

Increased Prevalence of Antibodies to Thyroid Peroxidase in Dry Eyes and Mouth Syndrome or Sicca Asthenia Polyalgia Syndrome

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ABSTRACT. Objective. A subset of patients presenting with sicca features suggestive of primary Sjögren's syndrome (pSS) do not fulfill diagnostic or histopathological criteria. This presentation was previously designated as dry eyes and mouth syndrome (DEMS) or sicca asthenia polyalgia syndrome (SAPS). We sought to define the underlying clinical, laboratory, and histological features of these patients.

Methods. The study population consisted of 27 consecutive patients with DEMS/SAPS; 54 patients with pSS served as controls. Medical charts were retrospectively evaluated for clinical and serological data and frozen sera were tested for the presence of antibodies against HIV, hepatitis C virus, and thyroid antigens. Immunohistochemical analysis of paraffin embedded tissues was also performed.

Results. Sicca symptoms and nonspecific musculoskeletal pain were the commonest clinical features of patients with DEMS/SAPS; positive titers of antibodies against thyroid peroxidase was the main underlying abnormality found in 16 out of 27 (59.2%) of patients with DEMS/SAPS compared to 11 out of 54 (20.4%) of pSS controls ($p = 0.0009$). Histological analysis of the minor salivary gland (MSG) biopsies of patients with DEMS/SAPS disclosed a mild inflammatory infiltration of the interstitial tissue with a predominantly perivascular distribution.

Conclusion. Patients with DEMS/SAPS present with sicca features and nonspecific musculoskeletal complaints, have high prevalence of antithyroid antibodies, and their MSG biopsies demonstrate a mild interstitial lymphocytic infiltration with a predominantly perivascular distribution. In the setting of clinical practice, we propose that in the presence of DEMS/SAPS testing for antithyroid antibody should be performed. (J Rheumatol First Release July 15 2009; doi:10.3899/jrheum.081326)

Key Indexing Terms:

DRY EYES AND MOUTH SYNDROME
ANTITHYROID ANTIBODIES

SICCA ASTHENIA POLYALGIA SYNDROME
SICCA SYNDROME

Symptoms of dry eyes and/or mouth, the so-called sicca syndrome, are among the most common symptoms for rheumatology consultation in everyday clinical practice. The differential diagnosis of dry eyes and/or mouth is quite extensive and includes drug side effects, diabetes mellitus, viral infections [human immunodeficiency virus (HIV), hepatitis C virus (HCV)], sarcoidosis, lymphoma, head and neck irradiation, and Sjögren's syndrome (SS)¹.

A subset of patients with sicca features without fulfilling

the diagnostic or histopathological criteria for primary SS has been described and designated as dry eyes and mouth syndrome (DEMS) or sicca asthenia polyalgia syndrome (SAPS)²⁻⁴. Patients with DEMS/SAPS are characterized by the presence of nonspecific clinical features resembling those found in fibromyalgia or chronic fatigue syndrome, antinuclear antibodies (ANA), hypothyroidism, and moderate lymphocytic infiltration in minor salivary glands (MSG)²⁻⁴. Due to the diversity of symptoms/signs it is highly likely that such patients constitute a heterogeneous group rather than a single disease entity.

Given that antithyroid antibodies are frequently encountered in ANA positive individuals⁵, and sicca features have been previously described in patients with autoimmune thyroiditis⁶, we hypothesized that thyroid autoimmunity might be the underlying abnormality at least in a subset of patients with DEMS/SAPS. In this context, we sought to present the clinical features, immunological profile (including antibodies against thyroid antigens), and histopathological features of patients with DEMS/SAPS and compare them with those of an age-and-sex-matched group of patients with pSS.

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Accepted for publication March 5, 2009.

MATERIALS AND METHODS

Patients. The study population (DEMS/SAPS cases) was recruited between 1998 to 2007 in our outpatient Rheumatology Clinic according to the following criteria: (1) presence of sicca symptoms; (2) presence of mild lymphocytic infiltrates in MSG biopsies without fulfilling histopathological criteria for pSS⁷; (3) absence of another underlying autoimmune or inflammatory disorder; and (4) absence of diagnostic SS criteria⁷. In addition, 54 consecutive patients with pSS, according to the American-European classification criteria⁷, who were matched for age, sex, and disease duration with the DEMS/SAPS cases, composed the control group. Both DEMS/SAPS cases and pSS controls were followed in the same period of time and were investigated according to a consistent protocol (described below). Frozen sera from patients with DEMS/SAPS and pSS, as well as paraffin embedded MSG tissues from 27 patients with DEMS/SAPS and 2 healthy volunteers were available for further evaluation. The prevalence of antithyroid positivity was also tested in a cohort of 75 healthy controls. Patients and controls provided informed consent prior to participation in the study.

Clinical and laboratory evaluation. Medical charts were evaluated for the presence of symptoms and signs related to systemic autoimmune disorders. Sicca features were elicited by validated questionnaires⁸, and objective evaluation of ocular dryness (Schirmer I test, Rose Bengal stain of the conjunctivae) was recorded. Conditions that could contribute to sicca symptomatology, such as diabetes mellitus, drug side effects, preexisting lymphoma, previous head and neck irradiation, or sarcoidosis were not present in any of the patients⁷.

Laboratory data, including routine serological and immunological studies, were also available in all patients' medical files. The latter included rheumatoid factor (RF), ANA, antibodies to extractable nuclear antigens (anti-Ro, anti-La, anti-Sm, anti-U1RNP), and IgG antibodies to double-stranded DNA. Additionally, patients' and controls' frozen sera were further tested for antibodies to thyroid peroxidase (anti-TPO) and to thyroglobulin (anti-TG) using commercially available kits (by radioimmunoassay and ELISA, respectively). Testing for thyroid stimulating hormone (TSH) (by radioimmunoassay; normal limits between 0.4-5.00IU/ml) and for HIV and HCV infection was also performed.

MSG biopsies. All H&E stained MSG biopsies were reassessed by an expert (FNS) blind to clinical data. Immunohistochemical analysis of paraffin embedded tissues — using specific monoclonal or polyclonal mouse antibodies against CD20 (B cell marker, DAKO), CD3 (T-cell marker, DAKO), CD8 (cytotoxic/suppressor T cells, Novocastra), CD4 (helper/inducer T cells, OPD4, DAKO) and CD68 (macrophages, DAKO) was performed by the avidin-biotin immunoperoxidase technique.

Statistics. Comparison of frequencies between the DEMS/SAPS and pSS group was performed using 2-sided Fisher's exact test. Comparison of the antithyroid antibody levels between the DEMS/SAPS and pSS groups was performed by Mann-Whitney test.

RESULTS

Descriptive analysis of the DEMS/SAPS group. The DEMS/SAPS group consisted of 27 patients (2 men and 25 women). The mean age of the DEMS/SAPS group was 52.9 ± 12.8 years. None of them fulfilled the classification criteria for either primary or secondary SS⁷.

The clinical and laboratory profile as well as results of sicca evaluation are presented in Table 1. Coexistence of sicca oral and ocular symptoms was present in 21 out of 27 patients (77.8%), while 3 had xerostomia alone (11.1%) and 3 (11.1%) isolated dryness of the eyes. Abnormal Schirmer I test was evident in 9 out of the 24 patients tested (37.5%), while Rose Bengal stain of the conjunctiva, suggestive of keratoconjunctivitis sicca, was present in 9 out of the 23

patients tested (39.1%). Routine laboratory evaluation was unrevealing for the great majority of the patients, including viral testing for HIV and HCV antibodies. Immunology testing revealed ANA and RF positivity in 12 (44.5%) and 3 (11%) patients, respectively. Fifteen patients (55.5%) had positive titers of anti-TPO antibodies and 3 (11.1%) of anti-TG antibodies, while 6 of them had positive titers for both specificities (22%). Thyroid function was normal, as reflected by normal TSH values (data not shown).

Comparative analysis with pSS. Table 2 illustrates clinical and serological comparative data between DEMS/SAPS and primary SS groups. The prevalence of subjective oral and ocular dryness was higher in the pSS group (88.8% vs 100%, $p = 0.03$). While keratoconjunctivitis sicca as detected by Rose Bengal stain did not differ significantly between the 2 groups (39.1% vs 54.5%, $p = 0.30$), abnormal Schirmer I test was found less frequently in patients with DEMS/SAPS than in those with pSS (37.5% vs 86.0%, $p = 0.001$). In addition, no differences in the prevalence of joint involvement and Raynaud's phenomenon were detected (48.1% vs 61.1%, $p = 0.34$ and 14.8% vs 16.6%, $p = 1.0$, respectively). Extraglandular features, such as pulmonary, liver, and renal involvement as well as vasculitis and lymphoma were not present in the DEMS/SAPS group (data not shown). In regard to immunological profile, the prevalence of ANA and RF positivity was lower in DEMS/SAPS compared to patients with primary SS (44.5% vs 88.9%, $p = 0.00003$, 11.1% vs 42.6%, $p = 0.005$, respectively). Interestingly, patients in the DEMS/SAPS group had a significantly higher prevalence of anti-TPO antibodies (59.2% vs 20.4%, $p = 0.0009$), but not of anti-Tg antibodies (22.2% vs 18.5%, $p = 0.77$), while the corresponding values in a cohort of 75 tested healthy controls were 10.7% for both reactivities. In Table 3, comparison of the median and range of anti-TPO and anti-Tg antibodies in the DEMS/SAPS and SS groups is also presented.

Histopathology of the MSG in patients with DEMS/SAPS. Histological analysis of H&E sections of MSG biopsies of the patients with DEMS disclosed scattered lymphocytes and some occasional focal (< 50 lymphocytes) infiltrates. In contrast to pSS, which is characterized by periductal and lymphoepithelial infiltrates with focus score > 1.0, MSG biopsies from patients with DEMS/SAPS demonstrated a predominantly perivascular lymphocytic infiltration with focus score < 1.0 (Figure 1A, B).

Immunohistochemistry was performed in serial sections of 5 μm. The scattered lymphocytes were almost mainly CD3+ of the CD4+ subset. The perivascular focal infiltrates consisted in their great majority of T lymphocytes (mainly CD4+) and surrounded a smaller number of B cells. No abnormalities were noted in the MSG biopsies from the 2 healthy volunteers (Figure 2A-D). Macrophages (CD68+) were occasionally seen in areas of infiltrations.

Table 1. Clinical, laboratory profile and sicca features of DEMS/SAPS patients.

Patient	Dryness of:	Other Clinical Features	Schirmer Test	Rose-Bengal Stain	Immunological Profile
1	Eyes and mouth	Arthralgias	A	A	RF, anti-TPO
2	Eyes	Telangiectasias, RP	A	A	ANA, anti-TPO
3	Eyes and mouth	Morning stiffness, arthralgias	A	A	ANA, anti-TPO
4	Eyes and mouth	None	NA	N	ANA, RF, anti-TPO, anti-Tg
5	Eyes and mouth	Migraines, arthralgias, fibromyalgia-like features, RP	N	A	ANA, anti-TPO, anti-Tg
6	Mouth	Arthralgias	N	N	Anti-TPO, anti-Tg
7	Eyes and mouth	Dry cough	NA	NA	Anti-TPO, anti-Tg
8	Eyes and mouth	Morning stiffness, arthralgias, arthritis, RP	N	A	Anti-TPO
9	Eyes and mouth	Parotid gland enlargement, thrombocytopenia	N	A	ANA, anti-TPO, anti-Tg
10	Eyes and mouth	Migraines	N	N	Neg
11	Mouth	None	N	N	Neg
12	Eyes and mouth	None	N	N	Neg
13	Eyes and mouth	Arthralgias, carpal tunnel syndrome	N	N	Neg
14	Eyes and mouth	Fibromyalgia-like features	N	A	Neg
15	Eyes and mouth	Arthralgias	A	A	ANA
16	Eyes and mouth	Arthralgias	A	N	ANA, anti-TPO
17	Mouth		N	N	Anti-TPO
18	Eyes and mouth	Arthralgias	N	N	ANA, anti-TPO
19	Eyes and mouth	Arthritis	A	NA	ANA, anti-TPO
20	Eyes and mouth	Photosensitive rash	A	N	ANA, anti-TPO
21	Eyes and mouth	Arthralgias-Myalgias-RP	N	N	Neg
22	Eyes and mouth	Arthralgias	A	N	ANA
23	Eyes and mouth	None	N	NA	Neg
24	Eyes and mouth	None	N	N	Neg
25	Eyes	None	NA	NA	ANA, anti-TPO, anti-Tg
26	Eyes and mouth	Arthralgias	N	N	Neg
27	Eyes	None	A	A	RF, anti-TPO

DEMS: dry eyes and mouth syndrome; SAPS: sicca asthenia polymyalgia syndrome; RF: rheumatoid factor; anti-TPO: antibodies to thyroid peroxidase; TG: thyroglobulin; ANA: antinuclear antibodies; NA: not applicable; RP: Raynaud's phenomenon. N: normal, A: abnormal.

Table 2. Comparison of clinical/serological features in patients with DEMS/SAPS versus primary Sjögren's syndrome.

	DEMS/SAPS, % (No.)	pSS, % (No.)	p
Subjective oral dryness	88.8 (24/27)	100.0 (54/54)	0.03
Subjective ocular dryness	88.8 (24/27)	100.0 (54/54)	0.03
Schirmer's (< 5mm/5 min)	37.5 (9/24)	86.0 (43/50)	0.001
Rose-Bengal stain (> 4/9)	39.1 (9/23)	54.5 (24/44)	0.30
Arthralgias/arthritis	48.1 (13/27)	61.1 (33/54)	0.34
Raynaud's phenomenon	11.1 (3/27)	16.6 (9/54)	1.0
Antinuclear antibodies	44.5 (12/27)	88.9 (48/54)	0.001
Rheumatoid factor	11.1 (3/27)	42.6 (23/54)	0.005
Positive anti-TPO titers	59.2 (16/27)	20.4 (11/54)	0.001
Positive anti-TG titers	22.2 (6/27)	18.5 (10/54)	0.77

pSS: primary Sjögren's syndrome; DEMS: dry eyes and mouth syndrome; SAPS: sicca asthenia polymyalgia syndrome; TPO: thyroid peroxidase; TG: thyroglobulin.

DISCUSSION

In our study, we have attempted to identify distinctive clinical and serological features in patients with DEMS/SAPS. Sicca features, nonspecific musculoskeletal pain, and Raynaud's phenomenon were the commonest symptoms,

Table 3. Comparison of median and range of titer of antithyroid autoantibodies between patients with DEMS/SAPS versus pSS.

	DEMS/SAPS	pSS	p
Anti-TPO, IU/ml, median (range)	299 (10–5100)	16 (0.24–186)	0.0028*
Anti-Tg, IU/ml, median (range)	43 (0–2700)	21 (4.1–804)	0.2713**

* Anti-TPO DEMS/SAPS vs pSS; ** anti-Tg DEMS/SAPS vs pSS. For abbreviations see Table 2.

and antibodies against thyroid antigens were the most prevalent underlying finding, suggesting the autoimmune nature of this often-encountered clinical syndrome in rheumatology outpatient clinics. Although sicca features have been reported in the setting of autoimmune thyroid disease, it is unclear whether they are directly related to the disease itself or to concomitant SS^{5,9}.

When compared with the pSS group, patients with DEMS/SAPS have shown a similar prevalence in the occurrence of subjective dry mouth symptoms and keratoconjunctivitis sicca, musculoskeletal complaints, and Raynaud's

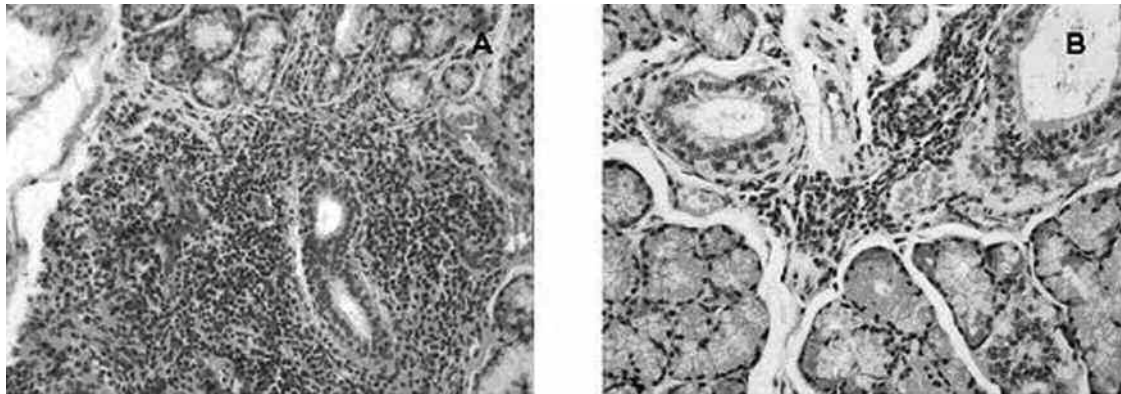


Figure 1. H&E sections of minor salivary glands from a patient with primary SS (A, original magnification 200 \times) and a patient with DEMS/SAPS (B, original magnification 400 \times). Mononuclear cells tend to surround the vessel in the interstitial tissue in the salivary gland of the DEMS/SAPS patient, whereas in the case of pSS the distribution of the infiltrate is clearly periductal.

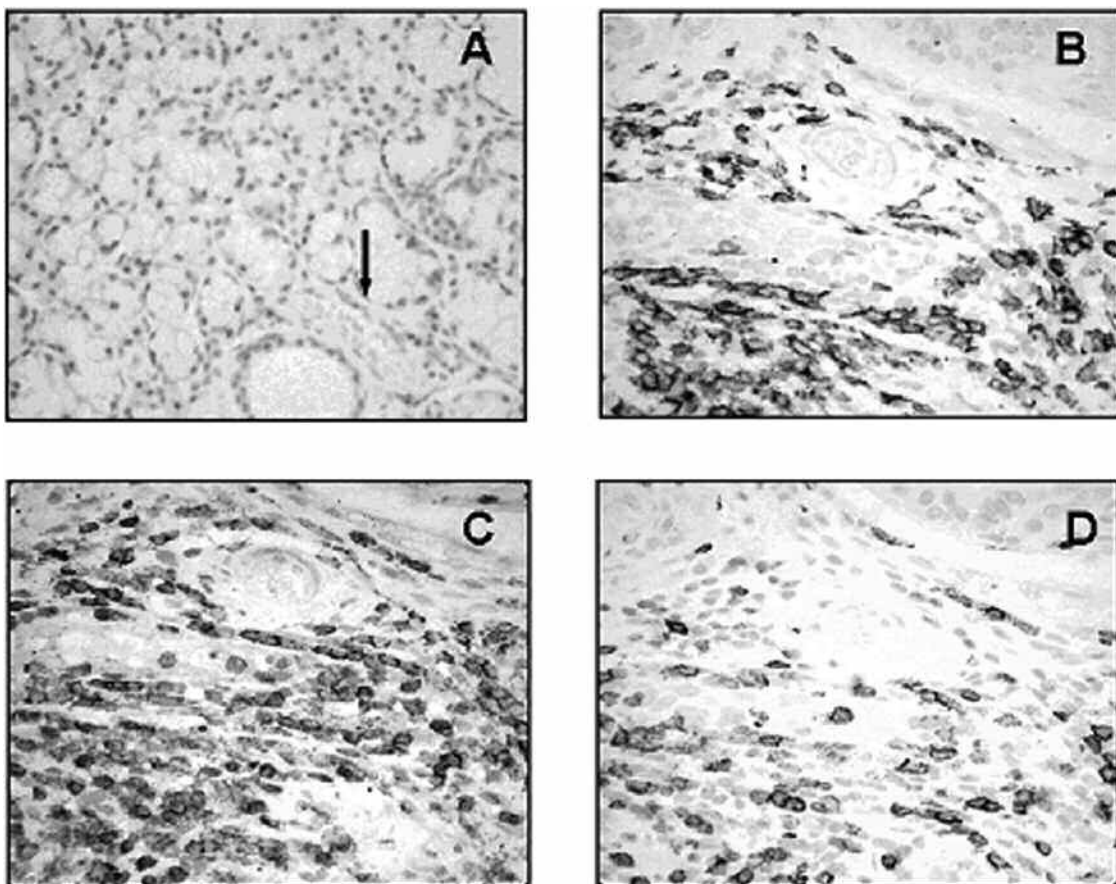


Figure 2. A. Minor salivary gland (MSG) tissue from a healthy volunteer. Arrow indicates a small vessel (hematoxylin staining, original magnification 200 \times). B. Immunohistochemical staining for CD20-positive B cells infiltrating a perivascular area in MSG biopsy from a patient with DEMS/SAPS and positive antithyroid antibodies (original magnification 400 \times). C. Serial section of the same MSG biopsy showing CD3-positive T cells (original magnification 400 \times). D. Serial section of the same MSG biopsy showing CD4-positive T cells (original magnification 400 \times).

phenomenon. However, severe extraglandular features, such as parenchymal involvement, vasculitis, and lymphoma known to occur in the setting of pSS, were not present in our

cohort of patients with DEMS/SAPS¹. Compared to the prevalence of antithyroid antibodies in SS reported by us and others (20-30%)¹⁰, patients with DEMS/SAPS had a

significantly higher prevalence of anti-TPO antibodies; they were present in approximately two-thirds of patients. It should, however, be acknowledged that the very high frequency of thyroid autoimmunity in our cohort could be attributed to the pattern of referral (to a referral autoimmune disease center) or to possible ascertainment bias due to the retrospective nature of the study.

Nevertheless, these findings highlight the importance of testing for underlying thyroid autoimmunity in patients presenting with sicca manifestations after known causes, including SS, are cautiously excluded and provides insights for the underlying diagnosis in the great majority of patients with DEMS/SAPS. As far as the remaining 40%, which were mainly characterized by fibromyalgia-like features previously associated with sicca manifestations¹¹, no underlying abnormality could be detected after extensive investigations. However, in these patients, the possibility of a “seronegative” subset of autoimmune thyroiditis, well recognized in the literature, could not be excluded since thyroid ultrasound, which can detect areas of thyroid hypoechogenicity relating to regional lymphocytic infiltration, was not performed. Thyroid status at the time of study entry was also assessed by measuring TSH levels. A great proportion of our patients had already been given thyroxine by their referring physician, giving a potential explanation for the normal TSH values in our patient cohort.

Histopathological analysis of MSG biopsies of patients with DEMS/SAPS disclosed the presence of perivascular infiltrates consisting mainly of cells of the T lymphocyte helper/inducer subset surrounding a smaller, but significant, number of B cells. This perivascular distribution is similar, although less intense, to that observed in those of SLE/SS overlap patients¹³. Of interest, brain autopsies from patients with Hashimoto’s encephalopathy had comparable findings¹⁴, suggesting a possible common vasculopathic denominator in these entities. However, such mild lymphocytic infiltration cannot adequately explain the occurrence of sicca features. It is possible that in the presence of an autoimmune condition, such as autoimmune thyroiditis, several natural autoantibodies¹⁵ with anti-epithelial cell or anti-muscarinic¹⁶ properties are upregulated and could cause significant impairment in the saliva production or secretion resulting in the development of sicca symptoms.

For the first time, we report a high prevalence of underlying thyroid autoimmune process in patients presenting with DEMS/SAPS. In the setting of clinical practice, we propose that in the presence of sicca features suggestive of SS, but without fulfilling specific classification criteria, antibody testing to thyroid antigens should be performed, after other secondary causes are carefully excluded.

ACKNOWLEDGMENT

We thank Dr. J. Tsonis for collecting the clinical/serological data and Mr. D. Liakos for technical assistance.

REFERENCES

1. Manoussakis MN, Moutsopoulos HM. Sjogren’s syndrome: autoimmune epithelitis. *Baillieres Best Pract Res Clin Rheumatol* 2000;14:73-95.
2. Price EJ, Venables PJ. Dry eyes and mouth syndrome—a subgroup of patients presenting with sicca symptoms. *Rheumatology* 2002;41:416-22.
3. Mariette X, Caudmont C, Berge E, Desmoulins F, Pinabel F. Dry eyes and mouth syndrome or sicca, asthenia and polyalgia syndrome? *Rheumatology* 2003;42:914-5; author reply 913-4.
4. Champey J, Corruble E, Gottenberg JE, et al. Quality of life and psychological status in patients with primary Sjögren’s syndrome and sicca symptoms without autoimmune features. *Arthritis Rheum* 2006;55:451-7.
5. Vlachoyiannopoulos PG, Tzavara V, Dafni U, Spanos E, Moutsopoulos HM. Clinical features and evolution of antinuclear antibody positive individuals in a rheumatology outpatient clinic. *J Rheumatol* 1998;25:886-91.
6. Coll J, Anglada J, Tomas S, et al. High prevalence of subclinical Sjogren’s syndrome features in patients with autoimmune thyroid disease. *J Rheumatol* 1997;24:1719-24.
7. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren’s syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-8.
8. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjogren’s syndrome. Results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;36:340-7.
9. Hansen BU, Ericsson UB, Henricsson V, Larsson A, Manthorpe R, Warfvinge G. Autoimmune thyroiditis and primary Sjogren’s syndrome: clinical and laboratory evidence of the coexistence of the two diseases. *Clin Exp Rheumatol* 1991;9: 137-41.
10. D’Arbonneau F, Ansart S, Le Berre R, Dueymes M, Youinou P, Penneec YL. Thyroid dysfunction in primary Sjogren’s syndrome: a long-term followup study. *Arthritis Rheum* 2003;49:804-9.
11. Bonafede RP, Downey DC, Bennett RM. An association of fibromyalgia with primary Sjogren’s syndrome: a prospective study of 72 patients. *J Rheumatol* 1995;22:133-6.
12. Raber W, Gessl A, Nowotny P, Vierhapper H. Thyroid ultrasound versus antithyroid peroxidase antibody determination: a cohort study of four hundred fifty-one subjects. *Thyroid* 2002;12:725-31.
13. Manoussakis MN, Georgopoulou C, Zintzaras E, et al. Sjogren’s syndrome associated with systemic lupus erythematosus: clinical and laboratory profiles and comparison with primary Sjogren’s syndrome. *Arthritis Rheum* 2004;50:882-91.
14. Duffey P, Yee S, Reid IN, Bridges LR. Hashimoto’s encephalopathy: postmortem findings after fatal status epilepticus. *Neurology* 2003;61:1124-6.
15. Jasani B, Ternynck T, Lazarus JH, Phillips DI, Avrameas S, Parkes AB. Natural antibody status in patients with Hashimoto’s thyroiditis. *J Clin Lab Immunol* 1999;1:9-20.
16. Fox RI, Stern M. Sjogren’s syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems. *Scand J Rheumatol* 2002;Suppl 116:3-13.