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Pain Severity and Neuropathic Pain symptoms in primary Sjogren's syndrome: A comparison study of seropositive and seronegative Sjogren's syndrome

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Abstract

Objectives—To compare clinical characteristics and patient-reported outcomes in seropositive versus seronegative primary Sjogren's syndrome patients (pSS) and to investigate the effect of serological status on the prevalence of chronic pain, comorbidity and health quality.

Methods—Pain severity and neuropathic pain symptoms, comorbidity and health status were assessed in 108 pSS patients. Differences between patient groups were assessed by t-test and chi-square tests and adjusted pain-affect associations. The effect of predictor variables on pain severity was examined with multivariate regression.

Results—Pain severity was greater (p=.003) and physical function (p=.023) reduced in the seronegative patients. Prevalence of neuropathic pain, depression, anxiety and disability were similar between groups. Chronic pain, defined as daily pain for greater than 3 months, was reported by 65% of seropositive (N=65) and 75% of seronegative patients (N=40). After adjustment for age, sleep quality and psychological distress, the difference in pain severity between seropositive and seronegative patients remained significant.

Conclusion—Chronic pain is pervasive in both seropositive and seronegative pSS patients, while pain severity and functional impairment is greater in seronegative patients. Neuropathic pain is equally prevalent and is the predominant pain phenotype in patients with moderate to severe pain. Accurate assessment of pain phenotypes is needed for more effective management of chronic pain in pSS. The focus of future research should be to standardize assessment of pain and to identify the factors contributing to more severe pain in seronegative patients.

Primary Sjogren's syndrome (pSS) is a common systemic autoimmune disorder characterized by sicca manifestations and extra-glandular organ involvement. World-wide the prevalence is between 0.1 to 0.5% with a female gender predominance of over 90% (1). While the presenting symptoms are usually oral and ocular dryness, some patients present

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with peripheral neuropathy, as well as variety of other neurological features (2–5). In a small percentage of patients, the disease slowly evolves into lymphoma (6, 7).

Previous studies have emphasized the association of anti-Ro/SSA antibody with the development of extra-glandular manifestations such as purpura, lung involvement, nephritis and risk of lymphoma (8–11). According to American European Consensus criteria, patients are classified as pSS if symptoms and signs of gland dysfunction are documented and either specific histopathology (focal lymphocytic infiltration) is demonstrated on biopsy of minor salivary gland tissue or serologic tests are positive for either anti-SSA/Ro or anti-SSB/La antibody (12). Patients who meet criteria for primary Sjogren's but do not have detectable antibody to either anti-Ro/SSA or anti-La/SSB are considered seronegative. The prevalence of anti-Ro/SSA and anti-La/SSB antibodies varies according to the method of detection and referral pattern at the center performing the study (13). While seronegative patients have less systemic involvement, the factors contributing to health status specifically in seronegative patients are not well described. There are very limited reported data on whether serologic status modulates functional outcomes or psychological comorbidity in pSS.

Despite the association of systemic manifestations with positive anti-Ro/SSA, fatigue is a common complaint influencing health quality in both seropositive and seronegative patients (10, 14). As many as 70% of pSS patients report persistent fatigue (10, 14–16). Anxiety and depression also reported by 25–50% of Sjogren's syndrome (17–19). Fibromyalgia, a non-inflammatory condition characterized by chronic widespread pain, fatigue and polysymptomatic distress can also complicate primary SS (16). Predictors of fatigue in pSS include helplessness, depression and pain, suggesting that both psychological stressors and behavioral variables such as coping style and lower perceived personal control contribute to fatigue in pSS (14). Unfortunately, very little is known regarding the prevalence of and impact of chronic pain in pSS.

The aim of this study was to investigate the clinical characteristics and to compare patient reported outcomes in seropositive and seronegative pSS patients. We assessed 1) the prevalence of chronic pain and neuropathic pain (NeP); 2) comorbidity and 3) the effect of serological status on clinical characteristics. Standardized instruments were used to assess pain severity, neuropathic pain symptoms, fatigue, sleep quality, anxiety and depression. Patients were asked questions about psychological symptoms, the duration and severity of pain symptoms and history of physician-diagnosed comorbidity. We hypothesized that psychological distress and pain might be greater in seronegative pSS patients, whereas objective measures of sicca severity would be similar.

Patients and Methods

Patient population

We evaluated participants in the Biomarkers in Primary Sjogren's project (BioSIPS). BioSIPs is an NIH-funded clinical database and biorepository of RNA, DNA, serum saliva, tears, urine, lymphocytes and minor salivary gland tissue from patients with confirmed pSS by American European Consensus Group Criteria and healthy matched controls (12). The BioSIPs Registry represents a uniquely valuable repository of clinical data and biologic

samples obtained from well characterized pSS patients and healthy matched controls free of sicca symptoms and autoimmune disease. The registry includes patients with seronegative pSS who are under-represented in some large cohorts because minor salivary gland biopsy is not uniformly obtained. Patients are recruited through referrals from the ophthalmology, oral surgery and rheumatology clinics at the University of Minnesota, and through referrals to the Oklahoma Medical Research Foundation Sjogren's Research Clinic. Participants are recruited as well through newspaper and website advertisements. While a small number of patients have participated from across the country, the majority of participants reside in either the upper Midwest (approximately 40%) or central US. All participants undergo oral, ocular and rheumatologic exams and relevant tissue and blood samples are collected at a clinic visit. Since 2001, over 400 confirmed pSS patients have been enrolled in the BioSIPs Registry.

All patients with sicca symptoms who wish to participate are screened, facilitating recruitment of patients with early disease. Patients undergo a thorough history and physical examination, phlebotomy and specialized tests of gland function on the day of their research clinic visit. The purpose of the physical examination is to detect signs of unrecognized medical illness, concurrent autoimmune disease other than primary Sjogren's and identification of extra-glandular features of Sjogren's such as peripheral neuropathy, arthritis and fatigue. Unstimulated whole salivary flow rate is measured for 15 minutes and bilateral Schirmer I tear tests are performed according to the AECG criteria. Complete ophthalmological examination including slit lamp exam, vital dye staining (lissamine green) and dilated retinal exam is also performed on the day of the research clinic visit. Finally patients have a minor salivary gland biopsy performed by an experienced oral surgeon. The laboratory evaluation includes complete blood count and immunoglobulin level, sedimentation rate, ds DNA, Sm, RNP, RF and ANA antibodies as well as anti-Ro/SSA and anti-La/SSB. All clinical data is reviewed by the study physicians and the principle investigator to determine if patients meet AECG 2002 criteria for primary Sjogren's or appear to satisfy criteria for pSS and an additional autoimmune disorder. Consistency in application of the criteria is assured since only a small number of study physicians are involved in evaluating patients. All participants are informed of the results of the clinical evaluation and provided with a report indicating whether the clinical criteria for primary Sjogren's syndrome were satisfied.

Tests for anti-Ro/SSA and anti-La/SSB serologies are performed by commercially available ELISA kits (Immunovision, Springfield, Arkansas), precipitin methodology using immunodiffusion (Oklahoma Medical Research Foundation Clinical Immunology Laboratory, Oklahoma City, Oklahoma), and immunoblotting (INNO-LIA™), (Innogenetics Inc., Alpharetta, Georgia). The care taken in accurately assigning serologic status is of major importance because descriptive data from existing clinical cohorts may be difficult to interpret due to a high rate of both false positive and false negative serologic test results from commercial labs.

Survey data was collected from a sample of 200 BioSIPs participants who satisfied criteria for primary Sjogren's syndrome. Patients, ages 18–80, received an extensive health questionnaire 3–5 years after their initial evaluation in the registry. Patients classified as

seronegative pSS were oversampled to ensure an adequate number of patients for comparison of seropositive and seronegative patient groups. Inclusion criteria were sufficient English language skills to complete the questionnaire and age ≥18 years. All participants met AECG criteria for primary Sjogren's syndrome. The study was approved by the local medical ethics review board.

Study variables

Demographic variables included age, sex, race, and education level. Work and disability status variables were based on patient self-report. Specifically, we asked patients to report the category that best characterized their current work status: paid work, homemaker, student, not employed and not-looking for work, retired or disabled due to health. Objective evaluation of gland function was performed only at the time of enrollment in the registry. All additional data, including updated demographic variables, medical history and the subjective assessment of the severity of sicca symptoms, were included in the patient survey.

Visual analog scales (VAS) were used to the assess severity of oral sicca symptoms (mean of 12 items related to oral and throat dryness each rated 0 to 100) and ocular sicca symptoms (sum of 2 items rated 0–100 related to eye dryness). VAS were used to assess perceived stress (1 item rated 0 to 100) and musculoskeletal pain (mean of scores for two items: joint pain and muscle pain). Questions relating to pain included: location of most severe pain and presence of chronic pain defined as "daily pain for greater than 3 months". For each comorbidity the patients were asked 3 questions: 1) "Have you been diagnosed previously with fibromyalgia, neuropathy, depression or sleep disorder" 2)"do you have current symptoms of fibromyalgia, neuropathy, depression or sleep disorder" and 3) "are you currently taking anti-depressant medication, medication for anxiety, for sleep disorder or narcotic pain medication?" Previous research has demonstrated that patients can accurately assess their current and past medical conditions including comorbidity (20–22). We found that there was very good agreement between patient-reported history of neuropathy and fibromyalgia and diagnosis based on chart review in a sample of 45 survey respondents.

The health questionnaire included multiple instruments to assess pain, fatigue, sleep, and mood. The Brief Pain inventory (23) is comprised of 2 components: pain intensity (mean of 4 items rated 0–10, cut off for mild pain=0–4, moderate pain 5–7, severe pain 8–10) and pain impact (mean of 7 items related to pain interference with activities of daily living rated 0–10). The Neuropathic Pain Questionnaire is a brief 12-item measure that characterizes pain symptoms as neuropathic or non -neuropathic based on verbal descriptors (24). Patients were asked to name the site of pain that was most severe and to rate their pain at that site. Presence or absence of neuropathic pain is determined by an adjusted weighted sum of 12 specific pain scales; each rated from 0–10. The Fatigue Severity Scale (25) was used to assess the impact of fatigue on daily activities (mean of 9 items rated 1–7 with 7 indicating the most severe fatigue, cut off for abnormal fatigue ≥4). The Pittsburgh sleep Inventory (26) was used to assess sleep quality (sum of 7 scores, each rated from 0–3; higher scores reflect increased likelihood of a sleep disorder). The Hospital Anxiety and Depression Scale (HADS) was used to assess psychiatric comorbidity (sum of 7 items each rated 0–3 reflecting generalized anxiety, cut off for anxiety >10, and 7 items each rated 0–3 cut off for

depression >10). The depression scale focuses on loss of interest in life and anhedonia. A composite score for psychological distress is the sum of HADS anxiety and HADS depression subscale scores (27).

Overall health status was assessed with the Short-Form Health Survey (SF-12) (28). The SF-12v2 includes two summary scores for the physical and mental domains. For each subscale, scores range from 0 to 100, with higher scores indicating better functioning. A slightly modified version of the Revised Fibromyalgia Impact Questionnaire, the Symptom Impact Questionnaire (SIQR) was included to provide a means to compare the burden of illness in the study population to that previously described in primary fibromyalgia (29). The SIQR is identical to the FIQR, but does not contain any reference to FM. The SIQR-total includes measures of physical impairment, pain, sleep, anxiety, morning stiffness, depression, work status, and overall well-being. The severity of fibromyalgia (FM) is measured by three summary domains: overall impact, function and symptoms which can be combined to provide a composite score. The SIQR-total has a score range of 0–100, with higher scores representing more severe impact.

Statistics

Differences between seropositive and seronegative patients (Table 1 and Table 2) were examined using t-tests and chi-square tests for continuous and categorical variables respectively. Linear and logistic regression were used to evaluate the adjusted pain-affect associations. Estimates or odds ratios along with 95% confidence intervals were calculated to describe the magnitude of the observed association between case status and specific psychological disorders and co-morbidities. Significance threshold was set as $p<0.05$. All analyses were conducted using R version 2.12.0. (30)

Results

The survey response rate was 60% overall and was similar in seropositive and seronegative patients. The questionnaire was returned by 123 patients. The clinical and serologic profile of the 40% non-responders to the survey was similar to the 60% who did respond. Instruments with missing data were scored according to the author's instruction whenever possible. Fifteen respondents who had missing values for the variables used in the multivariate regression model (10 missing NPQ, 2 missing BPI and 1 missing PSQI; 2 missing both NPQ and BPI) were eliminated from the final dataset. The demographics of the 15 patients who were excluded did not differ significantly from those patients whose data were analyzed.

Clinical Characteristics in Seropositive and Seronegative Sjogren's patients

PSS patients (N=108) were classified into seropositive (anti-Ro/SSA positive and /or anti-La/SSB positive) or seronegative (neither anti-Ro/SSA nor anti-La/SSB) (Table 1.) Respondents were predominantly female, white, and college educated. Seronegative patients were slightly older (p=.025). Seropositive and seronegative patients were otherwise similar in demographics. The proportion of seropositive (20%) and seronegative (21%) patients who reported disability due to health was also similar. Objective measures of salivary gland

function were similar, however more seropositive patients had ocular sicca as measured by the Schirmer's test (68% of seropositive patients versus 46% of seronegative patients) (p=.043) and ocular sicca symptoms were rated more severe by seropositive patients (p=.021). Fatigue (p=.031), pain interference with daily activity (p=.012) and average pain intensity (p=.003) were greater in the seronegative patients. SF-12 physical function was significantly lower in seronegative patients (p=.023).

Pain phenotype, Comorbidity and Psychological Profiles in Seropositive and Seronegative Patients

A majority of patients in both groups reported chronic pain (defined as daily pain for greater than 3 months)--65% of the seropositive and 75% of the seronegative patients (p=.370). Moderate or severe pain was reported by 35% of seropositive and 68% of seronegative patients (p=.002). The proportion of seropositive patients (37%) and seronegative patients (40%) with neuropathic pain symptoms was similar. There was no difference in the prevalence of abnormal fatigue (FSS ≥4), anxiety (HADS-A >10) or depression (HADS-D>10) (Table 2). Thirty-two percent of seropositive patients and 43% of seronegative patients reported a physician diagnosis of neuropathy (p=.381). A history of fibromyalgia was reported by twice as many seronegative patients (33%) as seropositive patients (17%), a difference which did not reach the threshold for significance (p=.128). The proportion of patients who had moderate or severe overall fibromyalgia summary scores on the SIQR (defined as ≥40) was also higher but not significant in the seronegative patients (57% vs. 39%) (p=.136). There was no significant difference in the use of opioid analgesics, treatment with anti-depressants, nor in medications used to treat anxiety or sleep disorder (data not shown).

Clinical Variables associated with Neuropathic Pain and Predictors of Pain Severity

Sixty-one percent of patients with neuropathic pain symptoms rated their pain as moderate or severe. The frequency of opioid analgesic use in patients with neuropathic pain symptoms was 32% compared to 13.6% in those without neuropathic pain (p=0.003, data not shown). Neuropathic pain symptoms were strongly associated with anxiety (p=0.005) and with depression (p=0.002). More severe pain was also associated with worse sleep quality, more severe oral dryness, greater perceived stress, and with more anxiety and depression. SF-12 physical and mental domain scores were more impaired in those with moderate or severe pain Neuropathic pain was predicted by psychological distress: odds ratio 1.12(95% CI 1.05–1.21) but not with serological status. Serological status was a significant predictor of overall pain severity in a model adjusted for age, sleep quality and psychological distress (Table 3).

Discussion

Pain is associated with functional limitations and psychological distress in Sjogren's syndrome as is the case in other chronic conditions. This study demonstrates several important new observations and raises some interesting questions regarding pain phenotypes in Sjogren's syndrome. The first important finding was that physical impairment was greater and pain more severe in seronegative pSS patients. Secondly, chronic pain was pervasive

and reported by the majority of both seropositive and seronegative patients. Neuropathic pain symptoms were frequently reported and equally prevalent in seropositive and seronegative patients.

Recent epidemiologic surveys of the general population have suggested that chronic pain affects 30 to 50% of the population and that the prevalence of pain of predominantly neuropathic origin is 8% (31–33). Neuropathic pain prevalence has not been studied previously to our knowledge in the Sjogren's population. Neuropathic pain, reported by 37–40% of the patients in the current study, is especially problematic because of its severity, chronicity and resistance to simple analgesics. The observation that neuropathic pain was equally prevalent in seropositive and seronegative patients is important to note because previous studies have emphasized the occurrence of peripheral nervous system involvement in seropositive patients (9). Neuropathic pain, particularly in seronegative patients may be under recognized and possibly under treated.

The precise reason for greater pain severity in the seronegative patients requires more study. Differences in pain perception between seropositive and seronegative patients could have a genetic basis, or could reflect an increased tendency for patients with unexplained pain to seek medical care and to be evaluated for Sjogren's even when serologic tests for pSS are negative. Depression and anxiety were associated with more severe pain, but rates of psychiatric comorbidity were similar in seropositive and seronegative patients. The data does suggest that comorbid fibromyalgia was more common among seronegative patients. Although we did not specifically assess tender points in this survey, higher fibromyalgia symptom impact scores in the seronegative patients, as well as a history of FM that was twice as high in the seronegative patients, suggests that fibromyalgia was a factor contributing to the increased pain severity in the seronegative patients.

Incorporating FM assessment into future studies of pSS should be considered, especially in intervention trials, to control for the effects of FM on patient reported outcomes. In the UK pSS registry there was no difference in fatigue, pain or dryness in anti-Ro/SSA, anti-La/SSB positive compared to seronegative patients; nevertheless, systemic activity was linked to symptoms of fatigue and pain only in seropositive patients (34). The prevalence of FM was not reported in that study and the lack of correlation between systemic activity and patient outcomes in the seronegative patients could reflect overestimation of sicca and fatigue due to the effects of FM.

Previous studies of pSS have reported wide variation in rates of FM from 12 to 44% (16). In order to design appropriate interventions for treatment of chronic pain in pSS, more precise understanding is needed of the factors contributing to the high prevalence of chronic pain in both seropositive and seronegative pSS. Chronic pain falls into 3 broad categories: 1) *nociceptive pain*, which occurs as a result of tissue damage in the presence of a functionally intact sensory nervous system; 2) *neuropathic pain*, which arises when the nervous system is damaged and 3) *chronic pain* that occurs without known somatic background. Neuropathic pain assessment tools such as the Neuropathic Pain Questionnaire used in this study are increasingly employed as the first step in the diagnostic work-up of persons with chronic pain. Classification of patients into neuropathic and non neuropathic pain syndromes based

on verbal descriptors alone, however, is not sufficient for diagnosis in individual patients, since chronic disorders such as painful neuropathy and fibromyalgia may in fact share very similar sensory phenomena (35).

Nociceptive and neuropathic processes can also coexist and contribute to a mixed clinical picture. Both the neuropathic pain that results from injury or disease to the nervous system, and nociceptive pain that arises from trauma or inflammation, can lead to central sensitization particularly in individuals with high anxiety and emotional distress (36). Central sensitization is thought to explain the association recently demonstrated between neuropathic pain and pain arising from severe OA of a weight bearing joint, as well as the association of neuropathic pain symptoms in patients fulfilling criteria for fibromyalgia(36,37) highlighting the complex mechanisms involved in chronic pain syndromes.

The Neuropathic Pain Questionnaire can be helpful to identify patients with sensory symptoms. Detailed sensory exam and ancillary tests may be required for accurate diagnosis. Patients with fibromyalgia and sensory symptoms are especially difficult to distinguish from those patients with only minor deficits on neurological examination who may have a painful small fiber neuropathy. Nerve conduction studies are insensitive to small fiber neuropathy, hence epidermal nerve fiber biopsy may be necessary to diagnose patients with pSS who suffer from small fiber neuropathy. While differentiation of neuropathic from pain of non-neuropathic origin may be quite difficult at times, there are still important messages here for clinicians. Pain extent and neuropathic pain symptoms are important clinical variables that should be elicited in the clinical interview.

Neuropathic pain presentations also contribute to delayed diagnosis of pSS, particularly when patients present with sensory polyneuropathy or polyganglionopathy and mild sicca symptoms. Grant et al reviewed 54 cases of idiopathic peripheral neuropathy associated with sicca symptoms (38). Minor salivary gland biopsy was positive in 73%, whereas antibodies to anti-SSA/Ro and anti-SSB/La were detected in only 10%. Association of non-ataxic sensory neuropathy with older age and negative serological status has recently been reported in multiple cohorts (2,4,5). Taken together these studies suggest that evaluation for ocular and salivary gland involvement and detailed sensory evaluation is necessary, especially in older patients with neuropathic pain symptoms. Older, seronegative Sjogren's syndrome patients with sensory neuropathy may constitute a unique subset lacking B cell activation markers and having a distinct pathophysiology.

Future research should focus on clarifying the mechanisms and origin of neuropathic pain symptoms underlying the chronic pain experienced by pSS patients. Among 14 pSS patients with chronic neuropathic pain and normal motor exam studied consecutively by Fauchais et al (39), small fiber neuropathy was confirmed by reduced epidermal nerve fiber density on skin biopsy in all 14 subjects. The prevalence of peripheral nervous system disorders including small fiber neuropathy in pSS remains uncertain however, as there is wide variation reflecting the lack of standardized nomenclature and referral bias. The reported prevalence of polyneuropathy in pSS ranges from 0–56% (40) and patients with immune-

mediated neuropathies of all types commonly experience moderate or severe neuropathic pain (41).

Our study does have several limitations. The results might not be generalisable to men with pSS or to non-English speaking pSS patient populations. Our findings could have been compromised by a selection bias. It is possible that the prevalence of psychological comorbidity, chronic pain and neuropathic pain were over-estimated in this study. However, the demographics of the respondents were similar to that of patients classified as pSS in the BioSIPs Registry, and the demographics and prevalence of depression, anxiety and fatigue was similar to that previously described in the UK pSS registry (34).

This study highlights the association of chronic pain with anxiety disorder and depression, fibromyalgia, and neuropathic pain symptoms in patients with pSS. More precise classification of pain phenotypes is needed to better understand the mechanistic pathways involved in chronic pain. Earlier recognition and appropriate management of neuropathic pain could improve health outcomes in patients with Sjogren's syndrome.

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Significance and Innovations

1. Chronic pain is reported by more than half of both seronegative and seropositive pSS patients.
2. Neuropathic pain is the predominant pain phenotype in pSS patients with moderate or severe pain and is strongly associated with anxiety and depression.
3. Seronegative pSS patients have more severe pain and greater impairment in functional status.

Table 1

Demographics and Clinical Characteristics in Seropositive and Seronegative PSS Patients

Variable	Seropositive		Seronegative		Difference (95% CI)	p-value
	N	Mean (sd) or N (%)	N	Mean (sd) or N (%)		
Total	68		40			
Demographics						
Age	68	57.25 (12.13)	40	61.98 (9.23)	−4.73 (0.61, 8.84)	0.025
Female	68	64 (94.12%)	40	36 (90.00%)	4.12 (−8.72, 16.95)	0.683
Caucasian	68	64 (94.12%)	40	39 (97.50%)	−3.38 (−12.76, 6.00)	0.739
College Educated	68	52 (76.47%)	39	33 (84.62%)	−8.14 (−25.32, 9.03)	0.450
Disabled Due to Health	61	12 (19.67%)	38	8 (21.05%)	−1.38 (−19.12, 16.36)	1.000
Objective Measures						
WUSF Positive†	66	46 (69.70%)	35	20 (57.14%)	12.55 (−9.42, 34.53)	0.297
Schirmer's Positive*	66	45 (68.18%)	39	18 (46.15%)	22.03 (0.73, 43.33)	0.043
Symptoms						
Pain Severity	68	3.45 (2.25)	40	4.70 (1.92)	−1.25 (0.44, 2.06)	0.003
Pain Interference	67	3.33 (3.06)	40	4.72 (2.51)	−1.39 (0.31, 2.47)	0.012
Fatigue Severity	68	4.73 (1.66)	40	5.36 (1.31)	−0.63 (0.06, 1.20)	0.031
Pittsburgh Sleep Quality Index	68	10.09 (5.07)	40	10.78 (4.14)	−0.69 (−1.10, 2.47)	0.447
Anxiety	68	6.84 (4.47)	40	6.28 (4.03)	0.56 (−2.23, 1.10)	0.503
Depression	68	6.24 (4.06)	40	6.05 (3.97)	0.19 (−1.77, 1.40)	0.817
Oral ($^{\Delta}$ VAS)	64	53.02 (23.02)	38	48.06 (21.04)	4.96 (−13.84, 3.92)	0.270
Ocular ($^{\Delta}$ VAS)	64	69.28 (26.45)	38	55.71 (28.90)	13.57 (−25.01, −2.13)	0.021
Perceived Stress	60	3.98 (3.56)	38	3.58 (3.15)	0.40 (−1.77, 0.96)	0.558
Quality of Life Measures						
** SF-12 Physical Score	53	37.55 (10.72)	38	32.41 (10.21)	5.14 (−9.55, −0.73)	0.023
** SF-12 Mental Score	53	47.18 (11.25)	38	48.08 (9.95)	−0.90 (−3.54, 5.34)	0.688
^{a} SIQR Total	59	35.16 (23.86)	37	41.05 (20.33)	−5.89 (−3.18, 14.96)	0.200

†WUSF= whole unstimulated salivary flow rate.

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[*] Average of left and right eye;

[Δ] VAS= Visual analog scale

[**] Short Form -12 Health Survey;

[α] VAS= Visual analog scaleSIQR= Symptom Impact Questionnaire-Revised.

Table 2

Prevalence of Chronic Pain, Neuropathic Pain, Anxiety, Depression and Comorbidity in Seropositive and Seronegative PSS Patients

Variable	Seropositive		Seronegative		Difference (95% CI)	p-value
	N	Mean (sd) or N (%)	N	Mean (sd) or N (%)		
Total	68		40			
Patient Reported Outcome						
Fatigue	68	48 (70.59%)	40	33 (82.50%)	−11.91 (−29.90, 6.07)	0.250
Pain (Moderate to Severe)	68	24 (35.29%)	40	27 (67.50%)	−32.21 (−52.62, −11.79)	0.002
Neuropathic Pain	68	25 (36.76%)	40	16 (40.00%)	−3.24 (−24.24, 17.77)	0.897
Chronic Pain	65	42 (64.62%)	40	30 (75.00%)	−10.38 (−30.16, 9.39)	0.370
Anxiety	68	18 (26.47%)	40	7 (17.50%)	8.97 (−8.78, 26.72)	0.406
Depression	68	9 (13.24%)	40	5 (12.50%)	0.74 (−13.04, 14.51)	1.000
SIQR ≥ 40	59	23 (38.98%)	37	21 (56.76%)	−17.77 (−40.21, 4.67)	0.136
History of Comorbidity						
Neuropathy	59	19 (32.20%)	37	16 (43.24%)	−11.04 (−33.16, 11.08)	0.381
Sleep Disorder	63	19 (30.16%)	35	18 (51.43%)	−21.27 (−43.56, 1.02)	0.062
Fibromyalgia	63	11 (17.46%)	40	13 (32.50%)	−15.04 (−34.36, 4.28)	0.128
Depression	62	32 (51.61%)	37	18 (48.65%)	2.96 (−19.54, 25.47)	0.938

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Table 3

Association of Serologic Status as a Predictor of Pain Severity or Neuropathic Pain Adjusted for Age, Sleep Quality and Psychological Distress.*

	Pain Severity Outcome		Neuropathic Pain Outcome	
Adjustor	**Effect Estimate (95% Confidence Interval)**	**p-value**	**Odds Ratio (95% Confidence Interval)**	**p-value**
Seropositive vs. Seronegative	−1.17 (−1.88, −0.47)	0.001	0.81 (0.32, 2.01)	0.642
Age (per decade)	0.17 (−0.13, 0.48)	0.264	0.98 (0.65, 1.49)	0.937
Sleep Quality	0.12 (0.04, 0.20)	0.005	1.05 (0.94, 1.17)	0.354
Psychological Distress†	0.12 (0.07, 0.17)	< 0.001	1.12 (1.04, 1.21)	0.003

*Estimates for “Pain Severity” outcome denote expected Pain Severity level per change in covariate, holding constant all others. Odds ratios for “Neuropathic Pain” outcome denote multiplicative odds of Neuropathic Pain vs. Non neuropathic pain for participants per unit difference in the covariate, holding constant all others.

†Psychological Distress variable = HADS composite score