictors that correlated with either objective or perceived ocular sicca symptoms into the model.

The Statistical Package for the Social Sciences (SPSS), Windows version 10.0, was used. All tests were 2-sided, and p values < 0.05 were considered significant.

RESULTS

No significant differences between patients with pSS and healthy control participants were seen for age, education, marital status, and employment (Table 1). The median disease duration of the patients was 5.0 (25th–75th percentiles:

2.4–10.0) years. The medians of surrogate disease activity indicators were: ESR 27.50 mm/h (13.25–40.25), Hb 8.10 mmol/l (7.63–8.68), and IgG 15.65 g/l (13.03–21.58).

Correlations between ocular dryness and serological markers of pSS. Patients with positive Ro/SSA and/or La/SSB autoantibodies had lower Schirmer I values than patients without these autoantibodies (median 5.00 vs 15.25, p = 0.022). Perceived ocular dryness was not associated with Ro/SSA or La/SSB. The possible association between ocular dryness, the autoantibodies Ro/SSA and/or La/SSB, and the salivary gland focus score was examined in 26 patients for whom the medical chart provided detailed (range 1–5) labial salivary focus scores. Presence of the autoantibodies Ro/SSA and/or La/SSB correlated with the Schirmer I test (r = 0.42, p = 0.035) and the focus score (r = –0.50, p = 0.010). The correlation between the Schirmer I test and the focus score was r = –0.39 (p = 0.051).

Ocular dryness, depression, fatigue, and pain. Patients with pSS had lower Schirmer I values than healthy controls (Table 2). A small overlap in tear flow rates was observed: the 75th percentile of pSS (15.0 mm/5 min) corresponded with the 25th percentile of the healthy controls (15.38 mm/5 min). One healthy control and 31 (52%) patients with pSS had a Schirmer I score ≤ 5.50 mm/5 min. Patients with pSS reported higher ocular dryness, depression, fatigue, and pain (Table 2).

Correlations with sicca scores. Table 3 shows the Spearman rank correlations between potential predictors and subjective and objective ocular dryness of 60 patients with pSS.

The objective tear production as measured by Schirmer I test was not correlated with the perceived ocular sicca symptoms (r = –0.12, p = 0.37); also not after controlling for the use of artificial tears. Perceived ocular sicca scores did not correlate with age, surrogate disease activity, pain, fatigue and depressed mood, or disease duration, but the use of artificial tears correlated highly with perceived ocular sicca symptoms (r = 0.51, p < 0.001).

Age (r = –0.47, p < 0.001) and surrogate disease activity (r = –0.27, p < 0.05) were correlated with reduced lacrimal secretion. Tear production was not related to depression, fatigue, use of artificial tears, or disease duration, but higher pain values correlated to higher Schirmer I values (r = 0.42, p < 0.001). This correlation remained significant (r = 0.37, p = 0.007) after adjustment for disease duration.

Adjustment for use of tear substitutes did slightly change the correlations of objective tear production with age (r = –0.50, p < 0.001), pain (r = 0.40, p < 0.001), and surrogate disease activity (r = –0.25, p = 0.057).

All predictors in one model. In multiple linear regression analysis Schirmer I test scores were predicted by age, surrogate disease activity, and pain. Age and pain together explained 42% of the variance of the lacrimal secretion. This reflects that pain predicted tear production, even after taking into account the influence of age.

Disease activity was no longer a significant predictor in the regression model with age and pain included. In an alternative regression model including age and disease activity but not pain, 35% of the variance of the objective ocular dryness was explained (data not shown).

DISCUSSION

We found that age and — less convincingly — disease activity were predictors of the tear production rate in female patients with primary Sjögren's syndrome, but we were unable to detect determinants of subjective ocular sicca manifestations. In contrast to our expectations, we found no evidence that pain, fatigue, or depression is associated with reduced ocular dryness. Pain was associated with more instead of less tear production as measured by Schirmer I test.

Studies in clinical[2,18-20] and population based settings[1,9,21] have demonstrated that clinical tests of lacrimal and salivary flow deficiency are associated, if only weakly,

Table 2. Median (25th–75th percentile) values of ocular tear production and perceived ocular sicca symptoms, disease activity indicators, and perceived symptoms of 60 female patients with pSS and 60 age matched healthy controls*.

	Patients with pSS†	Controls†
Ocular tear production		
Schirmer I test, mm/5 min	5.00 (3.00–15.00)	26.25 (15.38–34.63)
Perceived ocular sicca symptoms	53.50 (26.00–78.00)	2.00 (0.38–3.50)
Dry eyes, mm VAS	64.50 (25.50–82.00)	2.00 (0.00–3.00)
Sand, gravel in eyes, mm VAS	50.50 (16.00–78.75)	2.00 (0.00–3.00)
Perceived symptoms		
Depression, Zung score	41.00 (37.25–48.75)	32.00 (28.25–36.75)
Pain, mm VAS	33.00 (18.25–57.00)	4.00 (1.00–15.50)
Fatigue, MFI	14.20 (12.10–15.95)	5.60 (4.80–7.40)

* All group comparisons showed a significant difference by Mann-Whitney test between patients with pSS and controls (p < 0.001). † Scores from the Schirmer I test of one patient and 2 controls were missing. Scores for perceived ocular sicca symptoms and for fatigue of one control were missing. MFI: Multidimensional Fatigue Inventory[12].

Table 3. Spearman's rank correlations between possible predictors of perceived ocular sicca symptoms and objective tear production of 60 female patients with pSS.

	Perceived Ocular Sicca Symptoms (VAS scale)	Objective Tear Production (Schirmer I test)
Perceived ocular sicca symptoms		–0.119
Age	–0.179	–0.467†
Surrogate disease activity	–0.004	–0.271*
Erythrocyte sedimentation rate	–0.124	–0.201
Hemoglobin	–0.003	–0.245
Immunoglobulin G	0.119	–0.215
Perceived symptoms		
Depression (Zung score)	0.147	–0.045
Pain (VAS scale)	0.040	0.423†
Fatigue (MFI)	–0.005	0.101
Potential confounding variables		
Use of artificial tears	0.514†	–0.101
Disease duration	0.020	–0.240

* $p < 0.05$, † $p < 0.001$. MFI: Multidimensional Fatigue Inventory.

with perceived symptoms of ocular and oral dryness. In agreement with other studies[22,23], we could not confirm a relationship between clinically assessed and perceived ocular sicca symptoms of patients with pSS. This does not contradict the classification criteria for pSS[17], because pSS can be diagnosed in the absence of ocular sicca complaints. The finding that objective and perceived ocular sicca problems were not associated supports our procedure to separately examine the predictors of the 2 types of ocular dryness.

Fatigue and depression were not related to perceived ocular sicca symptoms. This contrasts with epidemiological studies showing that salivary secretion and subjective oral dryness were associated with psychological stress and distress[1,3,9,10]. Also, we could not find an association between perceived ocular dryness and age or disease activity. Thus, the model linking possible predictors to perceived ocular sicca symptoms was not supported by our findings.

Our study demonstrated that decreased tear production in pSS was related to age, in agreement with other studies[1,11,19,24,25]. The weak association between Schirmer I test scores and indicators of disease activity corresponds with a previous finding in rheumatoid arthritis[19], but is in contrast with a study in pSS[24]. Depression and fatigue did not predict objective ocular dryness, which is in contrast to findings in a small sample study in which psychological distress predicted clinically assessed gland function in patients with sicca symptoms unrelated to pSS[8].

We expected that pain would predict ocular dryness, but observed the opposite: more pain was associated with less severe lacrimal dysfunction. The Schirmer test, which was applied without local anesthesia, may by itself induce reflectory stimulation of tear production. If reflectory stimulation is more easily provoked in patients with more pain, this might explain the correlation between tear flow and pain. In a posthoc analysis we checked this hypothesis by comparing patients with (n = 16) and those without (n = 44) fibromyalgia, a chronic disorder characterized by widespread pain[26], and found that fibromyalgia did not explain the unexpected positive correlation between pain and lacrimal tear production. Other possible explanations are that older patients who have a lower tear volume may have become more adjusted to the pain or that pain decreases in the course of the disease. However, posthoc analysis using disease duration as a covariate ruled out these possibilities.

It is known that acute pain activates the parasympathetic nervous system and stimulates tear flow[27]. However, patients with pSS suffer from chronic pain. In such a situation the sympathetic nervous system is activated and as a consequence tear flow is expected to be reduced. It might be argued that the supposed mechanism linking pain, autonomic nervous system activity, and sicca symptoms was overruled by the existence of subgroups within the pSS population such as younger and older patients: pain has been observed to be more severe in younger patients, whereas ocular and oral problems tended to be more severe with greater age at onset of pSS[28]. In our study, however, age and pain were independently associated with the clinically assessed ocular sicca symptoms, suggesting that patients with pSS are a heterogeneous group, including patients characterized by moderate ocular sicca symptoms and severe pain, as well as patients with severe sicca symptoms and less pain, irrespective of the duration of the disease.

A limitation of our study may have been that we used the Schirmer I test instead of the Rose Bengal score[2,24,29] to assess lacrimal gland function. However, the Schirmer I test has shown sensitivity, specificity[16], and reliability[30]. Moreover, our analyses showed that Schirmer I values were related to autoantibodies and labial salivary focus score. Part of the keratoconjunctivitis may be due to evaporation, lipid film deficiency, or abnormal Meibomian gland function, but

this was not assessed in our study. Our results were not explained by possible confounders of perceived and objective ocular dryness, such as tear substitutes, xerogenic medication, and disease duration.

Our study emphasized the ocular component and cannot easily be generalized to oral sicca symptoms. Positive findings in studies that describe correlations between stress and oral dryness[1,3,9,10] perhaps suggest that sensitivity to stress of lacrimal and salivary gland function may differ[20]. Future research should take this discrepancy into account when addressing psychological processes in relation to objective and perceived sicca symptoms in pSS.

In summary, our patients with pSS showed decreased lacrimal tear production, increased perceived ocular dryness, and more severe pain, fatigue and depression compared to age matched healthy controls. Age and pain predicted the objective ocular dryness, whereas perceived ocular sicca symptoms could not be predicted by any of the potential determining variables. We did not find evidence that pain, fatigue, or depression is associated with reduced tear production or perceived ocular dryness.

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