Increased Severity of Lower Urinary Tract Symptoms and Daytime Somnolence in Primary Sjögren's Syndrome

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ABSTRACT. ***Objective.*** Functional antimuscarinic receptor autoantibodies have recently been described in both primary and secondary Sjögren's syndrome (SS) in a mouse bladder contraction assay. Most patients with these antibodies complained of severe lower urinary tract disturbances, which are not a recognized feature of SS. We compared the severity of self-reported urological symptoms, daytime somnolence, and fatigue between a cohort of patients with primary SS and controls with osteoarthritis (OA).

Methods. Female patients were recruited from rheumatology outpatient clinics at 2 hospitals. The American Urological Symptom Index (AUA-7), Epworth Sleepiness Scale, and FACIT-F fatigue self-administered instruments were employed. Results were obtained for 76 patients with primary SS and 43 controls (response rates 85% and 67%, respectively). The patient groups were matched for parity, hormone replacement and diuretic therapy, and number of bladder operations and urinary tract infections, although OA patients were slightly older.

Results. AUA-7 urological symptoms were more severe in patients with primary SS compared to OA controls ($p = 0.039$). Severe urological symptoms were reported by 61% of primary SS patients compared with 40% of OA controls. This difference was predominantly attributable to bladder irritability associated with urgency ($p = 0.015$) and not nocturia ($p = 0.85$). Epworth Sleepiness Scale scores were also more severe in primary SS patients compared to OA controls ($p = 0.02$), independent of nocturia. The FACIT-F fatigue severity scores were not significantly different between patient groups ($p = 0.14$).

Conclusion. Urological symptoms and daytime somnolence may be previously unrecognized symptoms of primary SS. These symptoms are consistent with functional disturbances of muscarinic receptors, possibly mediated by muscarinic receptor autoantibodies. (J Rheumatol 2003;30:2406–12)

Key Indexing Terms:
AUTOIMMUNE DISEASE | SJÖGREN'S SYNDROME | FATIGUE
URINATION DISORDERS | HYPERSOMNOLENCE

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Supported by grants from the National Health and Medical Research Council and the Arthritis Foundation of Australia.

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Submitted December 3, 2002; revision accepted April 2, 2003.

Primary Sjögren's syndrome (pSS) is a systemic rheumatic disease characterized by lymphocytic infiltration and exocrine failure of salivary and lacrimal glands, frequently complicated by extraglandular features including interstitial nephritis, renal tubular acidosis, peripheral neuropathy, and palpable purpura[1]. Nocturia in pSS is usually attributed to increased fluid intake to ameliorate symptomatic xerostomia, and lower urinary tract symptoms (LUTS) *per se* are not a recognized feature of this disease.

Diagnosis of pSS is aided by the finding in most patients of circulating autoantibodies specific for the ubiquitously expressed Ro/La ribonucleoproteins and positive rheumatoid factor (RF). Using a model of mouse bladder smooth muscle contraction, we recently reported the finding of serum autoantibodies in patients with primary and secondary SS that target muscarinic receptors of the M_3 subtype (M_3R)[2]. These autoantibodies were shown to antagonize the effects of endogenously released acetylcholine

from parasympathetic nerve endings, as well as exogenous carbachol on smooth muscle contraction. Since lacrimal and salivary gland secretion is mediated by the action of acetylcholine upon epithelial M_3R, we postulated that antagonistic effects of anti-M_3R antibodies within these target organs is a likely mechanism for the production of sicca symptoms in SS. Notably, 8/11 patients with SS whose serum contained anti-M_3R antibodies reported severe lower urinary tract disturbances including frequency, urgency, nocturia, and in 2 cases biopsy-proven interstitial cystitis, suggesting a potential role for anti-M_3R in the induction of bladder detrusor dysfunction in these patients. We designed the present cross-sectional study to investigate our hypothesis that severe LUTS are a feature of pSS.

Patients with pSS have reduced quality of life, with respect to all aspects of functional status and well being, comparable to that observed in patients with systemic lupus erythematosus (SLE)[3]. Primary SS patients commonly complain of fatigue that, unlike fatigue in SLE, is usually resistant to pharmacotherapy. We used 2 additional instruments to compare self-reported levels of fatigue and daytime sleepiness in patients with pSS and controls.

MATERIALS AND METHODS

Urological Symptom Score Instrument. The American Urology Symptom Index (AUA-7, Table 1)[4] was used to quantify urological symptoms in pSS patients and controls. The AUA-7, which is designed to be self-administered, consists of 7 questions addressing incomplete emptying, frequency, intermittance, urgency, weak urinary stream, hesitancy, and nocturia scored on a 6-point (0–5) severity scale. This instrument has been validated in terms of internal consistency, reliability, and sensitivity to change[4,5]. Originally designed to be administered to men, it has since been extensively used in the female population and is a useful tool to document the extent of LUTS[4,6-9].

Fatigue instrument. Functional Assessment of Chronic Illness Therapy (FACIT) instruments are a collection of quality of life questionnaires intended to illustrate the management of chronic illnesses, and the FACIT-F scale[10] was utilized to assess fatigue in pSS patients and controls. The FACIT-F instrument comprises 13 questions, stated both positively and negatively, scored on a 5-point (0–4) severity scale that address the impact of fatigue on daily life. The instrument may be self-administered and has been validated as a reliable and valid measure of fatigue[11].

Sleepiness instrument. The Epworth Sleepiness Scale (ESS)[12] was used to assess sleepiness in pSS patients and controls. The ESS is a simple self-administered questionnaire comprising 8 questions, scored on a 4-point (0–3) severity scale, that address the likelihood of falling asleep in a variety of situations. It has been validated as a simple and reliable method for measurement of persistent daytime sleepiness in adults[13] and is sensitive to a variety of sleep disorders including narcolepsy, sleep apnea, periodic leg movements in sleep, restless legs syndrome, and circadian rhythm disorder.

Patients. This study was approved by the Ethics of Human Research Committees at both The Queen Elizabeth Hospital and Flinders Medical Centre. Only female subjects were included because of the concern that undiagnosed prostatism among men might confound interpretation of results. Patients with primary SS were identified from the South Australian Sjögren's Syndrome Register made up of patients attending rheumatology clinics at both Flinders Medical Centre and The Queen Elizabeth Hospital. Patients with osteoarthritis (OA) were chosen as the control population. OA is a noninflammatory degenerative joint disorder that is not known to be associated with autoantibodies or extraarticular manifestations. Patients with OA in the absence of additional rheumatological diagnoses or diabetes were identified retrospectively from patients attending the Queen Elizabeth Hospital Rheumatology Outpatient Clinic between 1998 and 2000. The majority of patients were contacted by telephone and invited to participate in the study. If they were willing to complete the questionnaire, it was mailed to their home address. Nonresponders were contacted by telephone and invited again to complete the questionnaire. Some pSS patients attending the clinic for routine followup were also invited to complete the questionnaire. These were largely self-administered, but if necessary, assistance by medical staff was provided. In addition to the AUA-7 questionnaire, information was also sought on parity, menopausal status, hormone replacement therapy (HRT) and other medication use, bladder operations, and as a late addition to the study, culture-proven urinary tract infections within the previous 12 months. Menopausal status was not reliably reported (a number of women over 60 years of age and undergoing HRT did not

Table 1. The American Urology Association symptom (AUA-7) index.

Question	Not At All	< 1 Time in 5	< 1/2 the Time	About 1/2 the Time	> 1/2 the Time	Almost Always
1. During the last month or so, how often have you had the sensation of not emptying your bladder completely after you finished voiding?	0	1	2	3	4	5
2. During the last month or so, how often have you had to urinate less than two hours after you finished urinating?	0	1	2	3	4	5
3. During the last month or so, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. During the last month or so, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. During the last month or so, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. During the last month or so, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
7. During the last month or so, how many times did you most typically get up to urinate from the time you went to bed at night to the time you got up in the morning?	None	1 Time	2 Times	3 Times	4 Times	5 Times
	0	1	2	3	4	5

report that they were postmenopausal), therefore this information was not used for analysis in the study.

Eighty-nine pSS patients were asked to participate in the study. All consented, and responses were obtained from 76 patients (response rate 85%). Clinical and laboratory data were extracted from the Sjögren's Syndrome Research Database maintained at Queen Elizabeth Hospital. The diagnosis of each patient was then reviewed according to the European Classification criteria for pSS[14] with the modification that Ro/La seronegative patients must have a positive salivary gland biopsy with a focus score ≥ 1. A further 5 patients with insufficient information to meet the diagnostic criteria of pSS were excluded prior to analysis. Sixty-four OA patients were asked to participate in the study. Four declined and responses were obtained from 43 patients (response rate 67%).

Statistical analysis. The patient scores for the AUA-7, FACIT-F, and ESS were classified into ordinal severity groupings. For the AUA-7 urological scale, symptoms were categorized as mild, moderate, or severe, corresponding to total symptom scores of 0–7, 8–19, and ≥ 20, respectively[4]. Some analyses of urological symptoms utilized a total score for irritative and obstructive symptoms. The irritative symptom score was defined as the sum of the individual AUA-7 severity scores (Table 1) for Question 2 (frequency), Question 4 (urgency), and Question 7 (nocturia). The obstructive symptom score was defined as the sum of severity scores for Question 1 (incomplete bladder emptying), Question 3 (intermittent urinary flow), Question 5 (weak urinary stream), and Question 6 (strain on urination). There are no universally accepted standard interpretations of symptom severity for the FACIT-F and ESS instruments; therefore, the scores were divided into 4 severity groupings, based on the observed quartiles of the combined pSS and control data. The observed quartiles for the FACIT-F instrument were 0–11, 12–25, 26–35, and ≥ 36, and the observed quartiles for the ESS instrument were 0–3, 4–7, 8–11, and ≥ 12.

All analyses were performed using Statistica (Statsoft Inc.) Version 6.0, and p values < 0.05 were considered statistically significant. Comparison of the AUA-7, FACIT-F, and ESS severity score classifications between pSS patients and OA controls and within pSS patient subgroups were performed by ordinal (proportional odds) regression, and the proportional odds assumption was checked by the Score Test. The results are reported as a single odds ratio (similar to an average of all possible odds ratios) for greater symptom severity in pSS patients compared to OA controls. Comparisons of irritative and obstructive urological scores between patient groups were performed by the nonparametric Mann-Whitney U test. Correlations were assessed by the Spearman rank order correlation coefficient (R).

RESULTS

Clinical characteristics of the 43 OA patients and 71 pSS patients included in the study are shown in Table 2. The response rate in both groups was high (67% and 85%, respectively), although slightly lower in the OA patients. This difference in response rate may potentially mask differences between the 2 groups, as OA patients without significant symptoms may have been less motivated to return the study questionnaires. There were no differences between pSS and OA patients in terms of parity, hormone replacement and diuretic therapy, number of bladder operations, and occurrence of urinary tract infections, all of which may influence urological symptoms. However, OA patients were slightly older and this effect was most pronounced when analyzed as the proportion of women over 50 years of age (p = 0.01). It is therefore likely that proportionately more OA patients were postmenopausal.

Table 2. Osteoarthritis (OA) and primary Sjögren's syndrome (pSS) patient characteristics.

	OA	pSS	p
No.	43	71	
Response rate, %	67.2	84.6	
Median age (range), yrs	64 (32–84)	58 (31–85)	0.07
Age > 50 yrs, %	39 (91)	50 (70)	0.01
HRT use, %	9 (21)	20 (28)	0.39
Bladder operations, %	8 (19)	17 (24)	0.50
Urinary tract infections in last year*, %	9 (23)	12 (25)	0.78
Parous, %	38 (88)	61 (86)	0.70
Diuretic treatment, %	3 (7)	3 (4)	0.52

* The question on urinary tract infections was a late addition to the questionnaire and was evaluated in 40 OA and 48 pSS patients. HRT: hormone replacement therapy.

Lower urinary tract symptoms are increased in pSS. Urological symptoms were more severe in pSS patients. Severe urological symptoms (AUA-7 score ≥ 20) were reported by 61% of pSS patients compared with 40% of OA controls (Figure 1A). The proportional odds ratio for increased urological symptom severity in pSS patients compared to OA controls was 2.15 (p = 0.04). An age-adjusted analysis, adjusting for the difference in proportion of women over 50 years of age, gave essentially similar results (proportional OR 2.50, p = 0.02).

The AUA-7 assesses both irritative and obstructive symptoms. The total irritative symptom score was significantly increased in pSS patients compared to OA controls (p = 0.014, Mann-Whitney U test), whereas the total obstructive symptom score was not (p = 0.45, Mann-Whitney U test). Irritative symptoms assessed consisted of urinary frequency (Question 2, Table 1), urgency (Question 4), and nocturia (Question 7). Urgency was the only symptom that was individually significantly different between the 2 patient groups (OR 2.42, p = 0.015; Figure 1B), although urinary frequency approached significance (OR 1.86, p = 0.08). Urinary frequency and nocturia might be expected to be more pronounced in pSS patients due to a higher liquid consumption to alleviate a severely dry mouth; however, nocturia was not significantly associated with pSS patients (OR 0.93, p = 0.85). Therefore, the increase in LUTS severity in pSS patients observed in this study may be attributed to bladder irritability, primarily manifest as urgency, rather than nocturia.

Daytime somnolence but not fatigue is increased in pSS. While there was a trend for increased FACIT-F fatigue severity scores in pSS compared to OA patients, this did not reach statistical significance (OR 1.67, p = 0.14; Figure 2A). However, ESS scores were more severe in pSS patients compared to OA controls (OR 2.50, p = 0.01; Figure 2B), an association that was unchanged by the inclusion of nocturia severity or proportion of women over age 50 as covariates. Further, the correlation between the sleepiness and fatigue scores was greater in pSS patients (R = 0.53, p = 0.000003)

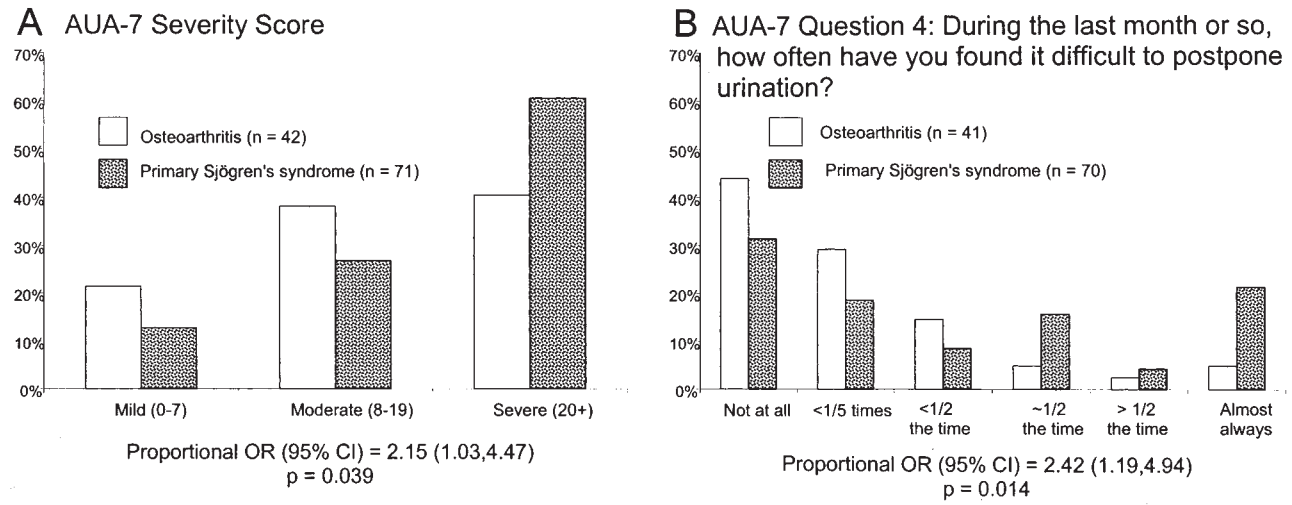

Figure 1. AUA-7 urological symptom severity score distribution in patients with primary SS and OA.

than OA controls (R = 0.27, p = 0.09). Taken together, these results suggest that fatigue, commonly reported in pSS patients, may be related to an underlying sleep disorder that cannot be simply attributed to increased nocturia.

HLA-DR2, which is strongly associated with narcolepsy, is increased in prevalence in Caucasian pSS patients[15]. Of the 65 pSS patients with HLA typing in this study, 28 (43%) were positive for HLA-DR2, but there was no association between DR2 and the ESS score (p = 0.83).

LUTS, daytime sleepiness, and fatigue in pSS are independent of anti-Ro/La status, but LUTS are negatively correlated with RF levels. Sixty-one (86%) pSS patients were positive for La and/or Ro autoantibodies and 10 were seronegative. No association was observed between the presence of Ro/La autoantibodies and severity score for the AUA-7 urological symptoms (p = 0.76), ESS (p = 0.87), or FACIT-F fatigue (p = 0.94).

RF levels were available for 56 pSS patients. Surprisingly, the RF levels were negatively correlated with both AUA-7 urological symptom severity (R = –0.31, p = 0.02) and FACIT-F fatigue symptom severity (R = –0.29, p = 0.03). For urological symptoms, the negative correlation with RF levels was greater for the obstructive symptom score (R = –0.47, p = 0.0004) than the irritative symptom score (R = –0.26, p = 0.05). A negative correlation was also observed between the ESS score and RF levels, but this was not significant (R = –0.20, p = 0.14). No significant correlations were observed between symptom severity and IgG levels.

AUA-7 urological, FACIT-F fatigue, and ESS scores are positively correlated. The 3 symptom scales were all significantly positively correlated with each other when assessed for pSS patients and OA controls combined (Table 3), and the trends were broadly similar when assessed separately in

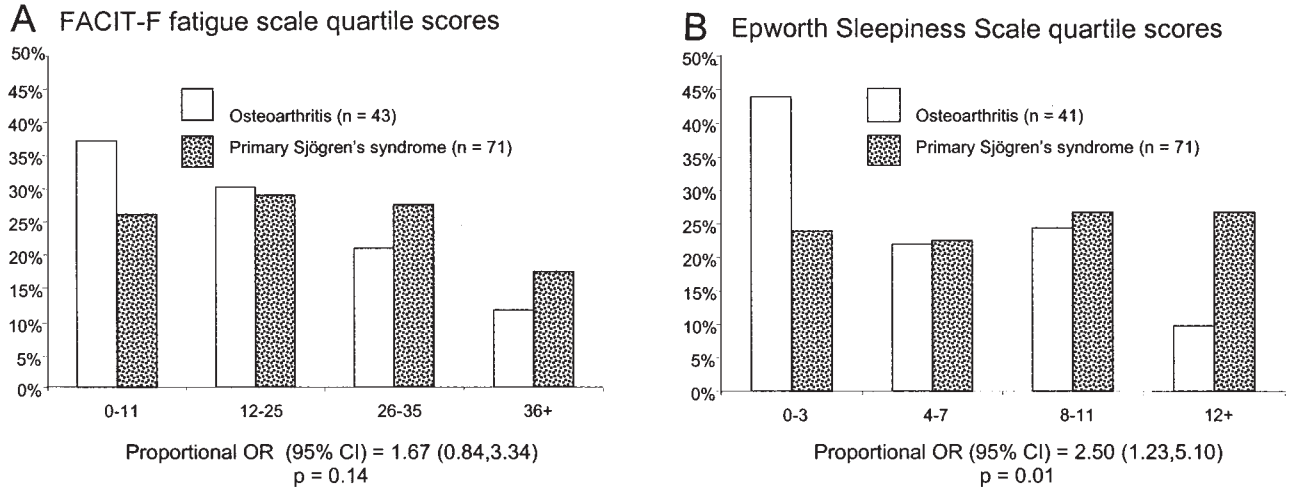

Figure 2. FACIT-F fatigue and Epworth Sleepiness Scale severity score distributions in patients with primary SS and OA.

Table 3. Correlations between the AUA-7 urological symptom, FACIT-F fatigue scale, and Epworth Sleepiness Scale (ESS) severity scores assessed over all patients.

Correlation Comparison	N	R*	p
AUA-7 and FACIT-F	111	0.30	0.001
AUA-7 and ESS	112	0.26	0.006
FACIT-F and ESS	110	0.43	0.00002

* Spearman rank order correlation coefficient.

each patient group (data not shown). While there is a logical relationship between sleepiness and fatigue, their relationship to urological symptoms is not obvious and suggests a common underlying etiology. When assessed individually, the only AUA-7 symptom not correlated with daytime sleepiness severity was Question 6, an obstructive symptom relating to pushing or straining to begin urination (R = 0.01, p = 0.9).

DISCUSSION

The recent finding of antimuscarinic receptor autoantibodies in the sera of patients with primary and secondary SS has altered our understanding of the pathogenesis of SS. Rather than a direct result of inflammatory destruction of exocrine glands, secretory failure is likely at least in part to be caused by parasympathetic dysfunction due to binding of these autoantibodies to muscarinic receptors on glandular epithelium. SS may thus be considered a disorder of receptor-mediated humoral autoimmunity, akin to myasthenia gravis or Graves' disease. The relationship between muscarinic receptor autoantibodies and glandular lymphocytic infiltrates is unknown.

Apart from nocturia due to increased fluid intake to ameliorate mouth dryness, lower urinary tract symptoms are not generally considered to be a feature of SS. Many of our pSS patients, including most patients with anti-M_3R in our preliminary study[2], report severe lower urinary tract disturbances including frequency, urgency, nocturia, and in 2 cases biopsy-proven interstitial cystitis. We therefore designed the present cross-sectional study to define the prevalence of lower urinary tract symptoms in a well defined population of female patients with pSS. We observed a significant increase in LUTS as measured by the AUA-7 severity score in pSS patients compared to OA controls (OR 2.15, p = 0.039). It is possible that this study was biased against a more significant result by using women with OA as controls, as they were, on average, slightly older than the pSS patients, and many studies suggest that LUTS severity may increase with age. Further, the OA patients were recruited from outpatient clinics at a tertiary referral center and were more likely to have underlying comorbidities, whereas the pSS patients were often referred to the investigators directly from their primary care physicians. Indeed, the frequency of severe LUTS in our OA patients (40%) was substantially higher than 2 American population-based studies using the AUA-7[6,16]. However, our data are generally consistent with 2 recent Australian population-based studies reporting 39%[8] and 43%[7] prevalence in women of troublesome or bothersome LUTS.

Published data examining the relationship between urinary symptoms and pSS have yielded mixed results. Van de Merwe, *et al*[17] screened a series of 10 patients with interstitial cystitis for autoimmune diseases and found that 2 patients had previously undiagnosed primary SS and a further 6 patients had either keratoconjunctivitis sicca or focal sialadenitis, both hallmarks of SS. They concluded that a high index of suspicion for pSS was indicated in patients with interstitial cystitis. Sacco, *et al*[18] reported a clinical case of unstable bladder in association with pSS and noted a moderate response to anticholinergic drugs. More recently, Haarala, *et al*[19] mailed a questionnaire to 46 pSS patients regarding possible urinary complaints. Of the 36 respondents, 14% reported severe urinary symptoms, defined as those that "recurred daily and constituted a significant problem for the patient." This was significantly higher than among an age and sex matched control population. Sankar, *et al*[20] addressed the possibility that urinary symptoms are a function of increased fluid intake due to sicca symptoms by comparing pSS patients with xerostomic controls. A total of 63 primary SS patients and 38 controls were screened by questionnaire (details not published), urinalysis and salivary flow. They concluded that there was no significant difference between pSS subjects and xerostomia controls, although a trend toward increased urinary symptoms among pSS patients was observed. Of particular interest, nocturia was only correlated with salivary flow among the xerostomia group, suggesting that factors other than xerostomia may be important in the nocturia of pSS patients. Among our patients, nocturia was not significantly different between pSS and OA patients. Taken together, these findings indicate that the causes of the observed increased urinary symptoms in pSS are likely to be more complex than increased fluid intake due to xerostomia. The lack of a standardized questionnaire in previous studies makes direct comparison between the pSS patient groups difficult. Overall, we feel our findings provide a template that will allow direct comparison with other pSS populations screened with the AUA-7.

It should be noted that the AUA-7 functions only as a symptom score, and the mechanism(s) underlying LUTS in pSS will require evaluation in studies incorporating fluid balance charts, urine chemistry, urodynamics, and, where appropriate, cystoscopy and biopsy. Pathological lesions of the urogenital tract that are known to occur in pSS include interstitial nephritis, interstitial cystitis, and vaginal dryness secondary to disordered exocrine gland function. Although the etiopathogenesis of interstitial cystitis is unknown,

infection seems unlikely, and several features support the role of an autoimmune process[21]; one might therefore speculate that lymphocytic infiltrates observed in bladder mucosa might mirror pathological changes in salivary and lacrimal glands. Human detrusor smooth muscle contains M_3 receptors, which mediate the effects of acetylcholine on smooth muscle contraction. Our recent finding that anti-M_3 receptor autoantibodies in the serum of patients with SS are able to agonize and/or antagonize the effects of acetylcholine at M_3 receptors in murine bladder detrusor muscle[2] raises the possibility that these autoantibodies may directly induce bladder irritability *in vivo*. A key question is the temporal relationship between anti-M_3R autoantibodies and lymphocytic infiltrates, which will require evaluation in experimental models of antimuscarinic receptor autoimmunity[22].

We observed some heterogeneity in LUTS severity in the pSS cohort in this study suggestive of modulation by factors associated with the underlying humoral autoimmunity. Obstructive urological symptoms, not increased in severity in pSS patients *per se*, were strongly negatively correlated with RF levels in these patients. Interpretation of these observations is open to speculation. One possibility may relate to the role of RF in the host's defence against infection[23]. Binding of IgM RF to IgG-antigen complexes inhibits their effective binding to Fc gamma receptors[24], which may promote clearance of immune complexes through less inflammatory pathways.

The other key finding of our study was that daytime somnolence, as measured by the Epworth Sleepiness Scale, is increased, independent of nocturia, in patients with pSS compared to OA controls. A trend toward increased fatigue, as measured by the FACIT-F scale, was also observed, but this did not reach statistical significance. This suggests that increased fatigue reported by patients with pSS[25] may be primarily attributable to a sleep disorder. An earlier study demonstrated that pSS patients suffer from a high sleep deficit compared to both healthy controls and patients with rheumatoid arthritis, which was attributed to significant difficulties in both initiating and maintaining sleep[26], i.e., characteristic symptoms of insomnia. However, while patients with insomnia complain of daytime fatigue, they do not exhibit signs of daytime hypersomnolence and typically score low (3–4 out of a possible maximum of 24) on the Epworth Sleepiness Scale[27]. In contrast, 32% of pSS patients, compared to 17% of OA patients, scored over 10 on the ESS, a score indicative of pathological hypersomnolence[12,13]. This suggests that pSS patients likely suffer from another sleep disorder in addition to insomnia. There is considerable evidence from animal models that muscarinic receptors play a key role in the generation of rapid eye movement sleep[28] and in the regulation of circadian rhythms[29]. It is possible, therefore, that hypersomnolence in pSS may be a direct manifestation of central nervous system autoantibody-mediated muscarinic receptor dysfunction. An alternative and perhaps equally plausible explanation for the hypersomnolence is obstructive sleep apnea. The surface tension properties of upper airway secretions are known to have a marked effect on upper airway stability during sleep[30]. If the xerostomia of pSS is associated with high surface tension forces on the pharyngeal mucosal surfaces, obstructive sleep apneas may be increased in pSS patients. Finally, periodic limb movement disorder of sleep may contribute to hypersomnolence. An increased prevalence of restless legs symptoms has been reported among pSS patients[26]. Restless legs symptoms are often associated with periodic limb movements of sleep that can cause daytime sleepiness. Clearly, further studies are required to determine which sleep disorder(s) are responsible for daytime sleepiness and fatigue in pSS.

An unexpected finding was the positive correlation, over all patients, between the AUA-7 urological symptom index, the Epworth Sleepiness Scale, and the FACIT-F fatigue scale. This argues for a shared mechanism for these symptoms in both patient groups, which, in view of their age and sex, may involve estrogen levels. Urological symptoms, fatigue, and sleep disturbances in middle-aged and elderly women are usually attributed to estrogen deficiency (menopause), although with the exception of urogenital problems, the evidence is not definitive[31] because of difficulty in distinguishing the specific effects of cessation of ovarian function from other effects of aging. In this context, there is evidence from animal models that muscarinic receptor density and/or function may decline with age[32-34], and estrogen has been shown to modulate muscarinic receptor function in experimental models[35,36].

This study has confirmed our suspicion that severe lower urinary tract symptoms are a common, previously unrecognized feature of pSS. Our findings also suggest that an underlying sleep disorder, possibly accounting for the common complaint of fatigue, may also be an unrecognized symptom of this disease. On the basis of these findings and those of other studies, we propose that urological and sleep disorder indices be included as outcome measures in the evaluation of disease activity and damage in pSS. We speculate that both may be manifestations of autonomic dysfunction due to the presence of circulating antimuscarinic receptor autoantibodies in a subset of patients with pSS. Future studies, following the development of a suitable anti-M_3R screening test, will aim to correlate their presence with LUTS, daytime somnolence, and neuropsychiatric symptoms. Although anticholinergic drugs are likely to remain the primary therapy for detrusor instability in the setting of pSS, results from such studies may lend support for the evaluation of less conventional treatments such as muscarinic agonists or immunomodulation in resistant cases.

ACKNOWLEDGEMENT

Many thanks to the Arthritis Foundation of South Australia Lupus/Scleroderma/Sjögren's Support Group and the many patients with Sjögren's who took part in these studies. Thanks also to Dr. Paul Duggin, Department of Obstetrics and Gynaecology, University of Adelaide, for reviewing the manuscript.

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